including patients with and without established CVD (Holman RR, et al., *Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes*, 377 N. ENGL. J. MED. 1228-1239 (2017) ("EXCSEL")). On the other hand, albiglutide, liraglutide and semaglutide were found to reduce the risk of major adverse cardiovascular events in patient populations comprised entirely (albiglutide) or predominantly (liraglutide and semaglutide) of patients with established CVD. (Hernandez AF, et al., *Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease (Harmony Outcomes): a Double-blind, Randomized Placebo-controlled Trial*, 392 LANCET 1519-1529 (2018) ("Harmony Outcomes"); Marso SP, et al., *Liraglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes*, 375 N. ENGL. J. MED. 311-322 (2016) ("LEADER")); Marso SP, et al., *Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes* 375 N. ENGL. J. MED. 1834–1844 (2016) ("SUSTAIN-6")).

Despite the therapies described above, the need for new treatment options capable of reducing the risk of major adverse cardiovascular events in T2DM patients remains. In particular, the need remains for treatment options capable of reducing the risk of major adverse cardiovascular events in T2DM patients who do not already have established cardiovascular disease.

Summary

In one aspect of the present disclosure, there is provided a use of dulaglutide in the manufacture of a medicament for reducing the risk of major adverse cardiovascular events in a patient with type 2 diabetes mellitus having multiple cardiovascular risk factors without established cardiovascular disease, wherein a therapeutically effective amount of dulaglutide is to be administered to the patient once weekly~~, wherein the patient has type 2 diabetes mellitus and either:~~

~~(a) multiple cardiovascular risk factors without established cardiovascular disease; or~~

~~established cardiovascular disease~~.

In another aspect of the present disclosure, there is provided a use of dulaglutide in the manufacture of a medicament for reducing the risk of ~~major adverse cardiovascular events~~non-fatal stroke in a patient with type 2 diabetes mellitus, wherein the patient has type 2 diabetes mellitus and multiple cardiovascular risk factors without established cardiovascular disease, and wherein a therapeutically effective amount of~~:~~

~~(a) a patient having type 2 diabetes mellitus and either:~~

~~i) multiple cardiovascular risk factors without established cardiovascular disease; or~~

~~ii) established cardiovascular disease~~

~~is identified; and~~

dulaglutide is to be administered ~~in a therapeutically effective amount~~ to the patient once weekly.

In a further aspect of the present disclosure, there is provided a use of dulaglutide in the manufacture of a medicament for improving glycemic control and reducing the risk of first occurrence of a major adverse cardiovascular event in a patient with type 2 diabetes mellitus, wherein the patient has type 2 diabetes mellitus and multiple cardiovascular risk factors without established cardiovascular disease, and wherein a therapeutically effective amount of dulaglutide ~~in a therapeutically effective amount~~ is to be administered to the patient once weekly.~~, wherein the patient has type 2 diabetes mellitus and either:~~

~~(a) multiple cardiovascular risk factors without established cardiovascular disease; or~~

~~(b) established cardiovascular disease.~~

In another aspect of the present disclosure, there is provided a use of dulaglutide in the manufacture of a medicament for reducing the risk of major adverse cardiovascular events for once weekly administration in a patient with type 2 diabetes mellitus having multiple cardiovascular risk factors without established cardiovascular disease.

In a further aspect of the present disclosure, there is provided a use of dulaglutide in the manufacture of a medicament for reducing the risk of non-fatal stroke for once weekly administration in a patient with type 2 diabetes mellitus, wherein the patient has type 2 diabetes mellitus and multiple cardiovascular risk factors without established cardiovascular disease.

In another aspect of the present disclosure, there is provided a use of dulaglutide in the manufacture of a medicament for improving glycemic control and reducing the risk of first occurrence of a major adverse cardiovascular event for once weekly administration in a patient with type 2 diabetes mellitus, wherein the patient has type 2 diabetes mellitus and multiple cardiovascular risk factors without established cardiovascular disease.

Description

The methods of the present invention seek to meet those needs. Indeed, dulaglutide was recently found to be capable of statistically significantly reducing the risk of major adverse cardiovascular events in a population that included patients both with and without established cardiovascular disease. Moreover, the overall reduction in risk seen was driven by and similar in both patients with and without established cardiovascular disease.

Accordingly, the present invention provides a method of reducing the risk of major adverse cardiovascular events in a patient with type 2 diabetes mellitus, comprising administering dulaglutide in a therapeutically effective amount to the patient once weekly, wherein the patient has type 2 diabetes mellitus and either: multiple cardiovascular risk factors without established cardiovascular disease; or established cardiovascular disease.

In another aspect, the present invention provides a method of reducing the risk of major adverse cardiovascular events in a patient with type 2 diabetes mellitus,

WE CLAIM:

1. Use of dulaglutide in the manufacture of a medicament for reducing the risk of major adverse cardiovascular events in a patient with type 2 diabetes mellitus having multiple cardiovascular risk factors without established cardiovascular disease, wherein a therapeutically effective amount of dulaglutide is to be administered to the patient once weekly~~, wherein the patient has type 2 diabetes mellitus and either:~~

~~(a) multiple cardiovascular risk factors without established cardiovascular disease; or~~

~~(b) established cardiovascular disease~~.

~~2. Use of dulaglutide in the manufacture of a medicament for reducing the risk of major adverse cardiovascular events in a patient with type 2 diabetes mellitus, wherein:~~

~~(a) a patient having type 2 diabetes mellitus and either:~~

~~i) multiple cardiovascular risk factors without established cardiovascular disease; or~~

~~ii) established cardiovascular disease is identified; and~~

~~(b) dulaglutide is to be administered in a therapeutically effective amount to the patient once weekly.~~

2. The use of claim 1 wherein the major adverse cardiovascular events are cardiovascular disease, non-fatal myocardial infarction or non-fatal stroke.

3. The use of claim 2 wherein the major adverse cardiovascular event is non-fatal stroke.

4. Use of dulaglutide in the manufacture of a medicament for reducing the risk of non-fatal stroke in a patient with type 2 diabetes mellitus, wherein the patient has type 2 diabetes mellitus and multiple cardiovascular risk factors without established cardiovascular disease, and wherein a therapeutically effective amount of dulaglutide is to be administered to the patient once weekly.

~~3~~5. Use of dulaglutide in the manufacture of a medicament for improving glycemic control and reducing the risk of first occurrence of a major adverse cardiovascular event in a patient with type 2 diabetes mellitus, wherein ~~dulaglutide in a therapeutically effective amount is to be administered to the patient once weekly, wherein~~ the patient has type 2 diabetes mellitus and ~~either:~~

~~(a)~~ multiple cardiovascular risk factors without established cardiovascular disease, and wherein a therapeutically effective amount of dulaglutide is to be administered to the patient once weekly~~; or~~

~~(b) established cardiovascular disease~~.

~~4. The use of any of claims 1-3 wherein the patient has multiple cardiovascular risk factors without established cardiovascular disease.~~

6. The use of any one of claims 1-5 as an adjunct to diet and exercise.

~~5~~7. The use of any one of claims 1-~~4~~6, wherein the cardiovascular risk factors are selected from the group consisting of (a), (b), (c), (d) and (e):

(a) tobacco use;

(b) at least 1 of:

i) use of at least 1 approved lipid modifying therapy to treat hypercholesterolemia; or

ii) a documented untreated low-density lipoprotein cholesterol (LDL-C) ≥3.4 mmol/L (130 mg/dL) within the past 6 months;

(c) at least 1 of:

i) high-density lipoprotein cholesterol (HDL-C) measurement within the past 6 months of: <1.0 mmol/L (40 mg/dL) for men; and <1.3 mmol/L (50 mg/dL) for women; or

ii) triglycerides ≥2.3 mmol/L (200 mg/dL) within the past 6 months;

(d) at least 1 of:

i) use of at least 1 blood pressure medication to treat hypertension; or

ii) untreated systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥95 mmHg; and

(e) measured waist-to-hip ratio >1.0 for men and >0.8 for women.

~~6. The use of any of claims 1-3 wherein the patient has established cardiovascular disease.~~

~~7~~8. The use of any one of ~~the preceding~~ claims 1-7 wherein ~~the method reduces~~there is reduction of the risk of a major adverse cardiovascular event by at least ~~about~~ 10%.

~~8~~9. The use of any one of ~~the preceding~~ claims 1-8 wherein the therapeutically effective amount of dulaglutide is ~~selected from the group consisting of~~ 1.5 mg, 3.0 mg ~~and~~ or 4.5 mg.

~~9~~10. The use of any one of ~~the preceding~~ claims 1-9 wherein the therapeutically effective amount of dulaglutide is 1.5 mg.

~~10~~11. The use of any one of ~~the preceding~~ claims 1-10 wherein the once weekly ~~administration~~ amount of dulaglutide is continued for approximately 5 years.

~~11~~12. The use of any one of ~~the preceding~~ claims 1-11~~,~~ wherein the dulaglutide is for use with one or more of ~~the following~~: an ACE inhibitor; an ARB; a beta blocker; a calcium channel blocker; a diuretic; an antithrombotic agent; ~~aspirin~~ acetylsalicyclic acid (ASA) or a statin ~~is to be administered to the patient~~.

13. Use of dulaglutide in the manufacture of a medicament for reducing the risk of major adverse cardiovascular events for once weekly administration in a patient with type 2 diabetes mellitus having multiple cardiovascular risk factors without established cardiovascular disease.

14. The use of claim 13, wherein the major adverse cardiovascular events are cardiovascular disease, non-fatal myocardial infarction or non-fatal stroke.

15. The use of claim 14 wherein the major adverse cardiovascular event is non-fatal stroke.

16. Use of dulaglutide in the manufacture of a medicament for reducing the risk of non-fatal stroke for once weekly administration in a patient with type 2 diabetes mellitus, wherein the patient has type 2 diabetes mellitus and multiple cardiovascular risk factors without established cardiovascular disease.

17. Use of dulaglutide in the manufacture of a medicament for improving glycemic control and reducing the risk of first occurrence of a major adverse cardiovascular event for once weekly administration in a patient with type 2 diabetes mellitus, wherein the patient has type 2 diabetes mellitus and multiple cardiovascular risk factors without established cardiovascular disease.

18. The use of any one of claims 13-17 as an adjunct to diet and exercise.

19. The use of any one of claims 13-18, wherein the cardiovascular risk factors are selected from the group consisting of (a), (b), (c), (d) and (e):

(a) tobacco use;

(b) at least 1 of:

i) use of at least 1 approved lipid modifying therapy to treat hypercholesterolemia; or

ii) a documented untreated low-density lipoprotein cholesterol (LDL-C) ≥3.4 mmol/L (130 mg/dL) within the past 6 months;

(c) at least 1 of:

i) high-density lipoprotein cholesterol (HDL-C) measurement within the past 6 months of: <1.0 mmol/L (40 mg/dL) for men; and <1.3 mmol/L (50 mg/dL) for women; or

ii) triglycerides ≥2.3 mmol/L (200 mg/dL) within the past 6 months;

(d) at least 1 of:

i) use of at least 1 blood pressure medication to treat hypertension; or

ii) untreated systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥95 mmHg; and

(e) measured waist-to-hip ratio >1.0 for men and >0.8 for women.

20. The use of any one of claims 13-19 wherein there is reduction of the risk of a major adverse cardiovascular event by at least 10%.

21. The use of any one of claims 13-20 wherein the amount of dulaglutide is 1.5 mg, 3.0 mg or 4.5 mg.

22. The use of any one of claims 13-21 wherein the amount of dulaglutide is 1.5 mg.

23. The use of any one of claims 13-22 wherein the once weekly amount of dulaglutide is continued for approximately 5 years.

24. The use of any one of claims 13-23 wherein the dulaglutide is for use with one or more of: an ACE inhibitor; an ARB; a beta blocker; a calcium channel blocker; a diuretic; an antithrombotic agent; acetylsalicyclic acid (ASA) or a statin.