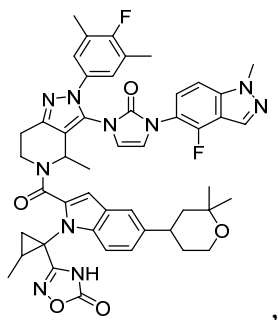
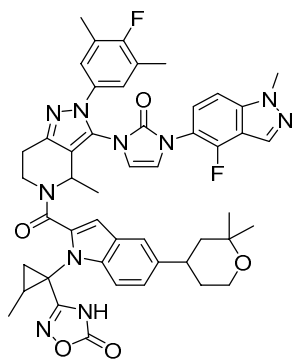


[004] Disclosed herein is a GLP-1 receptor NPA compound, Compound 1, having the following structure, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt:



for treating a subject with T2D, obesity, or overweight with at least one weight related comorbidity. As used herein, treating a subject with obesity or overweight with at least one weight related comorbidity is also known as chronic weight management (CWM).

[004a] In an aspect, there is provided use of a Compound 1 having the following structure:



or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt,

in the manufacture of a medicament for treating a subject with type 2 diabetes (T2D), obesity, or overweight with at least one weight related comorbidity, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is to be orally administered at a once daily (QD) dose selected from 1 mg, 2 mg, 3 mg, 6 mg, 12 mg, 24 mg, 36 mg, and a combination thereof.

[004b] In another aspect, there is provided use of a Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, in the manufacture of a medicament for treating a subject with type 2 diabetes (T2D), obesity, or overweight with at least one weight related comorbidity,

wherein the Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is to be orally administered at a once daily (QD) dose selected from 1 mg, 2 mg, 3 mg, 6 mg, 12 mg, 24 mg, 36 mg, and a combination thereof; and

wherein the subject is not restricted from food or water intake within 30 minutes before or after the oral administration of Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt.

[004c] In another aspect, there is provided use of Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, in the manufacture of a medicament for the treatment of a subject with T2D, obesity, or overweight with at least one weight related comorbidity, at a once daily (QD) dose selected from 1 mg, 2 mg, 3 mg, 6 mg, 12 mg, 24 mg, 36 mg, and a combination thereof.

[005] The specific doses and dose escalation schemes disclosed herein provide effective treatment options for T2D, obesity, or overweight with at least one weight related comorbidity while not being subject to the strict dosing limitations associated with other GLP-1 RA products.

BRIEF DESCRIPTION OF DRAWINGS

[006] Fig. 1 shows a clinical trial schema.

[007] Fig. 2 shows a clinical trial schema.

[008] Fig. 3 shows the effect of once daily OFG as compared to placebo on body weight. In Fig. 3, least square means are presented. Panel A shows the percentage change from baseline in body weight by week (efficacy estimand). Panel B shows the change from baseline in body weight (kg) by week. Panel C and D show the percentage of patients achieving $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ weight reduction at 26 and 36 weeks, respectively. * = P-value < 0.01 versus placebo. Doses 36 mg-1 and 36 mg-2 were combined for 36 mg and doses 45 mg-1 and 45 mg-2 were combined for 45 mg.

[009] Fig. 4 shows a clinical trial schema.

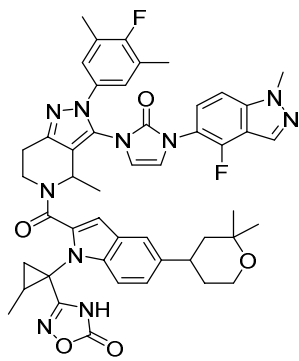
[0010] Fig. 5 shows LS Mean change in HbA1c.

[0011] Fig. 6 shows LS Mean change in body weight.

[0012] Fig. 7 shows the percent of participants achieving HbA1c and weight loss targets.

CLAIMS

1. Use of a Compound 1 having the following structure:



or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt,

in the manufacture of a medicament for treating a subject with type 2 diabetes (T2D), obesity, or overweight with at least one weight related comorbidity, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is to be orally administered at a once daily (QD) dose selected from 1 mg, 2 mg, 3 mg, 6 mg, 12 mg, 24 mg, 36 mg, and a combination thereof.

2. The use of claim 1, wherein Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is to be administered to the subject according to the following dosing schedule:

a starting dose of 1 mg QD, for 1, 2, 3, 4, 5, or 6 weeks at this dose;
 then the dose is to be increased to 3 mg QD, for 1, 2, 3, 4, 5, or 6 weeks at this dose;
 then the dose is to be increased to 6 mg QD, for 1, 2, 3, 4, 5, or 6 weeks at this dose;
 then the dose is to be increased to 12 mg QD, for 1, 2, 3, 4, 5, or 6 weeks at this dose;
 then the dose is to be increased to 24 mg QD, for 1, 2, 3, 4, 5, or 6 weeks at this dose; and
 then the dose is to be increased to 36 mg QD, and this dose is to be administered as a maintenance dose for at least 4 weeks.

3. The use of claim 2, wherein Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is to be administered to the subject according to the following dosing schedule:

a starting dose of 1 mg QD, and this dose is to be administered for 4 weeks;
then the dose is to be increased to 3 mg QD, and this dose is to be administered for 4 weeks;
then the dose is to be increased to 6 mg QD, and this dose is to be administered for 4 weeks;
then the dose is to be increased to 12 mg QD, and this dose is to be administered for 4 weeks;
then the dose is to be increased to 24 mg QD, and this dose is to be administered for 4 weeks; and
then the dose is to be increased to 36 mg QD, and this dose is to be administered as a maintenance dose for at least 4 weeks.

4. The use of claim 1, wherein Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is to be administered according to the following dosing schedule:

a starting dose of 1 mg QD, for 1, 2, 3, 4, 5, or 6 weeks at this dose;
then the dose is to be increased to 3 mg QD, for 1, 2, 3, 4, 5, or 6 weeks at this dose;
then the dose is to be increased to 6 mg QD, for 1, 2, 3, 4, 5, or 6 weeks at this dose; and
then the dose is to be increased to 12 mg QD, and this dose is to be administered as a maintenance dose for at least 4 weeks.

5. The use of claim 4, wherein Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is to be administered to the subject according to the following dosing schedule:

a starting dose of 1 mg QD, and this dose is to be administered for 4 weeks;
then the dose is to be increased to 3 mg QD, and this dose is to be administered for 4 weeks;

then the dose is to be increased to 6 mg QD, and this dose is to be administered for 4 weeks; and

then the dose is to be increased to 12 mg QD, and this dose is to be administered as a maintenance dose for at least 4 weeks.

6. The use of claim 1, wherein Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is to be administered to the subject according to the following dosing schedule:

a starting dose of 1 mg QD, and this dose is to be administered for 4 weeks;

then the dose is to be increased to 3 mg QD, and this dose is to be administered for 4 weeks; and

then the dose is to be increased to 6 mg QD, and this dose is to be administered as a maintenance dose for at least 4 weeks.

7. The use of claim 1, wherein Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is to be administered according to the following dosing schedule:

a starting dose of 1 mg QD, and this dose is to be administered for 4 weeks; and

then the dose is to be increased to 3 mg QD, and this dose is to be administered as a maintenance dose for at least 4 weeks.

8. The use of any one of claims 1-7, wherein the doses are to be administered to the subject for a total treatment period selected from at least 40 weeks, at least 52 weeks, at least 72 weeks, and at least 104 weeks; and

wherein the total treatment period comprises dose escalation period and dose maintenance period.

9. The use of any one of claims 1-8, wherein the medicament is for treating a subject with T2D mellitus for improved glycemic control; and

wherein the oral administration of Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is to result in a reduction of the subject's HbA1c level of at least 1.0%.

10. The use of claim 9, wherein the reduction of the HbA1c level is at least 1.2%.

11. The use of any one of claims 1-8, wherein the medicament is for treating a subject with obesity or overweight with at least one weight related comorbidity; and

wherein the oral administration of Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is to result in a weight reduction of at least 5%.

12. The use of claim 11, wherein the weight reduction is at least 10%.

13. The use of claim 11, wherein the weight reduction is at least 5 kg.

14. The use of any one of claims 1-13, wherein the subject is not restricted from food or water intake within 30 minutes before or after each oral administration of Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt.

15. The use of any one of claims 2-14, wherein oral administration of one or more escalation doses prior to the administration of a maintenance dose is to result in less treatment related side effects.

16. The use of any one of claims 1-15, wherein:

oral administration of Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is to be co-administered with a second active agent concomitantly or sequentially; and

wherein the second active agent is selected from the group consisting of: an amylin receptor non-peptide agonist, a glucagon receptor non-peptide agonist, a glucose-dependent

insulinotropic polypeptide (GIP) non-peptide agonist, a peptide tyrosine-tyrosine (PYY) non-peptide agonist, and a mixture thereof.

17. Use of a Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, in the manufacture of a medicament for treating a subject with type 2 diabetes (T2D), obesity, or overweight with at least one weight related comorbidity,

wherein the Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is to be orally administered at a once daily (QD) dose selected from 1 mg, 2 mg, 3 mg, 6 mg, 12 mg, 24 mg, 36 mg, and a combination thereof; and

wherein the subject is not restricted from food or water intake within 30 minutes before or after the oral administration of Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt.

18. The use of claim 17, wherein one or more escalation doses are to be administered to the subject prior to the administration of a maintenance dose; and

wherein the administration of the escalation doses is to result in less treatment related side effects as compared to a treatment without an escalation dose.

19. The use of claim 18, wherein the maintenance dose is 36 mg QD, and wherein Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is to be administered to the subject according to the following dosing schedule:

a starting dose of 1 mg QD, and this dose is to be administered for 4 weeks;

then the dose is to be increased to 3 mg QD, and this dose is to be administered for 4 weeks;

then the dose is to be increased to 6 mg QD, and this dose is to be administered for 4 weeks;

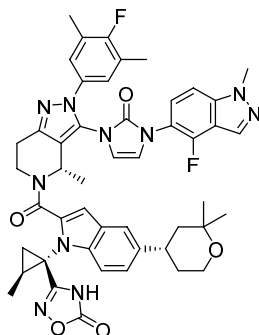
then the dose is to be increased to 12 mg QD, and this dose is to be administered for 4 weeks;

then the dose is to be increased to 24 mg QD, and this dose is to be administered for 4 weeks; and

then the dose is to be increased to 36 mg QD, and this dose is to be administered as a maintenance dose for at least 4 weeks.

20. The use of any one of claims 1-19, wherein each dose is a free acid equivalent amount of Compound 1.

21. The use of any one of claims 1-20, wherein Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is a hemicalcium salt of the following compound or a hydrate of the hemicalcium salt:



22. The use of any one of claims 1-21, wherein Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is to be administered to the subject as an adjunct to diet and exercise.

23. Use of Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, in the manufacture of a medicament for the treatment of a subject with T2D, obesity, or overweight with at least one weight related comorbidity, at a once daily (QD) dose selected from 1 mg, 2 mg, 3 mg, 6 mg, 12 mg, 24 mg, 36 mg, and a combination thereof.

24. The use of claim 23, wherein each dose is a free acid equivalent amount of Compound 1.

25. The use of claim 23 or 24, wherein the doses are to be administered to the subject as an adjunct to diet and exercise.

26. The use of any one of claims 23-25, wherein Compound 1, or a pharmaceutically acceptable salt thereof, or a hydrate of the compound or the pharmaceutically acceptable salt, is a hemicalcium salt of the following compound or a hydrate of the hemicalcium salt:

