[0005] Glial cell-derived neurotrophic factor (GDNF) receptor alpha-like (GFRAL) has been identified as the ligand binding receptor for GDF15. Loss of the anorectic effect of GDF15 in GFRAL-deficient mice as well as in rats administered an anti-GFRAL neutralizing monoclonal antibody illustrated that GFRAL is primarily responsible for the metabolic effects of GDF15 (Emmerson *et al.* (2017)).

[0006] The natural half-life ($t_{½}$) of mature circulating human GDF15 homodimer agonist is relatively short (about 2-3 hours). However, Intl. Patent Application Publication No. WO 2015/017710 generally describes extending the $t_{½}$ of GDF15 agonists through various conjugations including conjugation with a fragment crystallizable region (Fc).

[0007] The need exists for biologically active GDF15 compounds with extended time of action that may be used in therapy for inducing weight loss and for treating T2D, dyslipidemia, NASH and/or obesity. A therapeutically desirable compound would agonize the GFRAL receptor and provide advantageous properties. One advantageous property would be to induce weight loss. Another advantageous property would be stability *in vivo* for a prolonged window of time in the therapeutic range to enable a steady level of compound in the bloodstream with once weekly dosing to achieve the desired therapeutic effect. Further desirable properties also include decreased immunogenicity. Also, a desirable compound would have advantageous physical and/or chemical stability properties.

## SUMMARY

[0007a] In one aspect, the present disclosure refers to a compound comprising SEQ ID NO:2

[0007b] In another aspect, the present disclosure refers to a compound consisting of SEQ ID NO:2

[0007c] In yet another aspect, the present disclosure refers to a homodimer comprising two compounds disclosed herein, wherein the compounds are linked via at least one interchain disulfide bond between a cysteine residue of the first compound and a cysteine residue of the second compound.

[0007d] In a further aspect, the present disclosure refers to a pharmaceutical composition comprising the compound disclosed herein and one or more pharmaceutically acceptable excipients.

[0007e] In yet another aspect, the present disclosure refers to the compound disclosed herein for use in therapy.

[0007f] In another aspect, the present disclosure refers to the compound disclosed herein for use in inducing weight loss

[0007g] In yet another aspect, the present disclosure refers to the compound disclosed herein for use in the treatment of Type 2 diabetes.

[0007h] In a further aspect, the present disclosure refers to the compound disclosed herein for use in the treatment of obesity.

[0007i] In yet another aspect, the present disclosure refers to the compound disclosed herein for use in the treatment of dyslipidemia.

[0007j] In another aspect, the present disclosure refers to the compound disclosed herein for use in the treatment of NASH.

[0007k] In yet another aspect, the present disclosure refers to the use of a compound disclosed herein, in the manufacture of a medicament for inducing weight loss.

[0007l] In a further aspect, the present disclosure refers to the use of a compound disclosed herein, in the manufacture of a medicament for the treatment of Type 2 diabetes.

[0007m] In yet another aspect, the present disclosure refers to the use of a compound disclosed herein, in the manufacture of a medicament for the treatment of obesity

[0007n] In another aspect, the present disclosure refers to the use of a compound disclosed herein, in the manufacture of a medicament for the treatment of dyslipidemia.

[0007o] In yet another aspect, the present disclosure refers to the use of a compound disclosed herein, in the manufacture of a medicament for the treatment of NASH.

[0007p] In a further aspect, the present disclosure refers to a compound produced by cultivating a mammalian cell comprising a cDNA molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2, under such conditions that the polypeptide is expressed, and recovering the compound.

[0007q] In yet another aspect, the present disclosure refers to the use of a compound disclosed herein or the composition disclosed herein, in the manufacture of a medicament for inducing weight loss in a patient, for treating Type 2 diabetes, obesity, NASH and/or dyslipidemia, wherein the medicament is to be administered to a patient in need thereof once per week.

DESCRIPTION

[0008] In view of the above, the disclosure describes biologically active GDF15 analog compounds that have an extended $t_{½}$ and other desirable properties. More specifically, the compounds herein are recombinant fusion proteins having a hingeless monomeric (one Fc unit per GDF15) human IgG4 Fc linked via a rigid linker to the amino (N)-terminus of a GDF15 analog compound, whereby the compounds form a covalently linked homodimer via at least one interchain disulfide bond between the GDF15 portions of each of the monomers. An exemplary compound, Compound 2, is a homodimer of two molecules of Compound 1 (SEQ ID NO:2) and has surprisingly shown an enhanced $t_{½}$ of up to about 117 hours, which may provide for extended efficacy and may enable once weekly dosing of the compound. The compounds herein also have enhanced physical stability. For example, Compound 2 has a low 4.1 % High Molecular Weight (HMW) soluble aggregate in Protein A capture pool. Compound 2 also exhibits enhanced chemical stability, such as a low 0.75% Low Molecular Weight (LMW) percent growth at 1 mg/ml after 4 weeks of storage at 40°C in citrate at pH 6.0.

# CLAIMS

The invention claimed is:

1. A compound comprising SEQ ID NO:2.

2. A compound consisting of SEQ ID NO:2.

3. A homodimer comprising two compounds of Claim 1 or 2, wherein the compounds are linked via at least one interchain disulfide bond between a cysteine residue of the first compound and a cysteine residue of the second compound.

4. A pharmaceutical composition comprising the compound of Claims 1-3 and one or more pharmaceutically acceptable excipients.

5. The compound of Claims 1-3 for use in therapy.

6. The compound of Claims 1-3 for use in inducing weight loss.

7. The compound of Claims 1-3 for use in the treatment of Type 2 diabetes.

8. The compound of Claims 1-3 for use in the treatment of obesity.

9. The compound of Claims 1-3 for use in the treatment of dyslipidemia.

10. The compound of Claims 1-3 for use in the treatment of NASH.

11. Use of a compound of Claims 1-3, in the manufacture of a medicament for inducing weight loss.

12. Use of a compound of Claims 1-3, in the manufacture of a medicament for the treatment of Type 2 diabetes.

13. Use of a compound of Claims 1-3, in the manufacture of a medicament for the treatment of obesity.

14. Use of a compound of Claims 1-3, in the manufacture of a medicament for the treatment of dyslipidemia.

15. Use of a compound of Claims 1-3, in the manufacture of a medicament for the treatment of NASH.

16. A compound produced by cultivating a mammalian cell comprising a cDNA molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2, under such conditions that the polypeptide is expressed, and recovering the compound.

17. Use of a compound of Claims 1-3 or the composition of Claim 4, in the manufacture of a medicament for inducing weight loss in a patient, treating Type 2 diabetes, obesity, NASH and/or dyslipidemia, wherein the medicament is to be administered to a patient in need thereof once per week.