glycemic control in an individual in need of such treatment, while also preserving an overall acceptable benefit/risk profile to the individual.

BRIEF SUMMARY

The present disclosure reports doses and dosing regimens for a GLP-1/Gcg co-agonist that result in unexpectedly improved weight loss, improved body composition, robust glucose control, lipid lowering and / or insulin sensitization sparing beta-cell insulin secretory workload while at the same time exhibiting only mild or moderate adverse events.

In one example, the present disclosure provides a method for providing chronic weight management, improving glycemic control, and/or reducing LDL cholesterol or triglycerides, in a patient in need thereof, wherein said method comprises:

(1) administering a once weekly dose of a compound of the following formula:
His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Glu-Gly-Gly-Pro-Ser-Ser-Gly

wherein Xaa2 is Aib;

Lys at position 20 is chemically modified by conjugation of the epsilon-amino group of the Lys side chain with ([2-(2-aminoethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH$_2$)$_{18}$CO$_2$H; and

the C-terminal amino acid is amidated (SEQ ID NO:1),

or a pharmaceutically acceptable salt thereof,

to the patient in need thereof for at least about two weeks; and

(2) thereafter increasing the dose to greater than about 6 mg to about 16 mg and administering the increased dose to said patient once weekly for at least about two weeks.

In some examples, provided herein is a method for preventing and/or treating a condition selected from type 2 diabetes, hyperglycemia, non-insulin dependent diabetes, obesity; dyslipidemia, non-alcoholic fatty acid liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), major adverse cardiac events (MACE), obstructive sleep apnea, osteoarthritis, polycystic ovary syndrome, chronic kidney disease or diabetic kidney disease, reducing body weight, reducing food intake, and/or inducing satiety in a patient, wherein said method comprises:

(1) administering a once weekly dose of a compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, to a patient in need thereof for at least about two weeks; and

(2) thereafter increasing the dose to greater than about 6 mg to about 16 mg and administering the increased dose to said patient once weekly for at least about two weeks.

In another example of the present disclosure, there is provided a compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, for use in providing chronic weight management, improving glycemic control and/or reducing LDL cholesterol or triglycerides, wherein:

(1) a once weekly dose of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is administered for at least about two weeks; and

(2) thereafter the once weekly dose in increased to greater than about 6 mg to about 16 mg and is administered for at least about two weeks.

In some examples, there is provided a compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, for use in preventing and/or treating a condition selected from type 2 diabetes, hyperglycemia, non-insulin dependent diabetes, obesity, dyslipidemia, non-alcoholic fatty acid liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), major adverse cardiac events (MACE), obstructive sleep apnea, osteoarthritis, polycystic ovary syndrome, chronic kidney disease or diabetic kidney disease, for use in reducing body weight, for use in reducing food intake and/or for use in inducing satiety in a patient, wherein:

(1) a once weekly dose of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is administered for at least about two weeks; and

(2) thereafter the once weekly dose in increased to greater than about 6 mg to about 16 mg and is administered for at least about two weeks.

The present disclosure also provides use of a compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for providing chronic weight management, improving glycemic control, and/or reducing LDL cholesterol or triglycerides, wherein:

(1) a once weekly dose of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is administered for at least about two weeks; and

(2) thereafter the once weekly dose in increased to greater than about 6 mg to about 16 mg and is administered for at least about two weeks.

In an aspect, there is provided use of a compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for providing chronic weight management, improving glycemic control, and/or reducing LDL cholesterol or triglycerides, wherein:

(1) a once weekly dose of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is to be administered to a patient for at least about two weeks; and

(2) thereafter the once weekly dose is to be increased to greater than about 6 mg to about 16 mg and is to be administered for at least about two weeks.

In some examples, there is provided the use of a compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for preventing and/or treating a condition selected from type 2 diabetes, hyperglycemia, non-insulin dependent diabetes, obesity, dyslipidemia, non-alcoholic fatty acid liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), major adverse cardiac events (MACE), obstructive sleep apnea, osteoarthritis, polycystic ovary syndrome, chronic kidney disease or diabetic kidney disease, reducing body weight, reducing food intake and/or inducing satiety in a patient, wherein:

(1) a once weekly dose of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is administered for at least about two weeks; and

(2) thereafter the once weekly dose in increased to greater than about 6 mg to about 16 mg and is administered for at least about two weeks.

In a further example of the present disclosure, the once weekly increased dose is from about 6.25 mg to about 16.0 mg, from about 6.5 mg to about 16.0 mg, from about 8.0 mg to about 16.0 mg, from about 10 mg to about 16.0 mg, from about 11.0 mg to about 16 mg, from about 12.0 mg to about 16.0 mg, from about 13.0 mg to about 16.0 mg or from about 14.0 mg to about 16.0.

In a further example of the present disclosure, the once weekly increased dose is about 6.25 mg, about 6.5 mg, about 7.0 mg, about 8.0 mg, about 9.0 mg, about 10.0 mg, about 11.0 mg, about 12.0 mg, about 13.0 mg, about 14.0 mg, about 15.0 mg or about 16.0 mg. In some examples, the once weekly increased dose is about 6.5 mg. In some examples, the once weekly increased dose is about 7.0 mg.

In some examples, the once weekly increased dose is about 8.0 mg. In some examples, the once weekly increased dose is about 9.0 mg. In some examples, the once weekly increased dose is about 10.0 mg. In some examples, the once weekly increased dose is about 11.0 mg. In some example, the once weekly increased dose is about 12.0 mg. In some examples, the once weekly increased dose is about 13.0 mg. In some examples, the once weekly increased dose is about 14.0 mg. In some examples, the once weekly increased dose is about 15.0 mg. In some examples, the once weekly increased dose is about 16.0 mg.

In a preferred example of the present disclosure, the once weekly increased dose is from about 8.0 mg to about 16.0 mg. In a still further example of the present disclosure, the once weekly increased dose is about 8.0 mg, about 10.0 mg, about 11.0 mg, about 12.0 mg, about 13.0 mg, about 14.0 mg, about 15.0 mg or about 16.0 mg.

In another preferred example of the present disclosure, the once weekly increased dose is from about 10.0 mg to about 16.0 mg. In a still further example of the present disclosure, the once weekly increased dose is about 10.0 mg, about 11.0 mg, about 12.0 mg, about 13.0 mg, about 14.0 mg, about 15.0 mg or about 16.0 mg.

In one example of the present disclosure, the once weekly dose in step (1) is about 1.0 mg to about 6.0 mg. In a still further example of the present disclosure, the about weekly dose is about 1.0 mg about 1.5 mg, about 2.0 mg, about 2.5 mg, about 3.0 mg, about 3.5 mg, about 4.0 mg, about 5.0 mg, about 5.5 mg or about 6.0 mg.

In a still further example of the present disclosure, multiple different once weekly doses are administered to the patient in steps (1) and (2).

In one example of the present disclosure, the patient is administered a first or initial once weekly dose of about 1.0 mg to about 6.0 mg. Thus, in some examples, a first once weekly dose is about 1.0 mg to about 6.0 mg. In a further example of the present disclosure, the first once weekly dose is about 1.0 mg, about 1.5 mg, about 2.0 mg, about 2.5 mg, about 3.0 mg, about 3.5 mg, about 4.0 mg, about 4.5 mg, about 5.0 mg, about 5.5 mg or about 6.0 mg. In a preferred example of the present disclosure, the first once weekly dose is about 1.0 mg, about 1.5 mg, about 2.0 mg or about 3.0 mg. In some examples, the first once weekly dose is about 1.0 mg. In some examples, the first once weekly dose is about 1.5 mg. In some examples, the first once weekly dose is about 2.0 mg. In some examples, the first once weekly dose is about 3.0 mg.

In one example of the present disclosure, the first dose and each subsequent increased dose are increased in increments of about 1.5 mg, about 2.0 mg, about 2.5 mg, about 3.0 mg, about 3.5 mg, about 4.0 mg, about 4.5 mg, about 5.0 mg, about 5.5 mg, about 6.0 mg or any combination thereof, and wherein each dose is administered for at least about two weeks. Thus, the first dose is selected from about 1.0 mg, about 1.5 mg, about 2.0 mg, about 2.5 mg, about 3.0 mg, about 3.5 mg, about 4.0 mg, about 4.5 mg, about 5.0 mg, about 5.5 mg, about 6.0 mg, and about 6.5 mg, and each subsequent dose is increased over the previously administered dose in an increment of about 1.0 mg, about

1.5 mg, about 2.0 mg, about 2.5 mg, about 3.0 mg, about 3.5 mg, about 4.0 mg, about 4.5 mg, about 5.0 mg, about 5.5 mg, about 6.0 mg or any combination thereof. In a preferred example, the first dose is selected from about 1.5 mg, about 2.0 mg, and about 3.0 mg and each subsequent dose is increased over the previously administered dose in an increment of about 1.5 mg, about 2.0 mg, about 3.0 mg, about 4.0 mg or any combination thereof.

In another example of the present disclosure, the dose may be lowered after administering the maximal or highest dose for that patient. For instance, once weekly doses of 2.0 mg, 4.0 mg, 6.0 mg, 8.0 mg and 10.0 mg of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, are administered to the patient, each for three weeks. After three weeks at the maximal dose of 10 mg, the dose is reduced to 8 mg.

In another example of the present disclosure, the method or use comprises administering each once weekly dose for at least about four weeks. In a still further example of the present disclosure, the method or use comprises administering each once weekly dose for at least about six weeks. In a still further example of the present disclosure, the method or use comprises administering each once weekly dose for at least about eight weeks.

In one preferred example, the method or use comprises administering each dose once weekly for at least about two weeks and administering the maximal dose once weekly for at least about four weeks. In another preferred example, the method or use comprises administering each dose once weekly for at least about 4 weeks and administering the maximal dose once weekly for at least about 4 weeks. In another preferred example, the method or use comprises administering each dose once weekly for at least about 4 weeks and administering the maximal dose once weekly for at least about 8 weeks.

In another example, the administration of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, results in a decrease in the patient's body weight. In some examples, the administration of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, results in at least about 10% decrease in the patient's body weight. In some examples, the administration of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, results in at least about 15% decrease in the patient's body weight. In some examples, the administration of the

compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, results in at least about 20% decrease in the patient's body weight.

In another example, the administration of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, results in a decrease in the patient's HbA1c. In another example, the administration of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, results in a decrease in the patient's LDL cholesterol and/or triglycerides decreases. In another example, the administration of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, does not result in unacceptable tolerability.

In one example, the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is administered subcutaneously.

In one example, the patient is overweight. In another example, the patient is obese. In another example, the patient has type 2 diabetes.

FIGURES

Figure 1 illustrates the disposition of the participants in the clinical study of Compound 1 described in Example 1.

Figure 2 illustrates the mean body weight changes from baseline in the placebo, Cohort 1 and Cohort 2 treatment groups in the clinical study of Compound 1 described in Example 1.

Figure 3 illustrates the mean waist circumference changes from baseline in the placebo, Cohort 1 and Cohort 2 treatment groups in the clinical study of Compound 1 described in Example 1.

Figure 4 illustrates the mean fasting glucose for placebo, Cohort 1 and Cohort 2 treatment groups in the clinical study of Compound 1 described in Example 1.

Figure 5 illustrates the mean fasting insulin for placebo, Cohort 1 and Cohort 2 treatment groups in the clinical study of Compound 1 described in Example 1.

Figure 6 illustrates the mean fasting C-peptide for placebo, Cohort 1 and Cohort 2 treatment groups in the clinical study of Compound 1 described in Example 1.

Figure 7a illustrates the mean fasting cholesterol for placebo, Cohort 1 and Cohort 2 treatment groups in the clinical study of Compound 1 described in Example 1.

CLAIMS

1. Use of a compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for providing chronic weight management, improving glycemic control, and/or reducing LDL cholesterol or triglycerides,

wherein:

(1) a once weekly dose of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is to be administered to a patient for at least about two weeks; and

(2) thereafter the once weekly dose is to be increased to greater than about 6 mg to about 16 mg and is to be administered for at least about two weeks.

2. The use according to claim 1, wherein the once weekly increased dose is selected from the group consisting of about 6.25 mg to about 16.0 mg, from about 6.5 mg to about 16.0 mg of the compound, from about 8.0 mg to about 16.0 mg, from about 10 mg to about 16.0 mg, from about 11.0 mg to about 16 mg, from about 12.0 mg to about 16.0 mg, from about 13.0 mg to about 16.0 mg or from about 14.0 mg to about 16.0 mg.

3. The use according to claim 1, wherein the once weekly increased dose is about 6.25 mg, about 6.5 mg, about 7.0 mg, about 8.0 mg, about 9.0 mg, about 10.0 mg, about 11.0 mg, about 12.0 mg, about 13.0 mg, about 14.0 mg, about 15.0 mg or about 16.0 mg.

4. The use according to claim 2, wherein the once weekly increased dose is from about 8 mg to about 16.0 mg.

5. The use according to claim 4, wherein the once weekly increased dose is about 8.0 mg, about 9.0 mg, about 10.0 mg, about 11.0 mg, about 12.0 mg, about 13.0 mg, about 14.0 mg, about 15.0 mg or about 16.0 mg.

6. The use according to claim 2, wherein the once weekly increased dose is from about 10 mg to about 16.0 mg.

7. The use according to claim 6, wherein the once weekly increased dose is about 10.0 mg, about 11.0 mg, about 12.0 mg, about 13.0 mg, about 14.0 mg, about 15.0 mg or about 16.0 mg.

8. The use according to claim 1, wherein multiple different once weekly doses are to be administered to the patient in (1) and (2).

9. The use according to claim 8, wherein a first once weekly dose is about 1.0 mg to about 6.0 mg.

10. The use according to claim 9, wherein the first once weekly dose is about 1.0 mg, about 1.5 mg, about 2.0 mg, about 2.5 mg, about 3.0 mg, about 3.5 mg, about 4.0 mg, about 4.5 mg, about 5.0 mg, about 5.5 mg or about 6.0 mg.

11. The use according to claim 10, wherein the first once weekly dose is about 1.5 mg, about 2.0 mg or about 3.0 mg.

12. The use according to claim 9, wherein the first once weekly dose and each subsequent increased once weekly dose are to be increased in increments of about 1.0 mg, about 1.5 mg, about 2.0 mg, about 2.5 mg, about 3.0 mg, about 3.5 mg, about 4.0 mg, about 4.5 mg, about 5.0 mg, about 5.5 mg, about 6.0 mg or any combination thereof, and wherein each dose is to be administered for at least about two weeks.

13. The use according to claim 12, wherein the first once weekly dose is about 1.5 mg, about 2.0 mg or about 3.0 mg and wherein the first once weekly dose and each subsequent increased once weekly dose are to be increased in increments of about 1.5 mg, about 2.0 mg, about 3.0 mg, about 4.0 mg or any combination thereof.

14. The use according to claim 1, wherein:

(a) a first dose of about 1.5 mg of the compound, or a pharmaceutically acceptable salt thereof, is to be administered once weekly for at least about two weeks;

(b) the dose is to be increased to about 3.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(c) the dose is to be increased to about 6.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(d) the dose is to be increased to about 8.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks; and

(e) the dose is to be increased to about 10.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks.

15. The use according to claim 1, wherein:

(a) a first dose of about 2.0 mg of the compound, or a pharmaceutically acceptable salt thereof, is to be administered once weekly for at least about two weeks;

(b) the dose is to be increased to about 4.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(c) the dose is to be increased to about 6.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(d) the dose is to be increased to about 8.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks; and

(e) the dose is to be increased to about 10.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks.

16. The use according to claim 1, wherein:

(a) a first dose of about 1.5 mg of the compound, or a pharmaceutically acceptable salt thereof, is to be administered once weekly for at least about two weeks;

(b) the dose is to be increased to about 3.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(c) the dose is to be increased to about 6.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(d) the dose is to be increased to about 8.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(e) the dose is to be increased to about 12.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks; and

(f) the dose is to be increased to about 16.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks.

17. The use according to claim 1, wherein:

(a) a first dose of about 2.0 mg of the compound, or a pharmaceutically acceptable salt thereof, is to be administered once weekly for at least about two weeks;

(b) the dose is to be increased to about 4.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(c) the dose is to be increased to about 6.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(d) the dose is to be increased to about 8.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(e) the dose is to be increased to about 10.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(f) the dose is to be increased to about 13.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks; and

(g) the dose is to be increased to about 16.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks.

18. The use according to claim 1, wherein:

(a) a first dose of about 1.5 mg of the compound, or a pharmaceutically acceptable salt thereof, is to be administered once weekly for at least about two weeks;

(b) the dose is to be increased to about 3.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(c) the dose is to be increased to about 6.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(d) the dose is to be increased to about 9.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(e) the dose is to be increased to about 12.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks; and

(f) the dose is to be increased to about 16.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks.

19. The use according to claim 1, wherein:

(a) a first dose of about 1.5 mg of the compound, or a pharmaceutically acceptable salt thereof, is to be administered once weekly for at least about two weeks;

(b) the dose is to be increased to about 3.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(c) the dose is to be increased to about 6.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(d) the dose is to be increased to about 10.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks;

(e) the dose is to be increased to about 13.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks; and

(f) the dose is to be increased to about 16.0 mg of the compound, or a pharmaceutically acceptable salt thereof, and the dose is to be administered once weekly for at least about two weeks.

20. The use according to claim 1, wherein each once weekly dose is to be administered for at least about four weeks.

21. The use according to claim 1, wherein the compound, or a pharmaceutically acceptable salt thereof, is to be administered subcutaneously.

22. The use according to claim 1, wherein the administration of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof is to result in a decrease in the patient's body weight.

23. The use according to claim 1, wherein the administration of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is to result in a decrease in the patient's HbA1c.

24. The use according to claim 1, wherein the administration of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, is to result in a decrease in the patient's LDL cholesterol and/or triglycerides decreases.

25. The use according to claim 1, wherein the administration of the compound of SEQ ID NO:1, or a pharmaceutically acceptable salt thereof, does not result in unacceptable tolerability.

26. The use according to claim 1, wherein the patient is overweight.

27. The use according to claim 1, wherein the patient is obese.

28. The use according to claim 1, wherein the patient has type 2 diabetes.