There is a need for alternative compounds that agonize both the amylin and calcitonin receptors. In addition, the need exists for dual amylin and calcitonin receptor agonists with extended time action and preserved potency. Therapeutically desirable compounds would agonize both the amylin and calcitonin receptors and provide one or more advantageous properties such as lowering food intake, lowering body weight, lowering blood glucose levels, lowering triglycerides, and/or lowering insulin levels. In addition, therapeutically desirable compounds may have one or more additional advantageous properties such as extended time action with preserved or improved potency in agonizing both the amylin and calcitonin receptors, a low risk of immunogenic response, chemical stability at a neutral pH, and/or a low risk of fibrillation.

Further, combination of a dual amylin and calcitonin receptor agonist of the present disclosure, optionally combined with an incretin or incretin analog, is desired to provide treatment for diabetes, obesity, NASH, and/or dyslipidemia. Such combination will also preferably be more effective than either molecule alone. For example, such treatment with such combination may allow for use of lower doses of either or both molecules as compared to each molecule alone, potentially leading to lower side effects (or a shorter duration of one or the other therapy) while maintaining efficacy. It is believed that the novel combination(s) provided herein will be effective treatments for diabetes, obesity, NASH, and/or dyslipidemia.

Summary

In an aspect of the present disclosure, there is provided a compound comprising: Acetyl-ASHLSTAVLGK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH$_2$)$_{18}$-CO$_2$H)LS-Aib-ELHKLEDYPRTDVGAESP-NH$_2$ (SEQ ID NO:2), or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

In another aspect of the present disclosure, there is provided a pharmaceutical composition as disclosed herein for use in therapy.

In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of Type 2 diabetes.

In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of obesity.

In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of dyslipidemia.

In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of NASH.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition as disclosed herein for use in the treatment of a condition selected from the group consisting of Type 2 diabetes, obesity, dyslipidemia, and NASH.

In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein in the manufacture of a medicament for the treatment of Type 2 diabetes.

In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein in the manufacture of a medicament for the treatment of obesity.

In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein in the manufacture of a medicament for the treatment of dyslipidemia.

In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein in the manufacture of a medicament for the treatment of NASH.

In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for the treatment of a condition selected from the group consisting of Type 2 diabetes, obesity, dyslipidemia, and NASH.

Description

Accordingly, the present disclosure provides a method of treating diabetes, obesity, NASH, and/or dyslipidemia, comprising administering to a patient in need of

such treatment an effective amount of a dual amylin and calcitonin receptor agonist with an effective amount of an incretin or incretin analog. The present disclosure further provides a method of treating clinical or pre-clinical diabetes, obesity, NASH, and/or dyslipidemia comprising administering to a patient in need of such treatment an effective amount of a dual amylin and calcitonin receptor agonist in combination with an effective amount of incretin or incretin analog.

Certain presently disclosed compounds which agonize the amylin and calcitonin receptors show an effective reduction in food intake and body weight, as well as glucose and insulin lowering. Further, certain presently disclosed compounds show a decreased risk of immunogenicity and a low level of fibrillation. The pharmacokinetic properties of

We Claim:

1. A compound comprising: Acetyl-ASHLSTAVLGK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH$_2$)$_{18}$-CO$_2$H)LS-Aib-ELHKLEDYPRTDVGAESP-NH$_2$ (SEQ ID NO:2), or a pharmaceutically acceptable salt thereof.

2. The compound of ~~Claim~~ claim 1, wherein the compound consist~~sing~~ of: Acetyl-ASHLSTAVLGK((2-[2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γ-Glu)-CO-(CH$_2$)$_{18}$-CO$_2$H)LS-Aib-ELHKLEDYPRTDVGAESP-NH$_2$ (SEQ ID NO:2), or a pharmaceutically acceptable salt thereof.

~~3. A method of treating Type 2 diabetes in a patient in need thereof, comprising administering to the patient an effective amount of a compound of Claim 1 or 2, or a pharmaceutically acceptable salt thereof.~~

~~4. A method of treating obesity in a patient in need thereof, comprising administering to the patient an effective amount of a compound of Claim 1 or 2, or a pharmaceutically acceptable salt thereof.~~

~~5. A method of treating dyslipidemia in a patient in need thereof, comprising administering to the patient an effective amount of a compound of Claim 1 or 2, or a pharmaceutically acceptable salt thereof.~~

~~6. A method of treating NASH in a patient in need thereof, comprising administering to the patient an effective amount of a compound of Claim 1 or 2, or a pharmaceutically acceptable salt thereof.~~

~~7. A method of lowering food intake in a patient in need thereof, comprising administering to the patient an effective amount of a compound of Claim 1 or 2, or a pharmaceutically acceptable salt thereof.~~

~~8. A method of lowering body weight in a patient in need thereof, comprising administering to the patient an effective amount of a compound of Claim 1 or 2, or a pharmaceutically acceptable salt thereof.~~

~~9. A method of lowering blood glucose in a patient in need thereof, comprising administering to the patient an effective amount of a compound of Claim 1 or 2, or a pharmaceutically acceptable salt thereof.~~

~~10. A method of lowering triglycerides in a patient in need thereof, comprising administering to the patient an effective amount of a compound of Claim 1 or 2, or a pharmaceutically acceptable salt thereof.~~

~~11. The method of any one of Claims 3-10, wherein the compound of Claim 1 or 2 is administered once weekly.~~

~~12.~~3. A pharmaceutical composition comprising the compound of ~~Claim~~ claim 1 or 2, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

~~13. A method of treating Type 2 diabetes in a patient in need thereof, comprising administering to the patient an effective amount of the pharmaceutical composition of Claim 12.~~

~~14. A method of treating obesity in a patient in need thereof, comprising administering to the patient an effective amount of the pharmaceutical composition of Claim 12.~~

~~15. A method of treating dyslipidemia in a patient in need thereof, comprising administering to the patient an effective amount of the pharmaceutical composition of Claim 12.~~

~~16. A method of treating NASH in a patient in need thereof, comprising administering to the patient an effective amount of the pharmaceutical composition of Claim 12.~~

~~17. A method of lowering food intake in a patient in need thereof, comprising administering to the patient an effective amount of the pharmaceutical composition of Claim 12.~~

~~18. A method of lowering body weight in a patient in need thereof, comprising administering to the patient an effective amount of the pharmaceutical composition of Claim 12.~~

~~19. A method of lowering blood glucose in a patient in need thereof, comprising administering to the patient an effective amount of the pharmaceutical composition of Claim 12.~~

~~20. A method of lowering triglycerides in a patient in need thereof, comprising administering to the patient an effective amount of the pharmaceutical composition of Claim 12.~~

~~21. A method of treating a condition in a patient in need thereof, selected from the group consisting of: clinical or pre-clinical diabetes, obesity, NASH, and dyslipidemia, comprising administering to the patient an effective amount of the pharmaceutical composition of Claim 12 in combination with an effective amount of an incretin or incretin analog.~~

~~22.~~4. ~~The~~ A compound of ~~Claim~~ claim 1 or 2, or a pharmaceutically acceptable salt thereof, for use in therapy.

~~23.~~5. ~~The~~ A pharmaceutical composition of ~~Claim~~ claim ~~12~~ 3 for use in therapy.

~~24.~~6. ~~The~~ A compound of ~~Claim~~ claim 1 or 2, or a pharmaceutically acceptable salt thereof, for use in the treatment of Type 2 diabetes.

~~25.~~7. ~~The~~ A compound of ~~Claim~~ claim 1 or 2, or a pharmaceutically acceptable salt thereof, for use in the treatment of obesity.

~~26.~~8. ~~The~~ A compound of ~~Claim~~ claim 1 or 2, or a pharmaceutically acceptable salt thereof, for use in the treatment of dyslipidemia.

~~27.~~9. ~~The~~ A compound of ~~Claim~~ claim 1 or 2, or a pharmaceutically acceptable salt thereof, for use in the treatment of NASH.

~~28.~~10. ~~The~~ A pharmaceutical composition of ~~Claim~~ claim ~~12~~ 3 for use in the treatment of a condition selected from the group consisting of Type 2 diabetes, obesity, dyslipidemia, and NASH.

~~29.~~11. Use of ~~the~~ a compound of ~~Claim~~ claim 1 or 2 in the manufacture of a medicament for the treatment of Type 2 diabetes.

~~30.~~12. Use of ~~the~~ a compound of ~~Claim~~ claim 1 or 2 in the manufacture of a medicament for the treatment of obesity.

~~31.~~13. Use of ~~the~~ a compound of ~~Claim~~ claim 1 or 2 in the manufacture of a medicament for the treatment of dyslipidemia.

~~32.~~14. Use of ~~the~~ a compound of ~~Claim~~ claim 1 or 2 in the manufacture of a medicament for the treatment of NASH.

15. Use of a pharmaceutical composition of claim 3 in the manufacture of a medicament for the treatment of a condition selected from the group consisting of Type 2 diabetes, obesity, dyslipidemia, and NASH.