is proposed in WO2016/001185. US2016/0324932 describes fusion proteins having prolonged duration of action at the insulin receptor sufficient for dosing as infrequently as once-weekly, including BIF. A specific dosing regimen is not described.

Despite these disclosures, there remains a need for insulin therapies requiring fewer injections than currently available insulin products and that can be administered with simple and convenient dosing regimens while still providing sufficient glycemic control. There also remains a need for presentations of such therapies that provide for a simpler, more convenient and/or less painful patient experience. There also remains a need for methods of treatment using such insulin therapies either without increasing or with reducing the risk of hypoglycemia compared to currently available insulin products.

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 patient in need thereof with type 2 diabetes (T2D), wherein a fixed dose of insulin efsitora alfa selected from the group consisting of 100, 150, 250 and 400 U is to be administered once-weekly to said patient.

In another aspect of the present disclosure, there is provided a use of insulin efsitora alfa in the manufacture of a medicament for improving glycemic control in a patient in need thereof with type 2 diabetes (T2D), wherein:

a) 100 U of insulin efsitora alfa is to be administered to said patient once-weekly;

b) the dose of insulin efsitora alfa is increased to 150 U once-weekly after at least 4 weeks on the 100 U dose;

c) the dose of insulin efsitora alfa is increased to 250 U once-weekly after at least 4 weeks on the 150 U dose; and

d) the dose of insulin efsitora alfa is increased to 400 U once-weekly after at least 4 weeks on the 250 U dose.

In a further aspect of the present disclosure, there is provided an aqueous pharmaceutical composition comprising:

a) a fixed dose of insulin efsitora alfa in an amount selected from the group consisting of 100, 150, 250 and 400 U;

b) phosphate in a concentration between about 5 and 10 mM; and

c) glycerol in a concentration between about 15 and 35 mM;

and having a pH between about 5.5 and 7.5.

In another aspect of the present disclosure, there is provided a use of the composition as disclosed herein in the manufacture of a medicament for providing glycemic control in a patient with T2D.

In a further aspect of the present disclosure, there is provided a single-use autoinjector for use in the use as disclosed herein.

In another aspect of the present disclosure, there is provided a single-use autoinjector comprising the aqueous pharmaceutical composition as disclosed herein.

Accordingly, the present ~~invention~~ disclosure provides a method of providing glycemic control in a patient in need thereof with type 2 diabetes (T2D) comprising: administering to said patient once-weekly a fixed dose of BIF selected from the group consisting of 100, 150, 250 and 400 U.

The present ~~invention~~ disclosure also provides a method of providing glycemic control in a in a patient with type 2 diabetes (T2D) comprising:

a) administering to said patient an initial dose of 100 U of basal insulin-Fc (BIF) once weekly;
b) increasing the dose to 150 U of BIF once-weekly after at least 4 weeks on the 100 U dose;
c) increasing the dose to 250 U of BIF once-weekly after at least 4 weeks on the 150 U dose; and
d) increasing the dose to 400 U of BIF once-weekly after at least 4 weeks on the 250 U dose.

In certain ~~embodiments~~examples, steps b) through d) are performed when the patient's fasting glucose (FG) is > 130 mg/dL.

The present ~~invention~~ disclosure also provides an aqueous pharmaceutical composition comprising:

a) a fixed dose of BIF in an amount selected from the group consisting of 100, 150, 250 and 400 U;
b) phosphate in a concentration between about 5 and 10 mM; and

c) glycerol in a concentration between about 15 and 35 mM;

and having a pH between about 5.5 and 7.5.

The present ~~invention~~ disclosure also provides a single-use autoinjector for use in improving glycemic control in a patient with T2D comprising a fixed dose of BIF selected from the group consisting of 100, 150, 250 and 400 U.

DETAILED DESCRIPTION OF THE INVENTION

The present application provides multiple aspects of dosing regimens, uses and methods of treatment for a long-acting insulin receptor agonists suitable for once-weekly dosing, such as those described in U.S. Patent Application Publication No. 2016/0324932, including BIF. In certain aspects, the regimens and methods described herein include administration of a fixed dose of BIF. In other aspects, the regimens and methods described herein include determination of whether the fixed dose of BIF being used to treat a T2D patient should be changed. In other aspects, the regimens and methods described herein include identification of a simple and convenient device for administering a fixed dose of BIF. In other aspects, the regimens and methods herein describe a non-preserved formulation for use in providing a fixed dose of BIF.

BIF, also known as insulin efsitora alfa, comprises a dimer of an insulin receptor agonist fused to a human IgG Fc region, wherein the insulin receptor agonist comprises an insulin B-chain analog fused to an insulin A-chain analog through the use of a first peptide linker and wherein the C-terminal residue of the insulin A-chain analog is directly fused to the N-terminal residue of a second peptide linker, and the C-terminal residue of the second peptide linker is directly fused to the N-terminal residue of the human IgG Fc region. BIF is identified by CAS registry number 2131038-11-2, which provides the following chemical names: (1) Insulin [16-glutamic acid, 25-histidine, 27-glycine, 28-glycine, 29-glycine, 30-glycine] (human B-chain) fusion protein with peptide (synthetic 7-amino acid linker) fusion protein with insulin [47-threonine, 51-aspartic acid, 58-glycine] (human A-chain) fusion protein with peptide (synthetic 20-amino acid linker) fusion protein with immunoglobulin G2 (human Fc fragment), dimer; and (2) *Homo sapiens* Insulin B-chain [Y16>Y(16), F25>H(25), TPKT27-30>GGGG(27-30)] (1-30) fusion protein with diglycylseryltetraglycyl (31-37) Insulin A-chain [I10>T(47), Y14>D(51), N21>G(58)] (38-58) fusion protein with tris(tetraglycylglutaminyl)pentaglycyl (59-78) *Homo sapiens* Immunoglobulin heavy

WE CLAIM:

1. ~~A method of~~ Use of insulin efsitora alfa in the manufacture of a medicament for providing glycemic control in a patient in need thereof with type 2 diabetes (T2D), ~~comprising: administering to said patient once-weekly a fixed dose of basal insulin-Fc (BIF)~~ wherein a fixed dose of insulin efsitora alfa selected from the group consisting of 100, 150, 250 and 400 U is to be administered once-weekly to said patient.
2. The ~~method~~ use of claim 1, wherein the first dose of ~~BIF~~ insulin efsitora alfa to be administered to the patient is 100 U.
3. The ~~method~~ use of either of claims 1 or 2, wherein the patient is to be administered the same dose for at least 4 weeks, and wherein the dose is increased when the patient needs additional glycemic control.
4. The ~~method~~ use of any of claims 1-3, wherein the patient's dose is increased if the patient's fasting glucose (FG) is > 130 mg/dL after treatment with a first fixed dose for at least 4 weeks.
5. The ~~method~~ use of either of claims 3 or 4, wherein the patient's dose is only increased if the patient had 0 episodes of blood glucose < 70 mg/dL.
6. The ~~method~~ use of any of claims 1-5, wherein the patient's dose is decreased if the patient's FG is < 80 mg/dL.
7. ~~A method of~~ Use of insulin efsitora alfa in the manufacture of a medicament for improving glycemic control in a patient in need thereof with type 2 diabetes (T2D), ~~comprising~~wherein:
   a) ~~administering to said patient a~~ 100 U of ~~BIF~~ insulin efsitora alfa is to be administered to said patient once-weekly;
   b) ~~increasing~~ the dose of insulin efsitora alfa is increased to 150 U ~~of BIF~~ once-weekly after at least 4 weeks on the 100 U dose;
   c) ~~increasing~~ the dose of insulin efsitora alfa is increased to 250 U ~~of BIF~~ once-weekly after at least 4 weeks on the 150 U dose; and
   d) ~~increasing~~ the dose of insulin efsitora alfa is increased to 400 U ~~of BIF~~ once-weekly after at least 4 weeks on the 250 U dose.
8. The ~~method~~ use of claim 7, wherein steps b) through d) are performed to reduce the patient's FG.

9. The ~~method~~ use of claim 7, wherein steps b) through d) are performed when the patient's FG is > 130 mg/dL.
10. The ~~method~~ use of any of claims 7-9, wherein steps b) through d) are only performed when the patient had 0 episodes of blood glucose < 70 mg/dL.
11. The ~~method~~ use of any of claims 7-10, wherein the patient's dose is decreased to the previous lower dose if the patient's FG is < 80 mg/dL.
12. The ~~method~~ use of any of claims 1-11, wherein the patient discontinues treatment if the patient experiences one or more episodes of nocturnal hypoglycemia or 2 or more episodes of hypoglycemia.
13. The ~~method~~ use of any of claims 1-12, wherein the patient is insulin-naïve.
14. The ~~method~~ use of any of claims 1-13, wherein patient has uncontrolled hyperglycemia.
15. The ~~method~~ use of any of claims 1-14, wherein the patient has HbA1c between 7 and 10%.
16. The ~~method~~ use of any of claims 1-15, wherein the patient is ~~receiving~~ to receive 2 or more oral antihyperglycemic medications.
17. The ~~method~~ use of any of claims 1-16, wherein the patient is ~~receiving~~ to receive a GLP-1 receptor agonist.
18. The ~~method~~ use of any of claims 1-17, wherein ~~BIF is in~~insulin efsitora alfa is to be administered in an aqueous composition comprising: phosphate in a concentration between about 5 and 10 mM; and glycerol in a concentration between about 15 and 35 mM; and having a pH between about 5.5 and 7.5.
19. The ~~method~~ use of claim 18, wherein the composition further comprises poloxamer 188 in a concentration between about 0.1 to about 0.5 mg/mL.
20. The ~~method~~ use of claim 19, wherein the phosphate is in a concentration of about 10 mM; glycerol is in a concentration of about 25 mM; and poloxamer 188 is in a concentration of about 0.4 mg/mL; and wherein the pH of the composition is about 6.5.
21. An aqueous pharmaceutical composition comprising:
    a) a fixed dose of ~~BIF~~ insulin efsitora alfa in an amount selected from the group consisting of 100, 150, 250 and 400 U;
    b) phosphate in a concentration between about 5 and 10 mM; and

c) glycerol in a concentration between about 15 and 35 mM;

and having a pH between about 5.5 and 7.5.

22. The aqueous pharmaceutical composition of claim 21, further comprising poloxamer 188 in a concentration between about 0.1 to about 0.5 mg/mL.

23. The aqueous pharmaceutical composition of claim 22, wherein the phosphate is in a concentration of about 10 mM; glycerol is in a concentration of about 25 mM; and poloxamer 188 is in a concentration of about 0.4 mg/mL; and wherein the pH of the composition is about 6.5.

24. ~~A method of providing glycemic control in a patient in need thereof with type 2 T2D comprising administering to said subject~~Use of the composition of any of claims 21-23 in the manufacture of a medicament for providing glycemic control in a patient with T2D.

25. The ~~method~~ use of any of claims 1-20, wherein the fixed dose of ~~BIF~~ insulin efsitora alfa is provided in a single-use autoinjector.

26. A single-use autoinjector for use in the ~~method~~ use of any of claims 1-25.

27. A single-use autoinjector comprising the composition of any of claims 21-23.

28. The ~~method~~ use of ~~any of~~ any of claims 1-20 or 24-25, wherein the ~~method~~ use comprises improving glycemic control in the patient.

~~29. BIF for use in the treatment of T2D, wherein the treatment comprises improving glycemic control by administering once-weekly a fixed dose of BIF selected from the group consisting of 100, 150, 250 and 400 U.~~

~~30. BIF for use according to claim 29, wherein the first fixed dose of BIF is 100 U.~~

~~31. BIF for use according to claim 29 or claim 30, wherein the same dose is administered for at least 4 weeks, and wherein the dose is increased when additional glycemic control is needed.~~

~~32. BIF for use according to any one of claims 29-31 wherein the dose is increased if the patient's FG is > 130 mg/dL after treatment with a first fixed dose for at least 4 weeks.~~

~~33. BIF for use according to claim 29 or claim 30, wherein the dose is only increased if the patient had no (0) episodes of FG < 70 mg/dL.~~

~~34. BIF for use according to any one of claims 29-33 wherein the dose is decreased if the patient's FG is < 80 mg/dL.~~

~~35. BIF for use in the treatment of T2D, wherein the treatment comprises improving glycemic control by:~~

~~a) administering an initial dose of 100 U of BIF once weekly;~~

~~b) increasing the dose to 150 U of BIF once-weekly after at least 4 weeks on the 100 U dose;~~

~~c) increasing the dose to 250 U of BIF once-weekly after at least 4 weeks on the 150 U dose; and~~

~~d) increasing the dose to 400 U of BIF once-weekly after at least 4 weeks on the 250 U dose.~~

~~36. BIF for use according to claim 35, wherein steps b) through d) are performed to reduce the patient's FG.~~

~~37. BIF for use according to claim 35, wherein steps b) through d) are performed when the patient's FG is > 130 mg/dL.~~

~~38. BIF for use according to any one of claims 35-37 wherein steps b) through d) are only performed when the patient had no (0) episodes of blood glucose < 70 mg/dL.~~

~~39. BIF for use according to any one of claims 35-38, wherein the dose is decreased to the previous dose if the patient's FG is < 80 mg/dL.~~

~~40. BIF for use according to any one of claims 28-33, wherein the treatment is discontinued if the patient experiences one or more episodes of nocturnal hypoglycemia or 2 or more episodes of hypoglycemia.~~

~~41. BIF for use according to any one of claims 28-40, wherein the patient is insulin-naïve.~~

~~42. BIF for use according to any one of claims 28-41, wherein the patient has uncontrolled hyperglycemia.~~

~~43. BIF for use according to any one of claims 28-42, wherein the patient has HbA1c between 7 and 10%.~~

~~44. BIF for use according to any one of claims 28-43, wherein the patient is receiving 2 or more oral antihyperglycemic medications.~~

~~45. BIF for use according to any one of claims 28-44, wherein the patient is receiving a GLP-1 receptor agonist.~~

46. BIF for use according to any one of claims 28-45, wherein BIF is in administered in an aqueous composition comprising: phosphate in a concentration between about 5 and 10 mM; and glycerol in a concentration between about 15 and 35 mM; and having a pH between about 5.5 and 7.5.

47. BIF for use according to claim 46, wherein the composition further comprises poloxamer 188 in a concentration between about 0.1 to about 0.5 mg/mL.

48. BIF for use according to claim 47, wherein the phosphate is in a concentration of about 10 mM; glycerol is in a concentration of about 25 mM; and poloxamer 188 is in a concentration of about 0.4 mg/mL; and wherein the pH of the composition is about 6.5.

49. BIF for use according to any one of claims 29-48, wherein the dose of BIF is administered with a single-use autoinjector.

50. BIF for use in the treatment of T2D, wherein the treatment comprises improving glycemic control by administering a composition according to any one of claims 21-23.

51. Use of BIF in the manufacture of a medicament for use in the treatment of diabetes according to any of claims 29-50.