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(54) **SEMAGLUTIDE IN CARDIOVASCULAR CONDITIONS**

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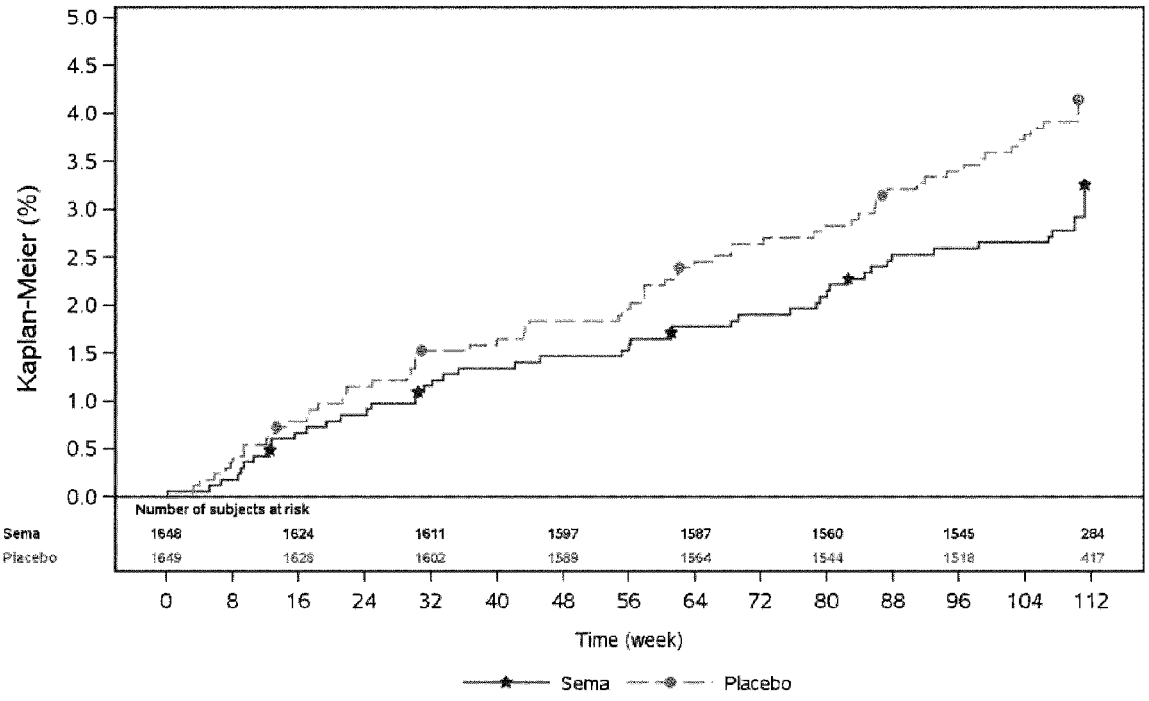
(57) **ABSTRACT**

The present invention relates to the GLP-1 receptor agonist semaglutide for use in medicine.



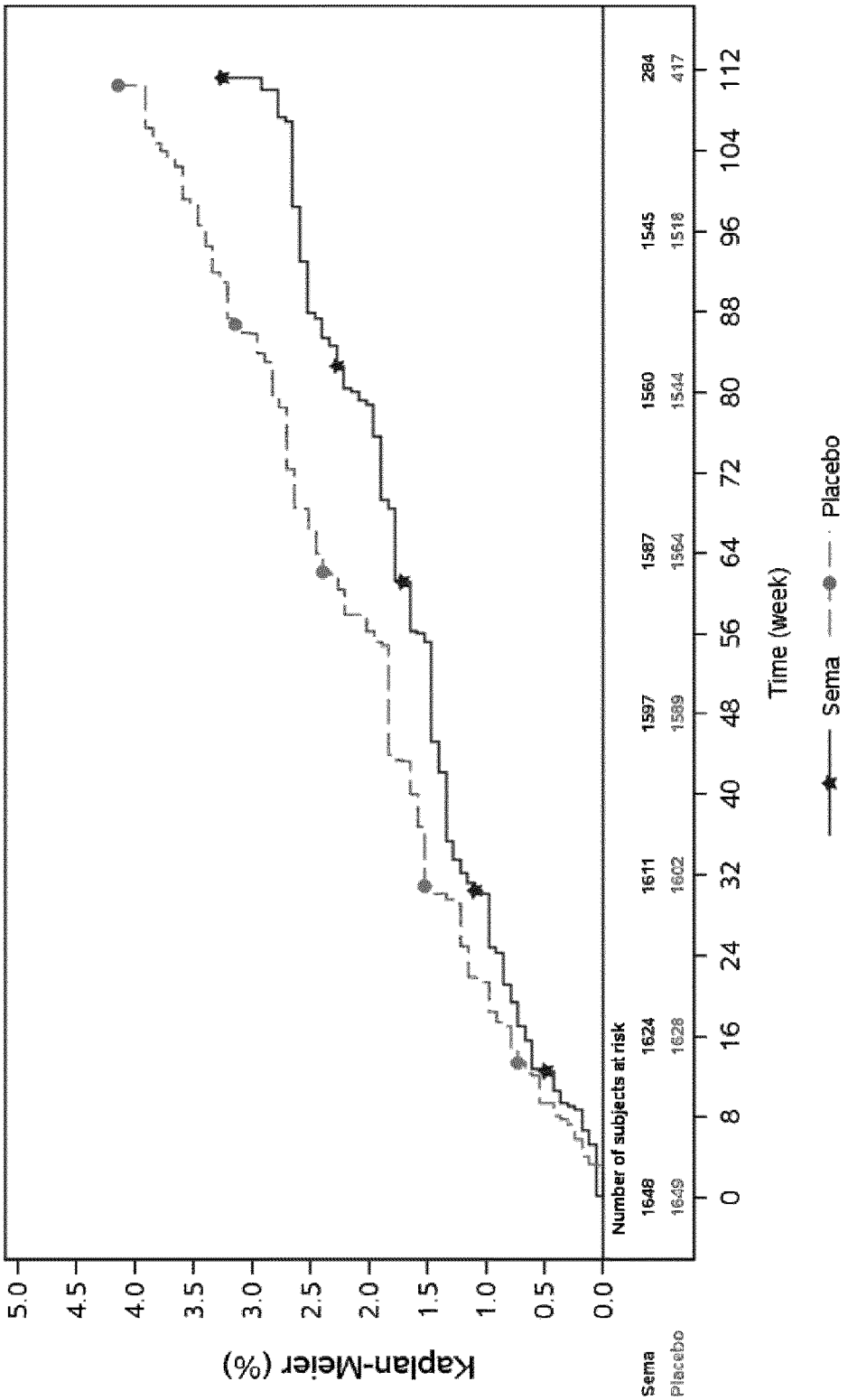


Fig. 1

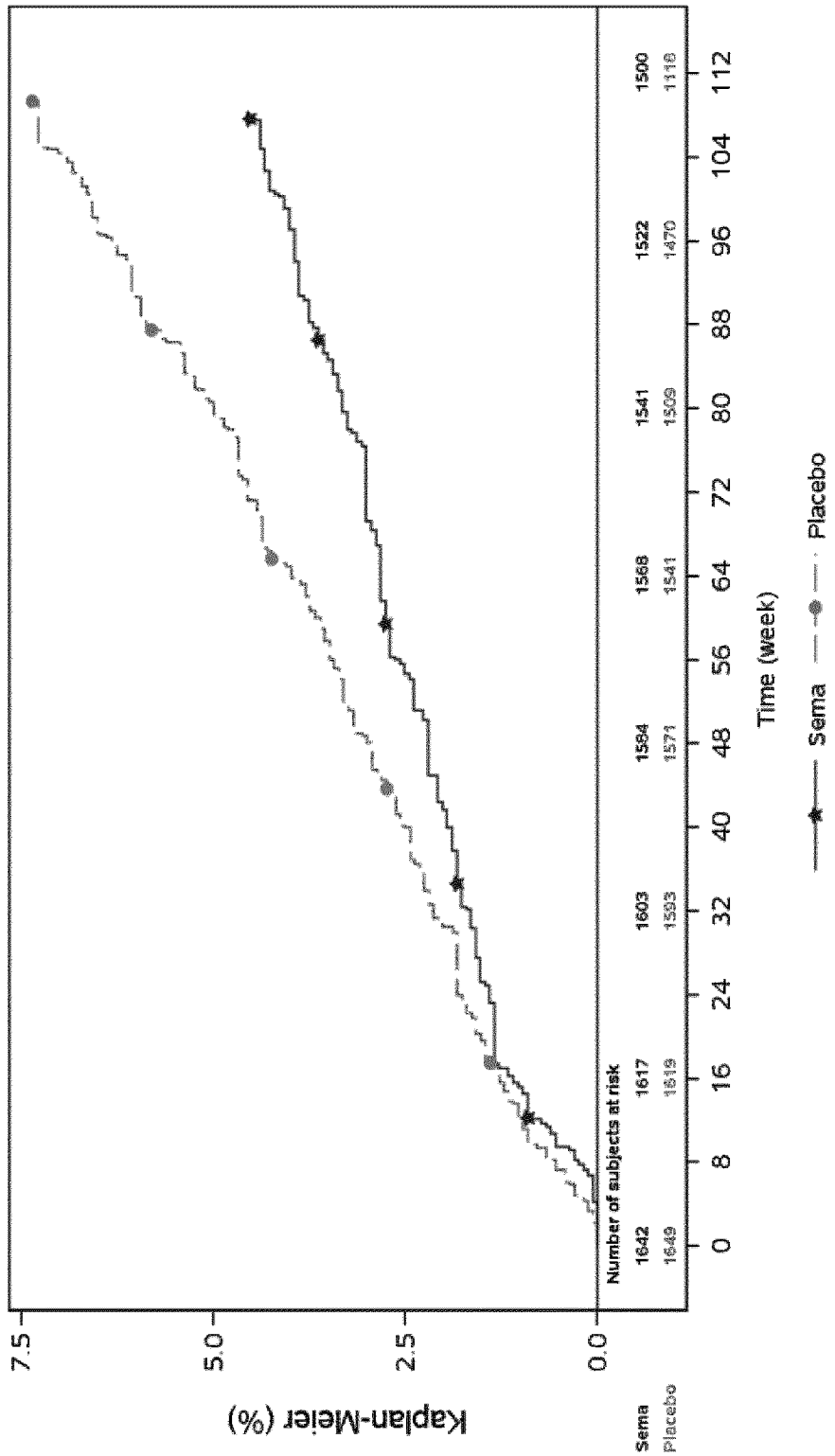


Fig. 2

SEMAGLUTIDE IN CARDIOVASCULAR CONDITIONS

[0001] The present invention relates to the GLP-1 receptor agonist semaglutide for use in treating a subject having diabetes and high cardiovascular risk.

BACKGROUND

[0002] Diabetes is a metabolic disorder characterized by hyperglycaemia that is associated with a high risk of cardiovascular and other serious health-related consequences. A person with diabetes is two to three times more likely to die from cardiovascular causes than people with no history of diabetes, even after controlling for other cardiovascular risk factors. They are also at very high risk of developing serious microvascular complications ultimately leading to premature death: nephropathy and renal failure, retinal disease and blindness, autonomic and peripheral neuropathy, as well as other conditions related to the cardiovascular system: hypertension, lower limb amputation, cognitive decline, and erectile dysfunction.

[0003] The majority of people with diabetes have type 2 diabetes, which is characterised by insulin resistance and eventually impaired insulin secretion. Optimal glycaemic control is the treatment goal in subjects with type 2 diabetes, since the risk of long-term complications is increased with poor glycaemic control. Despite the availability of several oral anti-diabetic drugs and insulin, a significant proportion of subjects with type 2 diabetes do not achieve the recommended target levels for glycaemic control and are at high risk of developing cardiovascular disease or microvascular complications. Thus, there is an unmet medical need for treatment alternatives that not only provide glycaemic control but also reduce the risk of cardiovascular disease in subjects with type 2 diabetes.

SUMMARY

[0004] In some embodiments the present invention relates to a method of treating type 2 diabetes, comprising administering semaglutide in a therapeutically effective amount to a subject in need thereof, wherein said subject has clinical evidence of cardiovascular disease and/or subclinical evidence of cardiovascular disease; wherein said method delays or reduces development of a major adverse cardiovascular event (MACE).

BRIEF DESCRIPTION OF DRAWINGS

[0005] FIG. **1** shows time from randomisation to first non-fatal MI following administration of semaglutide (Sema) or its placebo.

[0006] FIG. **2** shows time from randomisation to first revascularisation following administration of semaglutide (Sema) or its placebo.

[0007] FIG. **1-2** show the number of subjects at risk for the relevant event(s) at different time points after randomisation and are Kaplan-Meier plots of time to event.

DESCRIPTION

[0008] The present invention relates to methods of administering the GLP-1 receptor agonist semaglutide to a subject having diabetes and high cardiovascular risk. The term "high cardiovascular risk" in some embodiments means that the subject has clinical or subclinical evidence of at least one cardiovascular disease. In some embodiments high cardiovascular risk is present if the subject has clinical or subclinical evidence of at least one cardiovascular disease.

[0009] In some embodiments the present invention relates to a method of treating type 2 diabetes, comprising administering semaglutide in a therapeutically effective amount to a subject in need thereof, wherein said subject has clinical evidence of cardiovascular disease and/or subclinical evidence of cardiovascular disease; wherein said method reduces the risk of cardiovascular events compared to placebo. In some embodiments the clinical evidence of cardiovascular disease and/or subclinical evidence of cardiovascular disease were present before initiation of semaglutide administration.

[0010] In some embodiments the present invention relates to a method of reducing the risk of MACE in subjects with type 2 diabetes mellitus and high cardiovascular risk. In some embodiments the present invention relates to a method of reducing the risk of MACE in subjects with type 2 diabetes mellitus and high cardiovascular risk, wherein said MACE is selected from the group consisting of non-fatal MI, non-fatal stroke, CV death caused by MI, and CV death caused by stroke. In some embodiments said MACE is selected from the group consisting of non-fatal MI and CV death caused by MI. In some embodiments said MACE is selected from the group consisting of non-fatal stroke and CV death caused by stroke.

[0011] In some embodiments the present invention relates to a method of delaying myocardial infarction or stroke in subjects with type 2 diabetes mellitus and high cardiovascular risk. In some embodiments the terms "delaying" as used herein refers to "preventing". In some embodiments the present invention relates to a method of preventing cardiovascular events in subjects with type 2 diabetes, wherein said "cardiovascular events" is one or more major adverse cardiovascular events, and wherein "major adverse cardiovascular event" is as defined herein.

[0012] In some embodiments the present invention relates to a method of treating type 2 diabetes, comprising administering semaglutide in a therapeutically effective amount to a subject in need thereof, wherein said subject has clinical evidence of cardiovascular disease and/or subclinical evidence of cardiovascular disease; wherein said method reduces or delays a major adverse cardiovascular event (MACE).

[0013] In some embodiments MACE is events selected from the group consisting of cardiovascular (CV) death, non-fatal MI, non-fatal stroke, revascularisation, hospitalisation for unstable angina pectoris, and hospitalisation for heart failure. The term "non-fatal MI" as used herein refers to non-fatal myocardial infarction. In some embodiments MACE is events selected from the group consisting of CV death, non-fatal MI, and non-fatal stroke.

[0014] In some embodiments the method reduces or delays a major adverse cardiovascular event (MACE). In some embodiments the method reduces the risk of said subject developing a major adverse cardiovascular event (MACE). In some embodiments the method reduces the risk of said subject developing its first MACE. Thus, in some embodiments the MACE referred to herein is first MACE, e.g. after initiating administration of semaglutide. The term

[0015] In some embodiments MACE is selected from the group consisting of CV death, non-fatal MI, non-fatal stroke, revascularisation, hospitalisation for heart failure, and hospitalisation for unstable angina pectoris. In some embodiments MACE (e.g. selected from the group consisting of CV death, non-fatal MI, non-fatal stroke, revascularisation, hospitalisation for heart failure, and hospitalisation for unstable angina pectoris) is reduced or delayed by at least 1% compared to placebo. In some embodiments MACE (e.g. selected from the group consisting of CV death, non-fatal MI, non-fatal stroke, revascularisation, hospitalisation for heart failure, and hospitalisation for unstable angina pectoris) is reduced or delayed by from about 20% to about 35% compared to placebo. In some embodiments MACE (e.g. selected from the group consisting of CV death, non-fatal MI, non-fatal stroke, revascularisation, hospitalisation for heart failure, and hospitalisation for unstable angina pectoris) is reduced about 27% compared to placebo. In some embodiments the first MACE (e.g. selected from the group consisting of CV death, non-fatal MI, non-fatal stroke, revascularisation, hospitalisation for heart failure, and hospitalisation for unstable angina pectoris) is reduced or delayed by at least 1% compared to placebo. In some embodiments the first MACE (e.g. selected from the group consisting of CV death, non-fatal MI, non-fatal stroke, revascularisation, hospitalisation for heart failure, and hospitalisation for unstable angina pectoris) is reduced or delayed by from about 20% to about 27% compared to placebo. In some embodiments the first MACE (e.g. selected from the group consisting of CV death, non-fatal MI, non-fatal stroke, revascularisation, hospitalisation for heart failure, and hospitalisation for unstable angina pectoris) is reduced about 27% compared to placebo.

[0016] In some embodiments MACE is selected from the group consisting of CV death, non-fatal MI, and non-fatal stroke. In some embodiments MACE (e.g. selected from the group consisting of CV death, non-fatal MI, and non-fatal stroke) is reduced or delayed by at least 10% compared to placebo. In some embodiments MACE (e.g. selected from the group consisting of CV death, non-fatal MI, and non-fatal stroke) is reduced or delayed by from about 20% to about 30% compared to placebo. In some embodiments MACE (e.g. selected from the group consisting of CV death, non-fatal MI, and non-fatal stroke) is reduced or delayed about 26% compared to placebo. In some embodiments MACE (e.g. selected from the group consisting of CV death, non-fatal MI, and non-fatal stroke) has a hazard ratio of about 0.74 compared to placebo. In some embodiments MACE (e.g. selected from the group consisting of CV death, non-fatal MI, and non-fatal stroke) has a hazard ratio of 0.74 with a 95% CI of (0.58; 0.95) compared to placebo. In some embodiments the risk of said subject developing a MACE (e.g. selected from the group consisting of CV death, non-fatal MI, and non-fatal stroke) is reduced by at least 10% compared to placebo. In some embodiments the subject developing its first MACE (e.g. selected from the group consisting of CV death, non-fatal MI, and non-fatal stroke) is reduced or delayed by at least 10% compared to placebo. In some embodiments the first MACE (e.g. selected from the group consisting of CV death, non-fatal MI, and non-fatal stroke) is reduced or delayed by from about 20% to about 30% compared to placebo. In some embodiments the first MACE (e.g. selected from the group consisting of CV death, non-fatal MI, and non-fatal stroke) is reduced or delayed about 26% compared to placebo. In some embodiments the subject developing its first MACE (e.g. selected from the group consisting of CV death, non-fatal MI, and non-fatal stroke) has a hazard ratio of about 0.74 compared to placebo. In some embodiments the subject developing its first MACE (e.g. selected from the group consisting of CV death, non-fatal MI, and non-fatal stroke) has a hazard ratio of 0.74 with a 95% CI of (0.58; 0.95) compared to placebo.

[0017] In some embodiments the MACE is non-fatal MI. In some embodiments the non-fatal MI is reduced or delayed by at least 10% compared to placebo. In some embodiments the non-fatal MI is reduced or delayed by from about 15% to about 35% compared to placebo. In some embodiments the non-fatal MI is reduced or delayed by about 26% compared to placebo.

[0018] In some embodiments the MACE is non-fatal stroke. In some embodiments the non-fatal stroke is reduced or delayed by at least 10% compared to placebo. In some embodiments the non-fatal stroke is reduced or delayed by from about 20% to about 60% compared to placebo. In some embodiments the non-fatal stroke is reduced or delayed by from about 30% to about 50% compared to placebo. In some embodiments the non-fatal stroke is reduced or delayed by about 39% compared to placebo.

[0019] In some embodiments the MACE is revascularisation. In some embodiments the revascularisation is reduced or delayed by at least 10% compared to placebo. In some embodiments the revascularisation is reduced or delayed by from about 20% to about 60% compared to placebo. In some embodiments the revascularisation is reduced or delayed by from about 30% to about 50% compared to placebo. In some embodiments the revascularisation is reduced or delayed by about 38% compared to placebo. Revascularisation may be coronary revascularisation or peripheral revascularisation.

[0020] In some embodiments the MACE is hospitalisation for unstable angina pectoris. In some embodiments the hospitalisation for unstable angina pectoris is reduced or delayed by at least 10% compared to placebo. In some embodiments the hospitalisation for unstable angina pectoris is reduced or delayed by from about 10% to about 30% compared to placebo. In some embodiments the hospitalisation for unstable angina pectoris is reduced or delayed by about 18% compared to placebo.

[0021] In some embodiments the administration of semaglutide is a chronic treatment in which semaglutide is administered for at least 16 months (such as at least 30 months, and optionally up to 54 months), and wherein said method reduces or delays non-fatal myocardial infarction (MI).

[0022] In some embodiments the administration of semaglutide is a chronic treatment in which semaglutide is administered for at least 18 months (such as at least 30 months, and optionally up to 54 months), and wherein said method reduces the need or risk of requiring revascularisation.

[0023] In some embodiments the MACE is CV death. In some embodiments the CV death is reduced by at least 1% compared to placebo. In some embodiments the CV death is reduced or delayed by from about 1% to about 3% compared to placebo. In some embodiments the CV death is reduced or delayed by about 2% compared to placebo.

[0024] The term "placebo" as used herein refers to a

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