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, 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 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

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 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.

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, 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.

3. 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; 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.

5. The use of any of claims 1-4, 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. The use of any of the preceding claims wherein the method reduces the risk of a major adverse cardiovascular event by at least about 10%.

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

9. The use of any of the preceding claims wherein the therapeutically effective amount of dulaglutide is 1.5 mg.

10. The use of any of the preceding claims wherein the once weekly administration of dulaglutide is continued for approximately 5 years.

11. The use of any of the preceding claims, wherein one or more of the following: an ACE inhibitor; an ARB; a beta blocker; a calcium channel blocker; a diuretic; an antithrombotic agent; aspirin or a statin is to be administered to the patient.