SUMMARY ~~OF THE INVENTION~~

In an aspect of the present disclosure, there is provided a use of insulin efsitora alfa in the manufacture of a medicament for providing glycemic control in a subject in need thereof having diabetes, wherein:

a) an initial dose of insulin efsitora alfa that is a loading dose that is 3X larger than an expected weekly maintenance dose for the subject is to be administered to the subject; and

b) one or more weekly maintenance doses once-weekly starting one week after administration of the initial dose is to be administered to the subject.

Accordingly, the present disclosure~~invention~~ provides a method of providing glycemic control in a subject in need thereof having diabetes comprising:

a) administering to said subject an initial dose of BIF according to the following criteria:

i) the initial dose is a loading dose if the subject:

a. is insulin naïve;

b. has T2D and fasting glucose (FG) > 120 mg/dL; or

c. has type T1D;

ii) the initial dose is a weekly maintenance dose if the subject has T2D but does not meet the criteria set forth above in a. or b.; and

b) administering to said subject one or more weekly maintenance doses once-weekly starting one week after administration of the initial dose.

In another ~~aspect~~example, the present ~~invention~~ disclosure provides BIF for use in the treatment of diabetes, wherein the treatment comprises providing glycemic control by:

a) administering to said subject an initial dose of BIF according to the following criteria:

i) the initial dose is a loading dose if the subject:

a. is insulin naïve;

b. has T2D and FG > 120 mg/dL; or

c. has T1D;

ii) the initial dose is a weekly maintenance dose if the subject has T2D but does not meet the criteria set forth above in a. or b.; and

b) administering to said subject one or more weekly maintenance doses once-weekly starting one week after administration of the initial dose. The present disclosure~~invention~~ also provides criteria for selecting loading doses and maintenance doses of BIF for use the treatment of diabetes.

In another example~~aspect~~, the present ~~invention~~ disclosure provides a method of providing glycemic control in a subject having diabetes comprising:

a) determining a first dose of a long-acting insulin receptor agonist suitable for once-weekly dosing to be administered to the subject;

b) administering the first dose of the insulin receptor agonist suitable for once weekly dosing to the subject;

c) measuring the subject's fasting glucose (FG);

d) tallying the subject's frequency and severity of hypoglycemia;

e) determining a second dose of the insulin receptor agonist suitable for once weekly dosing to be administered to the subject based on the subject's FG determined in step c) and frequency and severity of hypoglycemia determined in step d); and

f) administering the second dose of the insulin receptor agonist suitable for once weekly dosing.

The present ~~invention~~ disclosure also provides methods of providing glycemic control in a subject having diabetes comprising administering a loading dose of a long-acting insulin receptor agonist suitable for once-weekly dosing to be administered to the subject.

In certain ~~embodiments~~examples, the loading dose is determined by: first determining the subject's expected weekly ~~-~~maintenance dose; and then multiplying the subject's expected weekly ~~-~~maintenance dose by the ratio of steady-state concentration : single dose peak concentration for the long-acting insulin receptor agonist suitable for once-weekly dosing.

DETAILED DESCRIPTION OF THE INVENTION

The present application provides dosing regimens, uses and methods of treatment for long-acting insulin receptor agonists suitable for once-weekly dosing.

When used herein, the term "insulin receptor agonist" refers to a protein that binds to and activates the insulin receptor, resulting in a lowering of blood glucose levels and/or suppression of hepatic glucose output, characteristics which can be tested and measured using known techniques, such as those shown in the studies described below. The term "long-acting insulin receptor agonist" refers to an insulin receptor agonist having a prolonged pharmacokinetic and pharmacodynamic profile to control blood glucose levels between meals when administered no more frequently than once or twice daily. When used herein in connection with an insulin receptor agonist, the term "suitable for once-weekly dosing" refers to a long-acting insulin receptor agonist with a pharmacokinetic and pharmacodynamic profile that is sufficiently prolonged to control blood glucose levels between meals when administered no more frequently than once weekly.

WE CLAIM:

1. ~~A method of~~ Use of insulin efsitora alfa in the manufacture of a medicament for providing glycemic control in a subject in need thereof having diabetes, wherein: ~~comprising:~~

a) ~~administering to said subject~~ an initial dose of ~~weekly basal insulin-Fc (BIF)~~ insulin efsitora alfa that is a loading dose that is 3X larger than an expected weekly maintenance dose for the subject is to be administered to the subject; ~~according to the following criteria:~~

~~i) the initial dose is a loading dose if the subject:~~

~~a. is insulin naïve;~~

~~b. has type 2 diabetes (T2D) and fasting glucose (FG) > 120 mg/dL; or~~

~~c. has type 1 diabetes (T1D);~~

~~ii) the initial dose is a weekly maintenance dose if the subject has T2D but does not meet the criteria set forth above in a. or b.;~~ and

b) ~~administering to said subject~~ one or more weekly maintenance doses once-weekly starting one week after administration of the initial dose is to be administered to the subject.

2. The ~~method~~ use of claim 1, wherein the ~~initial dose is a loading dose that is 3X larger than an expected weekly maintenance dose~~subject:

a) is insulin naïve;

b) has type 2 diabetes (T2D) and fasting glucose (FG) > 120 mg/dL; or

c) has type 1 diabetes (T1D).

3. The ~~method~~ use of either of claims 1 or 2 wherein the subject is insulin naïve, and the loading dose is 300 U.

4. The ~~method~~ use of claim 2 wherein the subject has T2D and FG > 120 mg/dL and wherein the expected weekly maintenance dose is approximately 7X larger than the subject's daily dose of basal insulin prior to initiation of treatment with insulin efsitora alfa~~BIF~~.

5. The ~~method~~ use of any of claims 1-4 wherein each weekly maintenance dose is selected according to the following criteria:

a) if the previous dose was a loading dose, the weekly maintenance dose is equal to the expected weekly ~~-~~maintenance dose adjusted, if necessary, according to items (i)-(iv) below:

i) decreased by 20 units if the subject's median FG during the previous week was <80 mg/dL;

ii) equal to the previous dose if the subject's median FG during the previous week was 80-120 mg/dL;

iii) increased by 20 units if the subject's median FG during the previous week was 121-140 mg/dL; or

iv) increased by 40 units if the subject's median FG was >140 mg/dL;

b) if the previous dose was not a loading dose, the weekly maintenance dose is equal to either: an expected weekly maintenance dose, if the maintenance dose is the initial dose of insulin efsitora alfa~~BIF~~; or the previous maintenance dose adjusted, if necessary, according to items (i)-(iv) above.

6. The ~~method~~ use of any of claims 1-5 wherein prior to initiation of treatment with insulin efsitora alfa~~BIF~~ the subject ~~is being~~was treated with > 10 units / day of a basal insulin.

7. The ~~method~~ use of any of claims 1-6 wherein prior to initiation of treatment with insulin efsitora alfa~~BIF~~ the subject ~~is being~~was treated with > 20 units / day of a basal insulin.

8. The ~~method~~ use of any of claims 1-4 wherein the subject has T2D and prior to initiation of treatment with insulin efsitora alfa~~BIF~~ has either baseline FG ≤ 120 mg/dL and/or ~~is being~~was treated with <20 units/day of a basal insulin, and wherein each weekly maintenance dose is selected according to the following criteria:

a) if the previous dose was a loading dose, the weekly maintenance dose is equal to the expected weekly maintenance dose adjusted, if necessary, according to items (i)-(iv) below:

i) decreased by 20 units if the subject's median FG during the previous week was <80 mg/dL;

ii) equal to the previous dose if the subject's median FG during the previous week was 80-120 mg/dL;

iii) increased by 10 units if the subject's median FG during the previous week was 121-140 mg/dL; or

iv) increased by 20 units if the subject's median FG during the previous week was >140 mg/dL;

b) if the previous dose was not a loading dose, the weekly maintenance dose is equal to the previous maintenance dose adjusted, if necessary, according to items (i)-(iv) above.

9. The ~~method~~ use of any of claims 1-4 wherein the subject has T2D and prior to initiation of treatment with insulin efsitora alfa~~BIF~~ ~~is being~~was treated with <10 units/day of a basal insulin, and wherein each weekly maintenance dose is selected according to the following criteria:

a) if the previous dose was a loading dose, the weekly maintenance dose is equal to the expected weekly maintenance dose adjusted, if necessary, according to items (i)-(iv) below:

i) decreased by 20 units if the subject's median FG during the previous week was <80 mg/dL;

ii) equal to the previous dose if the subject's median FG during the previous week was 80-120 mg/dL;

iii) increased by 5 units if the subject's median FG during the previous week was 121-140 mg/dL; or

iv) increased by 10 units if the subject's median FG during the previous week was >140 mg/dL;

b) if the previous dose was not a loading dose, the weekly maintenance dose is equal to the previous dose adjusted, if necessary, according to items (i)-(iv) above.

10. The ~~method~~ use of any of claims 5-9, wherein the weekly maintenance dose is not increased if the subject had blood glucose episode < 70 mg/dL in the previous week.

11. The ~~method~~ use of any of claims 1-10 wherein the weekly maintenance dose is decreased by 40 units if, in the previous week, the subject had any of:

a) ≥ 3 blood glucose episodes ≤ 70 mg/dL;

b) ≥ 1 nocturnal blood glucose episode ≤ 70 mg/dL;

c) ≥ 1 blood glucose episode ≤ 54 mg/dL; or

d) any episode of severe hypoglycemia.

12. The ~~method~~ use of any of claims 5-11 wherein the subject has not been treated with MDI.

13. The ~~method~~ use of any of claims 1-4, wherein the subject has T2D and is being treated with MDI, wherein each weekly maintenance dose is selected according to the following criteria:

a) if the weekly maintenance dose is the initial dose of insulin efsitora alfa~~BIF~~, the weekly maintenance dose is approximately 7X larger than the subject's daily dose of basal insulin prior to initiation of treatment with insulin efsitora alfa~~BIF~~;

b) if the weekly maintenance dose is not the initial dose of the insulin efsitora alfa~~BIF~~ and the subject has either baseline FG ≤ 120 mg/dL or daily basal dose prior to initiation of treatment with insulin efsitora alfa~~BIF~~ < 20 units, the weekly maintenance dose is equal to the previous maintenance dose adjusted, if necessary, according to the following criteria:

i) if the subject's median FG during the previous week was <80 mg/dL, the weekly maintenance dose is decreased by 10-20 units;

ii) if the subject's median FG during the previous week was 80-120 mg/dL, the weekly maintenance dose is not changed;

iii) if the subject's median FG during the previous week was 121-140 mg/dL, the weekly maintenance dose is increased by 10 units;

iv) if the subject's median FG during the previous week > 140 mg/dL, the weekly maintenance dose is increased by 20 units;

c) if the weekly maintenance dose is not the initial dose of the insulin efsitora alfa~~BIF~~ and if the subject has baseline FG > 120 mg/dL and basal dose ≥ 20 units / day prior to initiation of treatment with insulin efsitora alfa~~BIF~~, the weekly maintenance dose is equal to the previous maintenance dose adjusted, if necessary, according to the following criteria:

i) if the subject's median FG during the previous week was <80 mg/dL, the weekly maintenance dose is decreased by 20 units;

ii) if the subject's median FG during the previous week was 80-120 mg/dL, the weekly maintenance dose is not changed;

iii) if the subject's median FG during the previous week was 121-140 mg/dL, the weekly maintenance dose is increased by 20 units;

iv) if the subject's median FG during the previous week > 140 mg/dL, the weekly maintenance dose is increased by 40 units.

14. The ~~method~~ use of either of claims 1 or 2, wherein the subject has T1D and wherein the loading dose is determined according to the following criteria:

a) if the subject's baseline FG is ≤ 140 mg/dL, the loading dose = (the subject's daily dose of basal insulin prior to initiation of treatment with insulin efsitora alfa~~BIF~~) x 7 x 3;

b) if the subject's baseline FG is 140-160 mg/dL, the loading dose = (the subject's daily dose of basal insulin prior to initiation of treatment with insulin efsitora alfa~~BIF~~ increased by about 10-20%) x 7 x 3;

c) if the subject's baseline FG is > 160 mg/dL, the loading dose = (the subject's daily dose of basal insulin prior to initiation of treatment with insulin efsitora alfa~~BIF~~ increased by about 20-30%) x 7 x 3.

15. The ~~method~~ use of any of claims 1-2 or 14, wherein the subject has T1D and wherein the subject's first weekly maintenance dose is selected according to the following criteria:

a) if the subject's baseline FG is ≤ 140 mg/dL, the first weekly maintenance dose = (the subject's daily dose of basal insulin prior to initiation of treatment with insulin efsitora alfa~~BIF~~) x 7;

b) if the subject's baseline FG is 140-160 mg/dL, the first weekly maintenance dose = (the subject's daily dose of basal insulin prior to initiation of treatment with insulin efsitora alfa~~BIF~~ increased by about 10-20%) x 7;

c) if the subject's baseline FG is > 160 mg/dL, the first weekly maintenance dose = (the subject's daily dose of basal insulin prior to initiation of treatment with insulin efsitora alfa~~BIF~~ increased by about 20-30%) x 7.

16. The ~~method~~ use of any of claims 1-2 or 14-15, wherein the subject has T1D and wherein the subject's second and subsequent weekly maintenance doses are selected according to the following criteria:

a) if the subject's median FG during the previous week was <80 mg/dL, the weekly maintenance dose is decreased to the previous lower dose;

b) if the subject's median FG during the previous week was 80-120 mg/dL, the weekly maintenance dose is not changed;

c) if the subject's median FG during the previous week was 121-150 mg/dL, the weekly maintenance dose is increased either by: 5 units if the previous weekly maintenance dose was < 100 U; or 10 units if the previous weekly maintenance dose was ≥ 100 U;

d) if the subject's median FG during the previous week was 151-180 mg/dL, the weekly maintenance dose is increased either by: 10 units if the previous weekly maintenance dose was < 100 U; or 20 units if the previous weekly maintenance dose was ≥ 100 U;

e) if the subject's median FG during the previous week was > 180 mg/dL, the weekly maintenance dose is increased either by: 20 units if the previous weekly maintenance dose was < 100 U; or 30 units if the previous weekly maintenance dose was ≥ 100 U.

17. The ~~method~~ use of any of claims 13-16 wherein the weekly maintenance dose is not increased if the subject had one or more incidents of hypoglycemia believed to be attributed to insulin efsitora alfa~~BIF~~, rather than the subject's prandial insulin.

18. The ~~method~~ use of any of claims 13-17, wherein the weekly maintenance dose is not increased if the subject had one or more incidents of nocturnal hypoglycemia.

19. The ~~method~~ use of any of claims 13-18, wherein the weekly maintenance dose is not increased if the subject had one or more incidents of severe hypoglycemia.

20. The ~~method~~ use of any of claims 1-19 wherein the need for any weekly maintenance dose adjustments is determined: every week for the first 12 weeks after initiation of treatment with insulin efsitora alfa~~BIF~~; and every 4 weeks thereafter.

21. The ~~method~~ use of ~~any of~~ any of claims 1-20 wherein the ~~method~~ use comprises improving glycemic control in the patient.

~~22. BIF for use in the treatment of diabetes, wherein the treatment comprises providing glycemic control by:~~

~~a) administering to said subject an initial dose of BIF according to the following criteria:~~

~~i) the initial dose is a loading dose if the subject:~~

~~a. is insulin naïve;~~

b. has T2D and FG > 120 mg/dL; or

c. has T1D;

ii) the initial dose is a weekly maintenance dose if the subject has T2D but does not meet the criteria set forth above in a. or b.; and

b) administering to said subject one or more weekly maintenance doses once-weekly starting one week after administration of the initial dose.

23. BIF for use in claim 22, wherein the initial dose is a loading dose that is 3X larger than an expected weekly maintenance dose.

24. BIF for use in either of claims 22 or 23 wherein the subject is insulin naïve, and the loading dose is 300 U.

25. BIF for use in claim 23 wherein the subject has T2D and FG > 120 mg/dL and wherein the expected weekly maintenance dose is approximately 7X larger than the subject's daily dose of basal insulin prior to initiation of treatment with BIF.

26. BIF for use in any of claims 22-25 wherein each weekly maintenance dose is selected according to the following criteria:

a) if the previous dose was a loading dose, the weekly maintenance dose is equal to the expected weekly maintenance dose adjusted, if necessary, according to items (i)-(iv) below:

i) decreased by 20 units if the subject's median FG during the previous week was <80 mg/dL;

ii) equal to the previous dose if the subject's median FG during the previous week was 80-120 mg/dL;

iii) increased by 20 units if the subject's median FG during the previous week was 121-140 mg/dL; or

iv) increased by 40 units if the subject's median FG was >140 mg/dL;

b) if the previous dose was not a loading dose, the weekly maintenance dose is equal to either: an expected weekly maintenance dose, if the maintenance dose is the initial dose of BIF; or the previous maintenance dose adjusted, if necessary, according to items (i)-(iv) above.

27. BIF for use in any of claims 22-26 wherein prior to initiation of treatment with BIF the subject is being treated with > 10 units / day of a basal insulin.

28. BIF for use in any of claims 22-27 wherein prior to initiation of treatment with BIF the subject is being treated with > 20 units / day of a basal insulin.

29. BIF for use in any of claims 22-26 wherein the subject has T2D and prior to initiation of treatment with BIF has either baseline FG ≤ 120 mg/dL and/or is being treated with <20 units/day of a basal insulin, and wherein each weekly maintenance dose is selected according to the following criteria:

a) if the previous dose was a loading dose, the weekly maintenance dose is equal to the expected weekly maintenance dose adjusted, if necessary, according to items (i)-(iv) below:

i) decreased by 20 units if the subject's median FG during the previous week was <80 mg/dL;

ii) equal to the previous dose if the subject's median FG during the previous week was 80-120 mg/dL;

iii) increased by 10 units if the subject's median FG during the previous week was 121-140 mg/dL; or

iv) increased by 20 units if the subject's median FG during the previous week was >140 mg/dL;

b) if the previous dose was not a loading dose, the weekly maintenance dose is equal to the previous maintenance dose adjusted, if necessary, according to items (i)-(iv) above.

30. BIF for use in any of claims 22-26 wherein the subject has T2D and prior to initiation of treatment with BIF is being treated with <10 units/day of a basal insulin, and wherein each weekly maintenance dose is selected according to the following criteria:

a) if the previous dose was a loading dose, the weekly maintenance dose is equal to the expected weekly maintenance dose adjusted, if necessary, according to items (i)-(iv) below:

i) decreased by 20 units if the subject's median FG during the previous week was <80 mg/dL;

ii) equal to the previous dose if the subject's median FG during the previous week was 80-120 mg/dL;

iii) increased by 5 units if the subject's median FG during the previous week was 121-140 mg/dL; or

iv) increased by 10 units if the subject's median FG during the previous week was >140 mg/dL;

b) if the previous dose was not a loading dose, the weekly maintenance dose is equal to the previous dose adjusted, if necessary, according to items (i)-(iv) above.

31. BIF for use in any of claims 27-30, wherein the weekly maintenance dose is not increased if the subject had a blood glucose episode < 70 mg/dL in the previous week.

32. BIF for use in any of claims 22-31 wherein the weekly maintenance dose is decreased by 40 units if, in the previous week, the subject had any of:

a) ≥ 3 blood glucose episodes ≤ 70 mg/dL;

b) ≥ 1 nocturnal blood glucose episode ≤ 70 mg/dL;

c) ≥ 1 blood glucose episode ≤ 54 mg/dL; or

d) any episode of severe hypoglycemia.

33. BIF for use in any of claims 26-32 wherein the subject has not been treated with MDI.

34. BIF for use in any of claims 22-25, wherein the subject has T2D and is being treated with MDI, wherein each weekly maintenance dose is selected according to the following criteria:

a) if the weekly maintenance dose is the initial dose of BIF, the weekly maintenance dose is approximately 7X larger than the subject's daily dose of basal insulin prior to initiation of treatment with BIF;

b) if the weekly maintenance dose is not the initial dose of the BIF and the subject has either baseline FG ≤ 120 mg/dL or daily basal dose prior to initiation of treatment with BIF < 20 units, the weekly maintenance dose is equal to the previous maintenance dose adjusted, if necessary, according to the following criteria:

i) if the subject's median FG during the previous week was <80 mg/dL, the weekly maintenance dose is decreased by 10-20 units;

ii) if the subject's median FG during the previous week was 80-120 mg/dL, the weekly maintenance dose is not changed;

iii) if the subject's median FG during the previous week was 121-140 mg/dL, the weekly maintenance dose is increased by 10 units;

iv) if the subject's median FG during the previous week > 140 mg/dL, the weekly maintenance dose is increased by 20 units;

c) if the weekly maintenance dose is not the initial dose of the BIF and if the subject has baseline FG > 120 mg/dL and basal dose ≥ 20 units / day prior to initiation of treatment with BIF, the weekly maintenance dose is equal to the previous maintenance dose adjusted, if necessary, according to the following criteria:

i) if the subject's median FG during the previous week was <80 mg/dL, the weekly maintenance dose is decreased by 20 units;

ii) if the subject's median FG during the previous week was 80-120 mg/dL, the weekly maintenance dose is not changed;

iii) if the subject's median FG during the previous week was 121-140 mg/dL, the weekly maintenance dose is increased by 20 units;

iv) if the subject's median FG during the previous week > 140 mg/dL, the weekly maintenance dose is increased by 40 units.

35. BIF for use in either of claims 22 or 23, wherein the subject has T1D and wherein the loading dose is determined according to the following criteria:

a) if the subject's baseline FG is ≤ 140 mg/dL, the loading dose = (the subject's daily dose of basal insulin prior to initiation of treatment with BIF) x 7 x 3;

b) if the subject's baseline FG is 140-160 mg/dL, the loading dose = (the subject's daily dose of basal insulin prior to initiation of treatment with BIF increased by about 10-20%) x 7 x 3;

c) if the subject's baseline FG is > 160 mg/dL, the loading dose = (the subject's daily dose of basal insulin prior to initiation of treatment with BIF increased by about 20-30%) x 7 x 3.

36. BIF for use in any of claims 22-23 or 35, wherein the subject has T1D and wherein the subject's first weekly maintenance dose is selected according to the following criteria:

a) if the subject's baseline FG is ≤ 140 mg/dL, the first weekly maintenance dose = (the subject's daily dose of basal insulin prior to initiation of treatment with BIF) x 7;

b) if the subject's baseline FG is 140-160 mg/dL, the first weekly maintenance dose = (the subject's daily dose of basal insulin prior to initiation of treatment with BIF increased by about 10-20%) x 7;

c) if the subject's baseline FG is > 160 mg/dL, the first weekly maintenance dose = (the subject's daily dose of basal insulin prior to initiation of treatment with BIF increased by about 20-30%) x 7.

37. BIF for use in any of claims 22-23 or 25-26, wherein the subject has T1D and wherein the subject's second and subsequent weekly maintenance doses are selected according to the following criteria:

a) if the subject's median FG during the previous week was <80 mg/dL, the weekly maintenance dose is decreased to the previous lower dose;

b) if the subject's median FG during the previous week was 80-120 mg/dL, the weekly maintenance dose is not changed;

c) if the subject's median FG during the previous week was 121-150 mg/dL, the weekly maintenance dose is increased either by: 5 units if the previous weekly maintenance dose was < 100 U; or 10 units if the previous weekly maintenance dose was ≥ 100 U;

d) if the subject's median FG during the previous week was 151-180 mg/dL, the weekly maintenance dose is increased either by: 10 units if the previous weekly maintenance dose was < 100 U; or 20 units if the previous weekly maintenance dose was ≥ 100 U;

e) if the subject's median FG during the previous week was > 180 mg/dL, the weekly maintenance dose is increased either by: 20 units if the previous weekly maintenance dose was < 100 U; or 30 units if the previous weekly maintenance dose was ≥ 100 U.

38. BIF for use in any of claims 34-37 wherein the weekly maintenance dose is not increased if the subject had one or more incidents of hypoglycemia believed to be attributed to BIF, rather than the subject's prandial insulin.

~~39. BIF for use in any of claims 34-38, wherein the weekly maintenance dose is not increased if the subject had one or more incidents of nocturnal hypoglycemia.~~

~~40. BIF for use in any of claims 34-38, wherein the weekly maintenance dose is not increased if the subject had one or more incidents of severe hypoglycemia.~~

~~41. BIF for use in any of claims 22-40 wherein the need for any weekly maintenance dose adjustments is determined: every week for the first 12 weeks after initiation of treatment with BIF; and every 4 weeks thereafter.~~

~~42. BIF for use in any of any of claims 22-41 wherein the treatment comprises improving glycemic control in the patient.~~

~~24. Use of BIF in the manufacture of a medicament for use in the methods of any of claims 1-21 or the treatment of diabetes according to any of claims 22-42.~~