Semaglutide subcutaneous once-weekly

Treatment to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus

NDA 209637

Briefing Document

Endocrinologic and Metabolic Drug Advisory Committee

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Executive summary

Semaglutide is a next generation long-acting glucagon-like peptide-1 (GLP-1) analogue with 94% homology to human GLP-1 (Section 1.2, p. 28).

Semaglutide is a selective GLP-1 receptor agonist (GLP-1 RA) with a long plasma half-life suitable for once weekly dosing. The long half-life was obtained by applying the fatty acid acylation technology that provides specific high-affinity albumin binding. Furthermore, semaglutide has full stability against DPP-4 degradation. The inherent long half-life together with a low molecular weight of semaglutide is believed to ensure optimal efficacy. Semaglutide exhibits GLP-1 receptor mediated effects, leading to lowering of glucose and decreased appetite through physiologically relevant mechanisms. As a result, semaglutide provides strong glycemic control and weight loss. In addition, the cardiovascular safety of semaglutide has been confirmed. The mechanism of action of semaglutide was characterized in extensive nonclinical and clinical studies.

Novo Nordisk is seeking approval for semaglutide 0.5 mg and 1 mg, for once-weekly (OW) subcutaneous (s.c.) administration, as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D) (NDA 209637) (Section 1.1, p. 27).

As with other GLP-1 RA products, gradual dose escalation reduces the risk of gastrointestinal side effects. All patients will start on 0.25 mg for 4 weeks. Thereafter, the dose can be increased to 0.5 mg. The dose may be increased to 1 mg once weekly to further improve glycemic control, after a minimum of 4 weeks on 0.5 mg.

Unmet medical need (Section 1.3, p. 29)

The prevalence of diabetes is increasing worldwide.[6] T2D is a complex, progressive and chronic disease requiring continuous medical care using multifactorial risk-reduction strategies, with control of hyperglycemia balanced against the risk of hypoglycemia. While an increasing number of agents to treat diabetes are available, close to 50% of all patients treated for their T2D do not achieve the blood glucose target of HbA_{1c} <7% and are thus at increased risk of T2D-related complications.[7] These data indicate a medical need for a highly effective, convenient, easy to use treatment option for patients with T2D.

Overweight and obesity are well-known risk factors for hyperglycemia and T2D.[8,9] A moderate weight loss of 5% can improve glycemic control in patients with T2D.[10] Accordingly, current ADA treatment guidelines recommend that patients with T2D achieve modest weight loss (5–7%) to improve glycemic control.[8, 11] Thus, anti-glycemic drugs that in addition to lowering HbA_{1c} also reduce body weight provide additional clinical benefits in the treatment of T2D.

Nonclinical safety (Section 2, p. 31)

A comprehensive nonclinical safety program was performed in accordance with current regulatory guidance. The findings were consistent with what has been seen with other GLP-1 RAs and with the known GLP-1 RA pharmacology.

Clinical development program (Section 3, p. 33)

A comprehensive global clinical development program was conducted for semaglutide. At the time of cut-off for the NDA, 25 trials with semaglutide s.c. once-weekly had been completed: 16 clinical pharmacology trials, one dose-finding trial, and 8 phase 3a trials (including a 2-year cardiovascular outcomes trial [CVOT]). A total of 9,384 individuals were included in the clinical development program, of whom 5,710 were exposed to semaglutide and 3,674 to comparators including placebo. Approximately 1/3 of the total population was recruited from sites in the US.

Clinical pharmacology (Section 4, p. 34)

The pharmacokinetic characteristics of semaglutide support once weekly dosing and the pharmacodynamic characteristics of semaglutide are consistent with other marketed GLP-1 RAs.

After dosing with semaglutide, the median time to maximum concentration (t_{max}) is 1−3 days and the elimination half-life ($t_{½}$) approximately 1 week. The prolonged exposure to semaglutide is the result, in part, of the extensive binding of semaglutide to plasma albumin (>99%).

The steady state exposure of semaglutide was dose-proportional, similar between injection sites, and not influenced by the development of anti-semaglutide antibodies, which occurred at low frequency. Based on pharmacokinetic analyses, no dose adjustment of semaglutide is needed based on age, sex, race, ethnicity, body weight, or renal or hepatic impairment. No clinically relevant pharmacokinetic drug-drug interactions with semaglutide were identified; and no dose adjustment is required when drugs are co-administered with semaglutide. Semaglutide did not prolong the QT interval.

Consistent with known GLP-1 RA pharmacology, semaglutide lowered fasting and postprandial blood glucose by enhancing glucose-dependent stimulation of insulin secretion from the β-cells and by reducing glucagon secretion from the α-cell. A minor delay in gastric emptying also contributed to postprandial blood glucose lowering. Semaglutide-induced body weight loss was primarily from fat tissue. The mechanism of body weight loss was shown to be reduced energy intake, mediated by lowered overall appetite (reduced hunger and increased satiety).

Phase 3a program (Section 5, p. 38)

The semaglutide phase 3a program (denoted SUSTAIN) evaluated the efficacy and safety of semaglutide 0.5 mg and 1 mg in a broad, clinically relevant T2D population with relevant representation of minorities from sites in the US. Robust dose-response relationships for HbA_{1c} and

body weight were established based on clinical phase 3a data (see below) and confirmed by analyses using exposure-response models.

The program covered the continuum of T2D care from monotherapy in drug-naïve patients with short duration of T2D, to combination use with one or more OADs, to combination use with basal insulin in patients with long-standing T2D (Table 1).

The glycemic efficacy of semaglutide was assessed primarily in five pivotal controlled phase 3a trials (SUSTAIN 1-5). These five trials are referred to as the 'key efficacy trials' and comprise a placebo-controlled mono-therapy trial and head-to-head trials with the most relevant marketed anti-glycemic drugs (sitagliptin, exenatide ER and insulin glargine) available at the time of the program planning. In addition, a head-to-head trial versus dulaglutide, the currently most used OW GLP-1 RA, has been finalized after the NDA submission as part of the semaglutide phase 3b program.[12]

The effect of semaglutide on cardiovascular safety was assessed in a dedicated placebo-controlled cardiovascular outcomes trial (CVOT) (SUSTAIN 6) in adults with T2D at high risk of cardiovascular events.[5] In addition, SUSTAIN 6 (CVOT) was designed to provide long-term (2-year) safety and efficacy data and accounted for approximately 50% of the total exposure to semaglutide in the clinical development program. Efficacy data from SUSTAIN 6 (CVOT) are considered supportive to SUSTAIN 1-5.

Two Japanese phase 3a trials (SUSTAIN JP Mono and SUSTAIN JP OADs) were conducted to support registration in Japan. The trials were designed in accordance with the requirements noted in the Japanese guideline for development of medicines to treat diabetes[13] with the primary objective to evaluate the safety of semaglutide for treatment of T2D in Japanese patients. The major design features of the Japanese trials were identical to those of SUSTAIN 1-5.

Table 1 Phase 3a program: Overview of clinical trials

SUSTAIN (Trial ID)	Patients randomized	Treatment duration	Background	Comparator	Primary endpoint
SUSTAIN 1 (3623)	388	30 weeks	Drug-naïve – monotherapy	Placebo	HbA_{1c}
SUSTAIN 2 (3626)	1,231	56 weeks	Add-on to OADs	DPP-4 inhibitor: sitagliptin	HbA_{1c}
SUSTAIN 3 (3624)	813	56 weeks	Add-on to OADs	OW GLP-1 RA: Exenatide ER	HbA_{1c}
SUSTAIN 4 (3625)	1,089	30 weeks	Add-on to OADs	Basal insulin: insulin glargine	HbA_{1c}
SUSTAIN 5 (3627)	397	30 weeks	Add-on to basal insulin±metformin	Placebo	HbA_{1c}
SUSTAIN 6 - CVOT (3744)	3,297	104 weeks	Add-on to standard-of-care	Placebo	MACE
SUSTAIN JP Mono (4092)	308	30 weeks	Monotherapy	DPP-4 inhibitor: sitagliptin	Adverse events
SUSTAIN JP OAD (4091)	601	56 weeks	Add-on to OADs	OAD	Adverse events

Abbreviations: CVOT: cardiovascular outcomes trial; DPP-4: dipeptidyl peptidase-4; Exe ER: exenatide extended release; GLP-1 RA: glucagon-like peptide-1 receptor agonist; JP: Japan; MACE: major adverse cardiovascular event; Mono: monotherapy; OAD: oral anti-glycemic drug; OW: once-weekly.

To minimize the amount of missing data, all phase 3a trials were designed with complete follow-up ensuring that data collection for assessment of efficacy and safety continued for the full duration of the trials despite discontinuation of trial medication, with the only exception of patients who withdrew their informed consent or were lost to follow-up. The emphasis for efficacy evaluations in the key efficacy trial and Japanese trials was on data collected while patients were on treatment prior to initiation of rescue medication (on-treatment period without rescue) to avoid confounding effects from treatment with other anti-glycemic agents. Safety evaluations were based on data collected while patients were exposed to treatment (from first dose of trial product until 5 weeks after last dose, i.e., on-treatment period), except for deaths, neoplasms and cardiovascular events that were evaluated using data collected throughout the entire trial period (i.e., in-trial period). Multiple sensitivity analyses were performed to evaluate the consistency in results across data-cuts, as an integrated part of both efficacy and safety evaluations.

An independent external event adjudication committee (EAC) performed blinded adjudication of cardiovascular events and deaths, neoplasms, and pancreatitis in all phase 3a trials. The adjudication was performed using common, established definitions for each type of event adjudicated, as outlined in the EAC charter. Microvascular events of nephropathy and retinopathy complications were adjudicated in SUSTAIN 6 (CVOT) only. An independent external data monitoring committee (DMC) was established for SUSTAIN 6 (CVOT), see Section 5.2, p. 40.

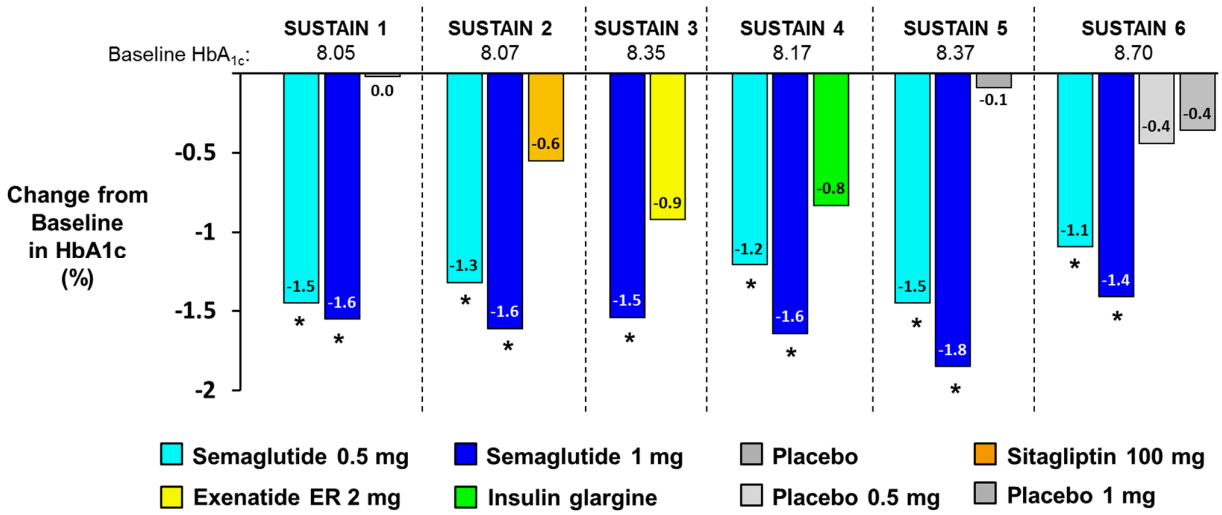
Glycemic control and body weight (Section 6, p. 52)

Statistical tests of differences in HbA_{1c} and body weight were controlled for multiplicity using a pre-defined hierarchical testing scheme; controlling the false-positive rate/type I error (see Section 6.1, p. 53).

HbA_{1c} (Section 6.2, p. 56)

The primary endpoint for assessing glycemic efficacy in SUSTAIN 1-5 was change from baseline in HbA_{1c} at end-of-treatment. Semaglutide 0.5 mg and 1 mg reduced HbA_{1c} in drug-naïve patients on semaglutide monotherapy, patients uncontrolled on OADs treated with semaglutide as add-on to 1−2 OADs, as well as in patients with long-standing T2D uncontrolled on basal insulin treated with semaglutide as add-on to basal insulin. The mean HbA_{1c} levels achieved at end-of-treatment (SUSTAIN 1–5), of 6.46−6.81% with semaglutide 1 mg and 6.60−6.96% with semaglutide 0.5 mg are lower than what has previously been seen in a large clinical trial program with T2D glucose lowering therapies.[1-4] The level of reduction in HbA_{1c} from baseline to the end-of-treatment with semaglutide was consistent across all trials with mean HbA_{1c} reductions of up to 1.8% (see Figure 1 below). The effects of semaglutide are clinically relevant and sustained for the duration of the trials (30 to 104 weeks) (Figure 10, p. 57).

In the individual trials semaglutide 0.5 mg and 1 mg were evaluated versus placebo and the active comparators sitagliptin, exenatide ER, or insulin glargine. Comparators were used at maximum recommended doses; sitagliptin 100 mg OD, and exenatide ER 2 mg OW. Insulin glargine was titrated based on pre-breakfast plasma glucose (target: 71- <100 mg/dL). Semaglutide was evaluated both as monotherapy or combination therapy with OADs and insulin. The reductions in HbA_{1c} from baseline to the end-of-treatment with semaglutide 0.5 mg and 1 mg were significantly greater and superior to the trial-specific comparators. The conclusions on superior glycemic efficacy of each dose of semaglutide versus comparator from SUSTAIN 1-5 were supported by all statistical sensitivity analyses showing significant and clinically relevant treatment differences. A larger reduction in HbA_{1c} was seen with semaglutide 1 mg than with 0.5 mg across trials that tested both doses.



Notes: *p<0.0001 vs. comparator. Estimates from a MMRM based on the FAS using the 'on-treatment without rescue medication' data for SUSTAIN 1-5 and the in-trial observation period for SUSTAIN 6 (CVOT). Mean estimates are adjusted according to observed baseline distribution in the FAS.
Abbreviations: CVOT: cardiovascular outcomes trial; ER: extended release; FAS: full analysis set; MMRM: mixed model for repeated measurements.

Figure 1 SUSTAIN 1-6: Estimated change from baseline in HbA_{1c} (%−point) at end-of-treatment

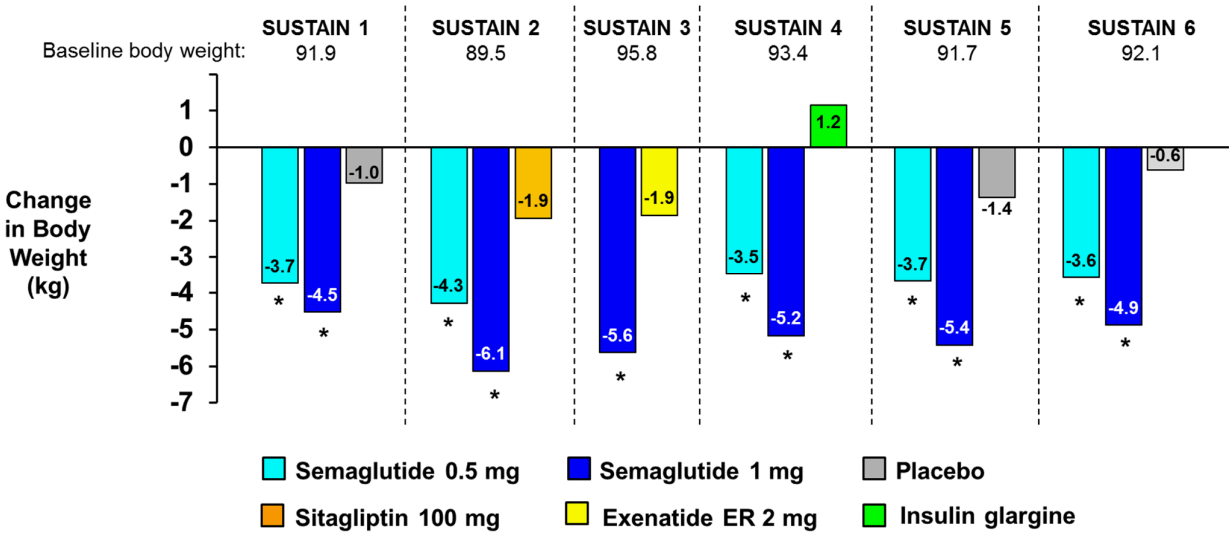
The efficacy of semaglutide (0.5 mg and 1 mg) in SUSTAIN 1–5 was consistent across sub-populations of major demographic factors (age, sex, race, and ethnicity), relevant disease factors at baseline (duration of diabetes, body weight, BMI, and renal function), background diabetes treatment (metformin monotherapy, metformin + SU, other) and region (Africa, Asia+Australia, Europe, North America [US+Canada], and South America), supporting the applicability of the data from the phase 3a trials across a broad population with T2D.

Superiority of semaglutide 0.5 mg and 1 mg on changes in HbA_{1c} obtained in SUSTAIN 1-5 was supported by data from SUSTAIN 6 (CVOT) and the 2 Japanese phase 3a trials. The reduction in HbA_{1c} with placebo (as add-on to standard-of-care) in SUSTAIN 6 (CVOT) is consistent with reductions reported with placebo in other recent CVOTs with GLP-1 RAs[14], DPP-4 inhibitors[15-18] and the SGLT-2 inhibitor empagliflozin[19] using similar recommendations for standard-of-care treatment.

In line with the reductions observed in mean HbA_{1c} with semaglutide, significantly greater proportions of patients with semaglutide than with comparators achieved a pre-defined treatment target of HbA_{1c} <7% (ADA target[8, 20]) in SUSTAIN 1-5 (semaglutide 0.5 mg: 57 to 74% of patients; semaglutide 1 mg: 67 to 79%; placebo: 11 and 25%; comparators: 36 to 40%) (Figure 15, p. 63). The proportion of patients achieving target glycemic levels with semaglutide are exceeding those obtained in other T2D clinical development programs.[1-4]

Weight loss (Section 6.3, p. 64)

Semaglutide monotherapy, or when used in combination with anti-glycemic drugs, provided durable and consistent weight loss across SUSTAIN 1–6 (see Figure 2 below). The mean weight loss achieved at end-of-treatment with semaglutide in SUSTAIN 1-6 was up to 6.1 kg; these weight reductions are clinically relevant[8] and greater than what has been previously reported with GLP-1 RAs for treatment of T2D.[1-4]



Notes: *p<0.0001 vs. comparator. Estimates from a MMRM based on the FAS using the 'on-treatment without rescue medication' data for SUSTAIN 1-5 and the in-trial observation period for SUSTAIN 6 (CVOT). Mean estimates are adjusted according to observed baseline distribution in the FAS.
Abbreviations: CVOT: cardiovascular outcomes trial; ER: extended release; FAS: full analysis set; MMRM: mixed model for repeated measurements.

Figure 2 SUSTAIN 1-6: Estimated change from baseline in body weight (kg) at end-of-treatment

A larger reduction in body weight was seen with semaglutide 1 mg than with 0.5 mg across trials. The reductions in body weight obtained with semaglutide were sustained for up to 104 weeks (Figure 16, p. 65).

The reductions in body weight achieved with semaglutide at end-of-treatment in SUSTAIN 1-5 were significantly greater and superior to placebo and the active comparators sitagliptin, exenatide ER, and insulin glargine (Figure 18, p. 67). Superior reductions were achieved when used as monotherapy and as add-on to OADs and basal insulin. The superior weight reduction with semaglutide in SUSTAIN 1-5 was supported by data from SUSTAIN 6 (CVOT) and the two Japanese trials.

A weight loss of ≥5% was achieved for significantly more patients with semaglutide 0.5 mg (37−46%) and 1 mg (45−66%) versus placebo (7 and 11%) or active comparators (4−18%) in SUSTAIN 1-5. Reductions in body weight with semaglutide were accompanied by significant and sustained reductions in waist circumference in all phase 3a trials.

Cardiovascular safety (Section 7, p. 70)

Methods for evaluation of cardiovascular safety (Section 7.1, p. 71)

The cardiovascular safety of semaglutide was established in SUSTAIN 6, a dedicated cardiovascular outcomes trial (CVOT)[5] designed and conducted in accordance with the 2008 FDA guidance for evaluating cardiovascular safety in new antiglycemic therapies[5] and advice from the FDA. SUSTAIN 6 (CVOT) was a 2-year, multicenter, multi-national, randomized, double-blind, placebo-controlled trial to evaluate cardiovascular and other long-term outcomes with semaglutide in 3,297 patients with T2D at high cardiovascular risk. The trial evaluated semaglutide (0.5 mg and 1 mg) versus placebo, each in combination with standard of care therapy. The primary endpoint was time from randomization to first occurrence of an adjudicated 3-component composite MACE (major adverse cardiovascular event) defined as cardiovascular death, non-fatal myocardial infarction (MI), or non-fatal stroke. SUSTAIN 6 (CVOT) had as a secondary objective to serve as a long-term safety and efficacy trial in the semaglutide development program and included secondary endpoints of time to first microvascular event including nephropathy and retinopathy.

The primary MACE endpoint was analyzed using a stratified Cox proportional hazards model based on the full analysis set (FAS, including all randomized patients) and based on the in-trial observation period. The primary analysis tested non-inferiority of semaglutide to placebo (upper bound of the 2-sided 95% CI for the estimated hazard ratio < 1.8) to exclude cardiovascular harm. A number of pre-specified sensitivity and subgroup analyses were performed to evaluate the robustness of the primary result.

SUSTAIN 6 (CVOT) was designed to be both *time* (minimum 104 weeks of treatment for each patients) and *event* (target: minimum 122 first MACEs) driven. However, as the observed in-trial MACE rate was higher than the estimated rate used in the power calculations, the time requirement became the defining factor for the trial duration. As a consequence the trial duration was fixed for all patients to 104 weeks followed by a 5-week follow-up period (see Section 7.1, p. 71). As a result of the high MACE rate, a total of 254 first MACEs were accrued. Accordingly, the trial provides substantial data for the evaluation of cardiovascular safety of semaglutide. The 95% confidence interval for the primary MACE endpoint, i.e., the measure of the uncertainty, was compared to the non-inferiority margin of 1.3, in line with the 2008 FDA guidance for evaluating cardiovascular safety in new antiglycemic therapies.[5] In addition, the *post-hoc* p-value for testing the 1.3 non-inferiority margin for the primary MACE endpoint was calculated, as a measure of the strength of statistical evidence for cardiovascular safety.

Baseline characteristics of SUSTAIN 6 (CVOT) population (Section 7.3, p. 74)

The SUSTAIN 6 (CVOT) inclusion criteria ensured enrollment of a clinically relevant subpopulation of patients with T2D at high cardiovascular risk. Patients with T2D and an HbA_{1c} ≥7.0% at screening (no upper limit) were eligible for enrolment, if they had established cardiovascular disease or chronic kidney disease and age ≥ 50 years; or had cardiovascular risk factors and were ≥60 years of age (see Table 5, p. 45). Of the 3297 patients randomized into SUSTAIN 6 (CVOT), the majority (83.0%) were enrolled based on the presence of established cardiovascular disease at baseline, while 17.0% were enrolled based on evidence of cardiovascular risk factors only (Table 13, p. 74). Demographics, baseline characteristics (Table 6, p. 46), and use of concomitant medication (Table 7, p. 48) were well-balanced across groups at baseline and were consistent with what would be expected in a population with a long duration of diabetes and a high prevalence of cardiovascular disease.

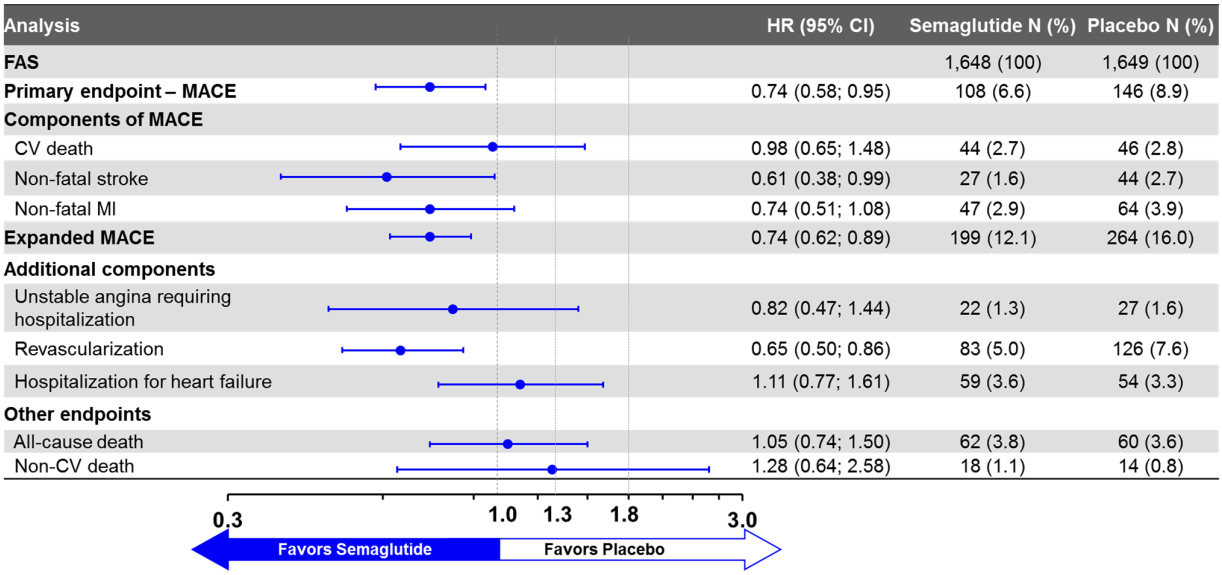
SUSTAIN 6 (CVOT) had high patient retention with 98% of randomized patients completing the trial (attended the end-of-trial follow-up visit or died during the trial). The vital status at end-of-trial was known in 99.6% of patients (vital status unknown for 13 patients [6 with semaglutide and 7 with placebo]), indicating that the results are both robust and reliable. For details regarding patient disposition, see Table 9, p. 51.

3-component MACE (primary endpoint) (Section 7.4.1, p. 75)

A total of 254 patients had an EAC-confirmed MACE during SUSTAIN 6 (CVOT); fewer with semaglutide (108 patients, 6.6% of patients) than with placebo (146 patients, 8.9% of patients) (Figure 3 below and Table 14, p. 76). The time to first EAC-confirmed MACE, as evaluated in the primary analysis, resulted in an estimated hazard ratio for semaglutide versus placebo of 0.74 $[0.58; 0.95]_{95\%CI}$. Non-inferiority of semaglutide versus placebo was confirmed with a margin of 1.8 (pre-planned, p <0.0001) as well as 1.3 (*post-hoc*, p <0.0001) with the upper bound of the 95% confidence interval being below 1.0. Hence, cardiovascular safety of semaglutide was established in SUSTAIN 6 (CVOT).

The cardiovascular safety of semaglutide was supported by all three components of MACE. The individual components of the MACE are presented in Figure 3 below.

The results of pre-specified and *post-hoc* sensitivity analyses consistently supported the outcome and robustness of the primary MACE analysis with hazard ratios that ranged from 0.72 to 0.75 (pre-planned analyses), and upper bounds of the 95% intervals all below 1.0 (Figure 21, p. 78).



Notes: Summary of results from analyses of time to individual and composite cardiovascular outcome. Expanded MACE comprised 3-component MACEs, plus unstable angina pectoris requiring hospitalization, revascularization (coronary and peripheral), and hospitalization for heart failure outcomes. Estimated HRs and associated CIs are from a Cox proportional hazard model with treatment (semaglutide, placebo) as fixed factor and stratified by all possible combinations of the three stratification factors used in the randomization procedure (9 levels).
Abbreviations: CI: confidence interval; CV: cardiovascular; FAS: full analysis set; HR: hazard ratio; MACE: major adverse cardiovascular events; MI: myocardial infarction.

Cross-reference: Figure 23, p. 81.

Figure 3 SUSTAIN 6 (CVOT): Forest plot of time to first individual and composite cardiovascular outcomes, semaglutide versus placebo

Cardiovascular safety was established for semaglutide versus placebo across a variety of relevant subpopulations including baseline demographics and prognostic disease characteristics, with no significant heterogeneity observed by statistical testing for interaction across the factors of stratification (see Section 7.4, p. 75 for detailed results).

Expanded MACE (Section 7.4.3, p. 80)

The establishment of cardiovascular safety of semaglutide was supported by results based on preplanned analyses using a broader definition of MACE (expanded MACE). This composite endpoint included the previously noted 3-component MACE events, plus unstable angina pectoris requiring hospitalization, revascularization (coronary and peripheral), and hospitalization for heart failure. A total of 463 patients had EAC-confirmed expanded MACEs; 199 with semaglutide and 264 with placebo (see Figure 3 above). The analysis of time to first expanded MACE resulted in an estimated hazard ratio of 0.74 $[0.62; 0.89]_{95\%CI}$, notably consistent with the outcome of the primary analysis.

MACE in phase 3a program (excl. CVOT) (Section 7.4.4, p. 81)

A total of 21 patients had EAC-confirmed MACEs in the seven phase 3a trials (excl. SUSTAIN 6 [CVOT]). The proportions of patients with MACE were similar with semaglutide (0.5 mg: 8 patients [0.6%], 1 mg: 5 patients [0.3%]) and comparator products (8 patients [0.5%]).

Cardiometabolic parameters (Section 7.6, p. 82)

Semaglutide lowered blood pressure (see Section 7.6.1, p. 82), which is of clinical relevance in patients with T2D who often have elevated blood pressure.[21-23] The effect was more apparent with systolic blood pressure even though a small reduction in diastolic blood pressure was also seen. This is consistent with findings for other GLP-1 RAs. The general decrease in blood pressure with semaglutide did not translate into more adverse events related to hypotension or syncope being reported for semaglutide than with placebo and comparator products.

A small, persistent increase in resting pulse rate (1 to 6 beats/minutes) was observed with semaglutide in the phase 3a trials (Section 7.6.2, p. 82), consistent with the GLP-1 RA class effects. No clinical consequences of the increased pulse rate (e.g., MACE, angina pectoris, heart failure, palpitations, or discontinuation of treatment due to tachycardia) were identified in the semaglutide development program including SUSTAIN 6 (CVOT), indicating that the increase in pulse rate induced with semaglutide is unlikely to be associated with cardiovascular harm.

Microvascular complications (Section 8, p. 86)

Secondary time-to-event analyses were pre-specified in SUSTAIN 6 (CVOT) for nephropathy, retinopathy and composite microvascular endpoints (Section 8.1, p. 86). Analyses were performed using the same method as the primary MACE endpoint. Microvascular complications were evaluated based on components related to both treatments and diagnoses of events, to be confirmed by the Event Adjudication Committee (EAC):

- 'New or worsening nephropathy' composite with 4 components: 'new onset of persistent macroalbuminuria', 'persistent doubling of serum creatinine and eGFR ≤ 45 mL/min/ 1.73 m^2 per MDRD', 'need for continuous renal replacement therapy', or 'death due to renal disease'.
- 'Diabetic retinopathy' composite with 4 components: 'need for retinal photocoagulation', 'need for treatment with intravitreal agents', 'vitreous hemorrhage' or 'diabetes-related blindness' (defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of less than 20 degrees, in the better eye with best correction possible. Note that the definition of 'diabetes-related blindness', does not mean it was a permanent loss of vision and could include a temporary reduction in visual acuity).

Due to opposite directional effects of treatment on the two components of the composite microvascular endpoint (new or worsening nephropathy and diabetic retinopathy complications), the results for the two components are presented separately.

Time to first event analysis of the nephropathy endpoint showed a hazard ratio (semaglutide versus placebo) below 1 (HR: 0.64 [0.46; 0.88]$_{95\%CI}$) (see Section 8.2, p. 89 and Figure 27, p. 89), mainly driven by a reduction in 'new onset of persistent macroalbuminuria'.

For time to first event analysis of diabetic retinopathy complications a hazard ratio above 1 (HR: 1.76 [1.11; 2.78]$_{95\%CI}$) was observed in SUSTAIN 6 (CVOT), see below and in Section 10.5, p. 133.

Clinical safety (Section 9, p. 91)

Safety methodology (Section 9.1, p. 92)

The evaluation of the safety profile of semaglutide (0.5 mg and 1 mg) was based both on data from all the completed phase 3a trials of 30 to 56 weeks duration as well as data from the 2-year CVOT. The primary evaluation of safety data was performed using 2 data-sets; pooled data from SUSTAIN 1–5 and the two Japanese safety trials (phase 3a pool) and 2-year data from SUSTAIN 6 (CVOT) (Figure 28, p. 94). Evaluation of adverse events in the phase 3a pool were based on adjusted proportions and rates, to avoid confounding due to differences between trials. Data from SUSTAIN 6 (CVOT) are presented separately from the other phase 3a trials, because of important differences in trial designs including randomization ratio, size, duration and population.

Semaglutide safety profile (Section 9.2, p. 94)

In the phase 3a pool, the safety profile of semaglutide was consistent with the GLP-1 RA class. Adverse drug reactions identified with semaglutide included gastrointestinal adverse events, reduced appetite and weight decrease, fatigue, dizziness, dysgeusia (altered taste perception), cholelithiasis, increased lipase and amylase levels and hypoglycemia (when combined with insulin or SU) (Table 18, p. 97). The overall proportion of patients reporting any adverse event or serious adverse event during the treatment period was higher with semaglutide (0.5 mg and 1 mg) than with comparators (see Table 2 below). The higher proportions of patients with adverse events observed with semaglutide were mainly due to a higher proportion of patients experiencing gastrointestinal disorders with semaglutide (0.5 mg: 41.7%; 1 mg: 42.1%) than with comparator products (22.0%). Overall, more patients discontinued treatment prematurely due to adverse events with semaglutide than with active comparators, primarily due to gastrointestinal adverse events.

Table 2 Phase 3a pool: Adverse events

	Semaglutide 0.5 mg		Semaglutide 1 mg		Comparators	
	N	(Adj.%)	N	(Adj.%)	N	(Adj.%)
Number of patients	1,373		1,777		1,657	
Adverse events	1,015	(73.4)	1,301	(72.7)	1,136	(68.7)
Serious adverse events (SAEs)	92	(6.6)	118	(6.7)	95	(5.8)
Deaths	7	(0.5)	3	(0.2)	6	(0.4)
AEs leading to premature treatment discontinuation	84	(6.1)	156	(8.7)	51	(3.0)

Notes: SAS on-treatment. % are the Cochran-Mantel-Haenszel-adjusted percentage. Please note that the number of fatal events occurring in the on-treatment period is based on the investigator-reported adverse event onset date.
Comparators: exenatide ER; insulin glargine; oral anti-glycemic drugs; sitagliptin, placebo.
Abbreviations: Adj.:adjusted; ER: extended release; N: number of patients with event; SAS: safety analysis set; SAE; serious adverse event; %: proportion of patients with event.

Cross-reference: Based on Table 16, p.96.

In the 2-year SUSTAIN 6 (CVOT), the overall proportions of patients with adverse events were similar with semaglutide (0.5 mg and 1 mg) and placebo (Table 3 below); however, rates were higher with semaglutide than placebo (Table 17, p. 96).

Table 3 SUSTAIN 6 (CVOT): Adverse events

	Semaglutide 0.5 mg		Semaglutide 1 mg		Placebo	
	N	(Adj.%)	N	(Adj.%)	N	(Adj.%)
Number of patients	823		819		1,644	
Adverse events	732	(88.9)	722	(88.2)	1,453	(88.4)
Serious adverse events (SAEs)	264	(32.1)	240	(29.3)	574	(34.9)
Deaths	24	(2.9)	23	(2.8)	44	(2.7)
AEs leading to premature treatment discontinuation	95	(11.5)	119	(14.5)	110	(6.7)

Note: SAS on-treatment. Please note that the number of fatal events occurring in the on-treatment period is based on the investigator-reported adverse event onset date.
Abbreviations: CVOT: cardiovascular outcomes trial; N: number of patients with event; SAE: serious adverse event; SAS: safety analysis set; %: proportion of patients with event.

Cross-reference: Based on Table 17, p.96.

As in the phase 3a pool, more patients in SUSTAIN 6 (CVOT) discontinued treatment prematurely due to adverse events with semaglutide than placebo, mainly due to gastrointestinal adverse events. Serious adverse events were reported by a lower proportion of patients and at lower rates with semaglutide (0.5 mg and 1 mg) than with placebo. Except for diabetic retinopathy complications (see further details below), no relevant differences were found between the safety profile in the less comorbid population in the phase 3a trials (excl. CVOT) compared to the heavily comorbid population in SUSTAIN 6 (CVOT) (Table 18, p. 97 and Table 19, p. 98).

In accordance with the trial selection criteria, the phase 3a program included a broad population including a substantial number of elderly patients, patients with heart failure and patients with moderate or severe renal impairment. The safety profile was consistent across subgroups of sex,

age, race, ethnicity, body weight, BMI, hypertension, cardiovascular comorbidities, renal function, hepatic function, region, anti-glycemic background medication and tobacco use, thus supporting the safety of semaglutide across these subpopulations (see Section 9.2, p. 94).

Deaths (Section 9.3, p. 103)

The proportion of patients who died during the trials included in the phase 3a pool was low and similar with semaglutide and comparator products (Table 23, p. 103).The proportion of patients who died during the SUSTAIN 6 (CVOT) trial was higher than in the phase 3a pool, reflecting the population enrolled. Fatal events occurred throughout the entire treatment period of SUSTAIN 6 (CVOT), with no clustering of events in any time interval and with similar patterns seen with semaglutide and placebo. The reported deaths do not differ with respect to cause between treatments or from what would be expected for the patient population enrolled in the clinical trials.

Gastrointestinal tolerability (see Section 9.4, p. 104)

Events of gastrointestinal disorders were as expected common and occurred more frequently with semaglutide than with placebo and comparator products. Gastrointestinal adverse events reported with semaglutide were consistent with regard to event types, outcomes, severity and seriousness with other GLP-1 RA based therapies.[24] Events were reported most frequently at initiation of therapy and in relation to dose escalation. They were typically short in duration with a median duration of nausea of 6 days, diarrhea of 3 days, and vomiting of 1 day. In patients who remained on treatment, tolerance to these effects, especially nausea, developed over time consistent with the pattern seen with other GLP-1 RAs including once-weekly exenatide ER and once-daily liraglutide.[25, 26]

Episodes of hypoglycemia (Section 9.5, p. 107)

As expected for a therapy with a glucose-dependent mechanism of action, hypoglycemia incidence with semaglutide was lower than with insulin glargine and similar to exenatide ER. This finding is consistent with previous findings with once-daily[27] and once-weekly[28] GLP-1 RAs. The risk of hypoglycemia with semaglutide was higher when co-administered with SU or insulin than when used as monotherapy or as add-on to metformin, consistent with other GLP-1 RAs.

Neoplasms (Section 9.6, p. 110)

EAC-confirmed events of neoplasms in the SUSTAIN trials were distributed across several tissue types with estimated hazard ratios for semaglutide versus placebo/comparators on either side of unity and with no observed clustering within specific organ sites for either treatment group. No medullary thyroid carcinomas (MTCs) were reported during the semaglutide development program.

Pancreatitis (Section 9.7, p. 114)

The incidences of EAC-confirmed events of acute pancreatitis were comparable with semaglutide and placebo/comparator products. In SUSTAIN 6 (CVOT), the number of patients with EAC-

confirmed acute pancreatitis was similar with semaglutide (8 patients) and placebo (10 patients) and all events were classified as 'mild acute pancreatitis' based on the revised Atlanta criteria.[29] In the phase 3a pool, few events of pancreatitis were confirmed (semaglutide 0.5 mg: 5 patients, 0.4%; semaglutide 1 mg: 3 patients, 0.2%; exenatide ER: 3 patients, 0.2%; other comparators: none). Few patients had EAC-confirmed malignant pancreatic cancer and events were evenly distributed both in SUSTAIN 6 (semaglutide: 1 of 1,648 patient; placebo: 4 of 1,649 patients) and in the phase 3a pool (semaglutide: 2 of 3,150 patients; comparators: 2 of 1,657 patients) (see Figure 33, p. 112).

Gallstones (Section 9.8, p. 115)

In the placebo-controlled 2-year SUSTAIN 6 (CVOT), the proportion of patients with gallbladder-related adverse events was similar with semaglutide (0.5 mg: 3.5%; 1 mg: 3.2%) and placebo (3.4%). Conversely, in the phase 3a pool, gallbladder-related adverse events were reported more frequently with semaglutide (0.5 mg: 1.3%; 1 mg: 1.7%) than with comparator products (0.8%) (Table 26, p. 115); the adverse events of cholelithiasis (0.5 mg: 0.7%; 1 mg: 1.1%; comparators: 0.5%) was the single type of event accounting for most of the difference. In SUSTAIN 6 (CVOT), events of cholelithiasis were also more frequent with semaglutide (0.5 mg: 2.3%; 1 mg: 2.1%) than with placebo (1.6%). The majority of events of cholelithiasis were non-serious, and the absolute risk was low. Events of cholelithiasis did not appear to be preceded by a large and rapid weight loss as previously reported for some GLP-1 RAs[30] and events did not lead to an increased risk of complications such as cholecystitis or pancreatitis.

Immunogenicity (Section 9.9, p. 116)

The risk of developing anti-semaglutide antibodies was low (1−2%), with no neutralizing antibodies or IgE's observed. Furthermore, allergic reactions (4−6%) and injection site reactions (~1%) were generally infrequent, non-serious, of mild or moderate severity, and no differences between semaglutide and placebo/non-exenatide comparators were observed. In SUSTAIN 3, antibody formation occurred in fewer patients with semaglutide (3.2%) than with exenatide ER 2 mg (87.7%); a similar difference was seen for injection site reactions (semaglutide 1 mg: 1.2%; exenatide ER 2 mg: 22.0%).

Diabetic retinopathy (Section 10, p. 121)

An increase in diabetic retinopathy complications with semaglutide was observed in SUSTAIN 6 (CVOT), this observation is consistent with early worsening of pre-existing diabetic retinopathy after improvements in glycemic control as seen with other highly efficacious blood glucose lowering therapies, including insulin. Besides the magnitude of HbA_{1c} reductions, the clinical characteristics and potential predictors of T2D patients at risk for diabetic retinopathy complications include pre-existing retinopathy, poor glycemic control, long duration of diabetes, and co-use of insulin.

Background (Section 10.1, p. 121)

Diabetic retinopathy affects the vascular component of the retina, the back portion of the eye. Diabetic retinopathy represents a spectrum of changes in the retina that progress in severity from no observed changes, to mild, moderate or severe non-proliferative retinopathy and ultimately to proliferative retinopathy representing the sight-threatening stage of the complication.[31] Macular edema can occur at any stage. Changes are similar in patients with T1D and T2D.

Maintaining glycemic control as close to that of individuals without diabetes (HbA_{1c} <7%), is known to prevent or delay microvascular complications (see Section 10.1, p. 121). Therefore, evaluations of microvascular complications including diabetic retinopathy were included as a secondary endpoint in SUSTAIN 6 (CVOT), see Section 8, p. 86. However, an increased risk of diabetic retinopathy complications was observed in SUSTAIN 6 (CVOT). Novo Nordisk has performed a thorough evaluation of these events and consulted with external ophthalmology experts to better understand the potential implications of the finding and to identify patients at risk.

Methods for evaluation of diabetic retinopathy in the phase 3a program (Section 10.2, p. 126)

Evaluations of diabetic retinopathy were based on:
a) events confirmed by an external event adjudication committee (EAC) to meet at least one of four pre-defined criteria for the microvascular endpoint 'diabetic retinopathy complications' (SUSTAIN 6 [CVOT] only).
b) investigator- reported adverse event as part of the general safety evaluation in all phase 3a trials including SUSTAIN 6 (CVOT).
c) scheduled eye examinations performed at baseline in all phase 3a trials, at end-of –treatment in the Japanese phase 3a trials, and after 1 year and after 2 years/at end-of-trial in SUSTAIN 6 (CVOT). The eye examination could be either direct fundoscopy or digital/fundus photography; details on the methods applied were not recorded. No central reading of fundus photographs was performed.

Accordingly, none of the trials in the phase 3a program employed a systematic evaluation of diabetic retinopathy progression, such as the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale.

Diabetic retinopathy complications at baseline including risk factors (Section 10.3, p. 129)

In SUSTAIN 6 (CVOT), there was no exclusion criterion related to advanced diabetic retinopathy (defined as retinopathy requiring specific eye treatment) or upper HbA_{1c} limit, whereas patients in very poor control and advanced diabetic retinopathy were excluded in the other phase 3a trials (see Section 10.3, p. 129). Consequently, the frequency of retinopathy at baseline was higher in SUSTAIN 6 (CVOT) (29.5% of patients) than in the other phase 3a trials (1.6% to 14.5%) (Table 28, p. 130). The patients enrolled in SUSTAIN 6 (CVOT) were generally older, had cardiovascular disease, longer duration of diabetes, higher baseline HbA_{1c}, and more insulin use

than patients in the other phase 3a trials. Thus, the patient population enrolled in SUSTAIN 6 (CVOT) was at higher risk of development and/or progression of diabetic retinopathy, since the development of diabetic retinopathy correlates with diabetes duration and level of glycemic control, and the risk of worsening or progression is increased with the severity of any existing retinopathy.

Adverse events related to diabetic retinopathy (Section 10.4, p. 130)

A low proportion of patients in the phase 3a pool (excluding the CVOT) had investigator-reported adverse events of diabetic retinopathy (see Section 10.4, p. 130). Events were overall evenly-balanced with semaglutide (0.5 mg: 2.1%; 1 mg: 1.5%) and comparator products (2.0 %) (Table 29, p. 131). In SUSTAIN 6 (CVOT), the proportion of patients with adverse events of diabetic retinopathy was higher with semaglutide (0.5 mg: 9.0%; 1 mg: 10.0%) than with placebo (7.6%). The higher event rate observed in SUSTAIN 6 (CVOT) than in the phase 3a pool is consistent with the population included in the trial patients being at higher risk of development or progression of diabetic retinopathy than the patients enrolled in the other phase 3a trials. There were no treatment differences regarding severity or type of events; most events were non-serious events of mild or moderate severity.

EAC-evaluation of diabetic retinopathy complications in SUSTAIN 6 (Section 10.5, p. 133)

In SUSTAIN 6 (CVOT), a significant increased risk of EAC-confirmed events of diabetic retinopathy complications was observed with semaglutide (50 [3.0%] patients, evenly distributed between doses) as compared with placebo (29 [1.8%] patients) (HR: 1.76 $[1.11; 2.78]_{95\%CI}$) (see Section 10.5, p. 133). Events of diabetic retinopathy complications occurred mainly in patients with pre-existing diabetic retinopathy (especially proliferative retinopathy), long duration of diabetes, and with a pronounced decrease in HbA_{1c} (Table 34, p. 137). However, among patients without pre-existing diabetic retinopathy or large reductions in HbA_{1c}, the frequency of EAC-confirmed diabetic retinopathy complications was low and similar with semaglutide and placebo. To further evaluate the potential impact of the initial decline in blood glucose levels on risk of diabetic retinopathy complications, a *post-hoc* mediation analysis was performed. This result suggests that the vast majority of the overall effect of semaglutide can be explained by the initial decline in blood glucose associated with semaglutide treatment (Table 35, p. 140). This would be consistent with what has been observed for other highly efficacious blood glucose lowering therapies, including insulin products as reflected in the product information for these medicines.[32-37]

Fundoscopy or fundus photography findings (Section 10.6, p. 141)

Results from the 1- and 2-year fundoscopy assessments in patients with abnormal baseline findings, do not indicate a detrimental effect of semaglutide (Section 10.6, p. 141 and Figure 41, p. 141). The changes in fundoscopy results at year 1 could be considered consistent with an early worsening of diabetic retinopathy with semaglutide, whereas the 2-year data indicate beneficial long-term effects of semaglutide treatment on diabetic retinopathy similar to the effect of stringent glycemic control on diabetic retinopathy seen in the DCCT, UKPDS and ACCORD.[11, 34, 35, 38-42]

Discussion of diabetic retinopathy (Section 10.8, p. 142)

Despite a potential risk of an initial deterioration of diabetic retinopathy following intensified glycemic control, several long-term studies have established that tight glycemic control in the longer term provides substantial reduction in the risk of development and/or progression of diabetic retinopathy, indicating that the increased risk following intensification is transient.[11, 38, 43-45] The studies have also shown that it can take more than 3 years before the potential benefit is evident. The risk of an initial worsening of diabetic retinopathy can be mitigated by routine eye examinations in patients with established diabetic retinopathy, followed by treatment when appropriate in accordance with good clinical practice and standards of care.[46]

Risk minimization activities proposed by Novo Nordisk include labelling (see Section 11.1, p. 144), with specific wording addressing the risk of diabetic retinopathy complications in high risk patients in the 'warning and precautions' section of the product information.

Benefit-risk assessment (Section 12, p. 145)

Semaglutide 0.5 mg and 1 mg as monotherapy or in combination with other anti-glycemic agents is a new treatment option for patients with T2D, including those at high risk of cardiovascular events.

Semaglutide showed an unprecedented ability to control elevated blood glucose providing superior long-term glycemic control in addition to clinically relevant reductions in body weight as compared with commonly used marketed products. The safety profile of semaglutide is well-documented based on data from the large nonclinical and clinical development programs, and consistent with the safety profile of other drugs within the GLP-1 RA drug class. Cardiovascular safety of semaglutide was established in a 2-year CVOT (SUSTAIN 6) with a hazard ratio of 0.74 and associated 95% confidence interval of 0.58; 0.95.

Some semaglutide-associated health benefits are immediate, such as the effects on glycemic control, weight loss and blood pressure and may encourage patients to remain on treatment and undertake enduring lifestyle changes. The benefits on glycemic control and weight loss are known to be associated with improvements in perceived physical and mental health and quality-of-life.[47, 48] In addition, semaglutide treatment has the potential to increase adherence to therapy with a simple and flexible once-weekly regimen and easy to use, pre-filled, multi-use pens. Other benefits manifest with longer-term semaglutide treatment as direct effects or as results of improved glycemic control and weight loss.

Semaglutide was found to be generally safe and well-tolerated. However, as expected for a GLP-1 RA, semaglutide was associated with a higher frequency of gastrointestinal adverse events compared with placebo and active comparators. In addition, reduced appetite and weight decrease, fatigue, dizziness, dysgeusia (altered taste perception), cholelithiasis, increased lipase and amylase levels and hypoglycemia (when combined with insulin or SU) are adverse drug reactions related to semaglutide treatment. There was no indication of a dose- or exposure-response relationship for

safety/tolerability parameters, except for gastrointestinal side effects, which generally occurred early during dose-escalation, were of mild or moderate severity and resolved without sequelae. Adverse effects were mostly predictable based on the known effects of GLP-1 RAs, infrequent in the case of serious adverse drug reactions, easily diagnosed and monitored, and reversible upon treatment discontinuation.

One safety finding emerged from SUSTAIN 6 (CVOT); semaglutide treatment was associated with an increased risk of diabetic retinopathy complications in patients with pre-existing diabetic retinopathy. The available data are consistent with early worsening of diabetic retinopathy being associated with pronounced improvement in glycemic control. As seen with other glucose-lowering therapies, such as insulin therapy, a risk of worsening of diabetic retinopathy can be mitigated by routine eye examinations in patients with pre-existing diabetic retinopathy, followed by treatment when appropriate in accordance with existing good clinical practice and standards of care.[49] Specific wording addressing the risk of diabetic retinopathy complications is proposed for the 'warning and precautions' section of the product information. Importantly, the absolute risk of diabetic retinopathy was low.

In order to assess if the cardiovascular safety of semaglutide was preserved for patients at risk of diabetic retinopathy complications, a *post-hoc* subgroup analysis of MACE by pre-existing diabetic retinopathy (yes/no) was made, demonstrating cardiovascular safety both in patients with pre-existing diabetic retinopathy (HR: 0.52 $[0.34; 0.80]_{95\%CI}$) and in those without (HR: 0.77 $[0.55; 1.08]_{95\%CI}$) (see p. 137). Furthermore, a beneficial ratio of 19 patients needed to treat with semaglutide for 2 years to prevent one patient from having a MACE versus 36 patients needed to treat to observe diabetic retinopathy complications in one patient, was shown for patients with pre-existing diabetic retinopathy (Table 36, p. 142). In addition, other benefits of semaglutide include efficient glycemic control, a once-weekly treatment regimen, reductions in blood pressure and weight loss, as well as a potential for long-term reduced risk of microvascular complications, which are also important benefits in this group of patients. Hence, in the subgroup of patients at highest risk of diabetic retinopathy complications, the benefit-risk profile of semaglutide remains positive.

The efficacy and safety of semaglutide was established across a broad range of patients in terms of age, race, regions, duration of diabetes, level of HbA_{1c} control at baseline, and comorbidities including some of the most vulnerable patient populations such as elderly patients (≥75 years of age), patients with established cardiovascular disease, and patients with severe renal impairment. Across all subgroups and populations investigated, semaglutide provided improved glycemic control and clinically relevant weight loss with established cardiovascular safety and no differences in safety profile, thus supporting the use of semaglutide in these subpopulations without a need for dose adjustment. Specifically in patients with renal impairment across all stages, the efficacy and safety profile of semaglutide were comparable to patients with normal renal function. Many anti-diabetic medications have restrictions in their label, often precluding treatment in patients at later stages of renal dysfunction, and hence, this T2D subpopulation currently has more limited treatment

options. The results from the SUSTAIN program support the use of semaglutide in patients across all stages of renal impairment without a need for dose adjustment.

Data from the clinical development program demonstrate that semaglutide is a significantly improved treatment option for patients with T2D, including those at high risk of cardiovascular events. Semaglutide allows patients to manage their disease by providing superior glycemic control and weight loss, with the potential to favorably impact their diabetes-related complications. Hence, semaglutide offers an additional valuable choice in the armamentarium for patients and physicians in treatment of patients with T2D. Based on these benefits taken together with the potential and identified risks, Novo Nordisk evaluates the benefit-risk balance for semaglutide as positive.

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List of abbreviations and definitions

%	proportion of patients with event
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin-converting enzyme
ADA	American Diabetes Association
Adj	adjusted
ADVANCE	Action in Diabetes and Vascular Disease: PreterAx and Diamicron MR Controlled Evaluation
AE	adverse event
ALT	alanine aminotransferase (also referred to as ALAT or serum glutamic-pyruvic transaminase, SGPT)
ANCOVA	analysis of covariance
AR	angiotensin-receptor
AST	aspartate aminotransferase (also referred to as ASAT or serum glutamic oxaloacetic transaminase, SGOT)
AUC	area under the concentration–time curve
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CABG	coronary artery bypass graft surgery
Cavg	the average, model-derived semaglutide plasma concentration
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CV	cardiovascular
CVOT	cardiovascular outcomes trial
DBL	data-base lock
DBP	diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DDI	drug-drug interaction
DMC	data monitoring committee
DPP-4	dipeptidyl peptidase-4
E	number of events
EAC	event adjudication committee
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ER	extended release (exenatide)
ESRD	end-stage renal disease
ETD	estimated treatment difference
ETDRS	Early Treatment Diabetic Retinopathy Study

FAS	full analysis set
FPG	fasting plasma glucose
GI	gastrointestinal
GLP-1 RA	glucagon-like peptide-1 receptor agonist
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated hemoglobin A1c
HDL	high density lipoprotein
HR	hazard ratio
ICH	International Conference on Harmonization
IGlar	insulin glargine
ITT	intention-to-treat
JP	Japan
LDL	low-density lipoprotein
LOCF	last observation carried forward
MACE	major adverse cardiovascular event comprising CV-death and non-fatal MI and stroke
MAR	missing at random
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MEN2	multiple endocrine neoplasia syndrome type 2
met	metformin
MI	myocardial infarction
MMRM	mixed model repeated measurement
MoA	mechanism of action
Mono	monotherapy
MTC	medullary thyroid carcinoma
N	number of patients
n	number of patients with event
NA	not applicable
NDA	new drug application
NNH	number needed to harm
NNT	number needed to treat
NPH	neutral protamine Hagedorn
NYHA	New York Heart Association
OAD	oral antiglycemic drug
OD	once daily
OR	odds ratio
PBP	placebo
PCI	percutaneous coronary intervention
PD	pharmacodynamics
PI	product information
PK	pharmacokinetics

PP	per protocol
PYE	patient-years of exposure
PYO	patient- years of observation
QW	once weekly
R	event rate per 100 PYE/PYO
RR	relative risk
s.c.	subcutaneous
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SEM	standard error of the mean
sema	semaglutide s.c. OW
SGLT-2	sodium-dependent glucose transporter 2
sita	sitagliptin
SMQ	standardized MedDRA query
SoC	standard-of-care
SOC	system organ class
STEMI	ST-elevation myocardial infarction
SU	sulfonylurea
SUSTAIN	Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes
t½	elimination half-life
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
tmax	time to maximum plasma concentration
TTT	treat-to-target
TZD	thiazolidinediones
UACR	urinary albumin to creatinine ratio
UAP	unstable angina pectoris
UKPDS	UK Prospective Diabetes Study
ULN	upper limit normal
VA	visual acuity
VLDL	very low-density lipoprotein
w	week
yrs	years
α-GI	alpha-glucosidase inhibitor

1 Introduction

Summary

- The proposed indication for semaglutide 0.5 mg and 1 mg s.c. once-weekly is an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D).
- Semaglutide is a uniquely optimized GLP-1 RA with a plasma half-life consistent with once weekly dosing that display high potency, stability against DPP-4 degradation, and with known pharmacological effects of the GLP-1 RA class.
- Semaglutide is metabolized by proteolytic cleavage of the peptide backbone and by sequential beta-oxidation of the fatty acid side-chain.
- Semaglutide will be provided in ready-for-use prefilled multiple-dose disposable pens for once-weekly use.
- Despite the number of agents available to treat T2D, many patients still do not reach or maintain their glycemic target and remain at increased risk of T2D-related complications. Thus, there remains a need for improved therapies that help more patients reach target HbA_{1c}, reduce weight, and prevent long-term complications.

This briefing document provides background information for the members of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) for a meeting on October 18, 2017. The Committee will be asked to discuss the results from Novo Nordisk's semaglutide development program including a CVOT within the context of the overall efficacy and safety of semaglutide s.c. once-weekly treatment to improve glycemic control in adults with T2D submitted in the new drug application (NDA) 209637.

1.1 Proposed indication and dosing

The proposed indication for semaglutide 0.5 mg and 1 mg s.c. once-weekly is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Semaglutide offers the convenience of once-weekly administration delivered in ready-for-injection prefilled multiple-dose disposable auto-injector pens designed to deliver the weekly dose in a single injection with the use of thin needles (32G). Semaglutide should be administered once-weekly at any time of day by a subcutaneous injection in the abdomen, thigh, or upper arm. In order to reduce the risk of gastrointestinal side effects, the semaglutide dose will be escalated over time when treatment is initiated. The starting dose of semaglutide is 0.25 mg subcutaneously once-weekly. After 4 weeks the dose can be increased to 0.5 mg once-weekly. After at least 4 weeks on 0.5 mg, the semaglutide dose can be increased to 1 mg once-weekly for additional glycemic control.

This document provides the scientific foundation for the following conclusions:

- The pharmacokinetic characteristics of semaglutide support once weekly dosing and the pharmacodynamic characteristics of semaglutide show that semaglutide is a highly potent and efficacious molecule with a mechanism-of-action (MoA) consistent with expectations for a GLP-1 RA.
- Superiority of semaglutide 0.5 mg and 1 mg is demonstrated in glycemic control and weight loss versus placebo (as monotherapy or combination therapy with insulin), as well as in comparison with sitagliptin, exenatide ER, or insulin glargine. The effects of semaglutide are assessed to be sustained for up to 104 weeks, clinically relevant, observed both in drug-naïve patients and in those concomitantly treated with other anti-glycemic agents. Findings were consistent across trials and subpopulations.
- Overall, the safety profile of semaglutide was consistent with the GLP-1 RA class. One new safety finding emerged from SUSTAIN 6 (CVOT); semaglutide treatment was associated with an increased risk of diabetic retinopathy complications in patients with pre-existing diabetic retinopathy.
- Cardiovascular safety of semaglutide was established in SUSTAIN 6 (CVOT) with an estimated hazard ratio for semaglutide versus placebo of 0.74 $[0.58; 0.95]_{95\%CI}$. Non-inferiority of semaglutide versus placebo was confirmed with a margin of 1.8 (pre-planned) as well as 1.3 (*post-hoc)* with the upper bound of the 95% confidence interval being below 1.0.
- Semaglutide offers the convenience of once-weekly administration delivered in a ready-for-use prefilled multiple-dose disposable auto-injector pens designed to deliver the weekly dose in a single injection with the use of thin needles (32G).
- Results from the clinical development program provide consistent and convincing evidence of a favorable benefit-risk profile for semaglutide 0.5 mg and 1 mg for the treatment of patients with T2D including those at high cardiovascular risk.

Novo Nordisk consulted FDA throughout the development of semaglutide on the comprehensive program to obtain advice regarding submission and approval of semaglutide.

1.2 Semaglutide

Semaglutide is a long-acting human GLP-1 receptor agonist (GLP-1 RA), that specifically activates the GLP-1 receptor, using similar signaling pathways and with similar cellular actions as native GLP-1. GLP-1 is a physiological hormone that has numerous beneficial effects resulting in glycemic control and weight loss. The metabolism and mechanism of action of semaglutide were characterized in extensive nonclinical and clinical studies.

Semaglutide was engineered to make it suitable for once-weekly administration in humans, while still retaining a high structural homology to native GLP-1 (94%). Semaglutide is highly potent, more hydrophilic than liraglutide, and has a low molecular weight to facilitate uptake in the brain, resulting in appetite regulation effects and clinical relevant weight loss. As compared to other long-

acting GLP-1 RAs like dulaglutide and albiglutide, semaglutide has a substantially lower molecular weight (4KDa). More specifically, the protraction for semaglutide is achieved by non-covalent binding to albumin through a long-chain fatty di-acid side-chain and a hydrophilic spacer attached to the peptide backbone. In both animals and humans, semaglutide is extensively bound to plasma albumin (>99%). In addition, semaglutide was modified by substitution of alanine in position 8 to reduce degradation by the DPP-4 enzyme.[50] Both these modifications of semaglutide result in a plasma half-life of approximately 1 week in humans.

Semaglutide is slowly metabolized by common degradation pathways in the body, including proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid side-chain. The intact spacer is subsequently excreted into urine. The primary excretion routes of semaglutide metabolites are via the urine and feces. Approximately 3% of the administered dose was excreted in urine as intact semaglutide.

Data from nonclinical and clinical studies have demonstrated that semaglutide exhibits GLP-1 receptor mediated effects i.e., stimulates insulin secretion, lowers glucagon secretion, and improves β-cell function, all in a glucose-dependent manner, which results in a lowering of fasting and post-prandial glucose. The mechanism of post-prandial blood glucose lowering also involves a minor delay in gastric emptying. Animal studies have demonstrated that semaglutide can access brain regions that are critical to the regulation of energy intake, and semaglutide was shown to activate satiety-related neurons and inhibit hunger-related neurons. The ability of semaglutide to decrease food intake and induce weight loss was confirmed in nonclinical studies and a clinical pharmacology trial. In addition, nonclinical studies in non-diabetic mice showed that semaglutide attenuates the development of atherosclerosis by reducing plaque formation and reducing inflammation in the affected plaque. Furthermore, a clinical pharmacology trial showed reduced postprandial response of triglycerides.

1.3 Medical need and rationale for semaglutide in the treatment of T2D

In 2016, more than 29 million people in the US were estimated to have diabetes, with T2D accounting for approximately 90-95% of the cases.[51] According to projections from the US Center for Disease Control, one in three US adults could have diabetes by 2050.[52]

T2D is a progressive chronic metabolic disease characterized by chronic hyperglycemia which, if left untreated, is associated with progressive β-cell failure and increased risk of long-term micro- and macrovascular complications.[6] Long-term glycemic control is thus fundamental, [33, 43, 53] but data collected from 2007−2010 demonstrate that close to 50% of all patients treated for their T2D do not achieve the blood glucose target of HbA_{1c} <7%.[7]

Overweight and obesity are well-known risk factors for hyperglycemia and T2D.[8,9] A moderate weight loss of 5% can improve glycemic control in patients with T2D.[10] Accordingly, current ADA treatment guidelines recommend that patients with T2D achieve modest weight loss (5–7%) to

improve glycemic control.[8, 11] Thus, anti-glycemic drugs that in addition to lowering HbA_{1c} also reduce body weight provide additional clinical benefits in the treatment of T2D.

Due to the progressive nature of T2D, most patients will require treatment intensification, which can be in the form of additional anti-glycemic oral agents or an injectable therapy such as insulin or GLP-1 RAs.[54] However, complex or inflexible treatment regimens can restrict the patients' lifestyle and can contribute to lack of adherence and failure to achieve the desired glycemic control.[55-58] A requirement of multiple injections is a perceived burden in T2D patients[59] and once-weekly GLP-1 RAs may improve patient adherence and health-related quality-of-life, compared with daily formulations,[60] as has been demonstrated with less frequent dosing for patients with other chronic illnesses.[61] Other therapy related barriers to adherence in patients with T2D include weight gain and fear of hypoglycemia. In addition, a number of existing T2D treatments have label restrictions for patients with renal impairment[62-64], a frequent microvascular complication in T2D. Hence, a T2D drug that can be prescribed regardless of renal function will provide clinical benefits to a population of T2D patients with otherwise limited treatment options.

In summary; despite the numerous treatment options available for patients with T2D, it is clear that they share many limitations and additional options are needed. Semaglutide s.c. once-weekly has the potential to improve patient adherence and targets several aspects of the treatment of T2D including glycemic control, body weight loss, with low rates of hypoglycemia and safe use, also in patients at high cardiovascular risk.

2 Nonclinical development of semaglutide s.c. once-weekly

Summary

- A comprehensive nonclinical safety program was performed in accordance with current regulatory guidance to evaluate the safety profile of semaglutide.
- The nonclinical findings were associated with known GLP-1 RA pharmacology (reduced food intake and reduced body weight gain).
- Thyroid C-cell tumors
  - The known GLP-1 RA class effects of thyroid C-cell hyper- and neoplasia were observed in rodents. Based on the totality of available data, the human relevance of this effect in rodents is considered to be low.
- Developmental toxicity
  - In rats, embryo-fetal development was adversely affected via a GLP-1 receptor mediated inhibition of the nutritional function of the yolk sac. Due to species differences in yolk sac anatomy, function, and GLP-1 receptor expression, this mechanism is considered unlikely to be of relevance to humans.
  - In rabbits and monkeys, increased incidence of pregnancy losses and fetal abnormalities were observed. These findings coincided with a marked maternal body weight loss, and were considered to be either incidental or related to maternal stress.
  - Consistent with other GLP-1 RAs, semaglutide is not recommended for use during pregnancy.

2.1 Overview and nonclinical testing strategy

The comprehensive nonclinical development program for semaglutide was designed in accordance with international regulations.[65] Pivotal nonclinical safety studies were conducted in accordance with Good Laboratory Practice (GLP). Throughout the development, regular contacts were made and advice was sought from the FDA.

2.2 Nonclinical safety pharmacology and toxicology of semaglutide

2.2.1 Safety pharmacology

Semaglutide was investigated in a standard series of dedicated safety pharmacology studies assessing acute effects on the central nervous system, the cardiovascular system and on respiratory and renal functions. These studies raised no safety concerns.

2.2.2 General toxicity and carcinogenicity

The general toxicity of semaglutide was assessed after s.c. administration to rats and cynomolgus monkeys for up to 26 and 52 weeks, respectively. The potential for carcinogenicity was evaluated in a standard set of genotoxicity studies and in 2-year carcinogenicity studies in mice and rats.

Semaglutide mainly caused effects considered to be related to activation of the GLP-1 receptor. The dose limiting effects in the studies were pharmacology mediated reductions in food consumption and initial body weight loss, with subsequent reductions in body weight gain. Semaglutide was not genotoxic.

Thyroid

Consistent with other GLP-1 RAs, semaglutide-induced hyperplasia and neoplasia in C-cells (parafollicular cells) of the thyroid in the 2-year carcinogenicity studies performed in mice and rats. The C-cell changes are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive.[66] No C-cell changes were observed in cynomolgus monkeys dosed with semaglutide for up to 52 weeks, and no cases of medullary thyroid carcinoma (MTC) were observed in the clinical trials with semaglutide (Section 9.6). Published data have shown that the GLP-1 receptor is not expressed in normal human thyroid C-cells or in C-cells of monkeys.[67, 68] Based on the totality of the data, the human relevance of the rodent C-cell findings is considered to be low.

2.2.3 Reproductive and developmental toxicity

Reproductive toxicity has been observed in animal studies for the currently marketed GLP-1 RAs, and therefore the GLP-1 RAs are generally not recommended for use during pregnancy. The potential for semaglutide to affect reproduction and development was investigated in rats, rabbits and cynomolgus monkeys.

In rats, semaglutide caused reductions in embryonic survival and growth at clinically relevant exposures. In fetuses, major skeletal and visceral malformations were observed, including effects on long bones, ribs, vertebrae, tail, major blood vessels and brain ventricle dilatation. Mechanistic evaluations indicated that the embryotoxicity involved a GLP-1 receptor mediated impairment of the nutrient supply to the embryo across the inverted yolk sac during a period of organogenesis when the inverted yolk sac function is critical for embryonic nutrition. Due to species differences in yolk sac anatomy and function, and due to the absence of GLP-1 receptor expression in cynomolgus monkey yolk sac, this mechanism is unlikely to be of relevance to humans. In rabbits and monkeys, an increase in early pregnancy losses and sporadic fetal abnormalities were observed at clinically relevant exposures (rabbit) and ≥5-fold the clinical exposures (monkey). These findings were considered incidental or secondary to the large maternal body weight loss.

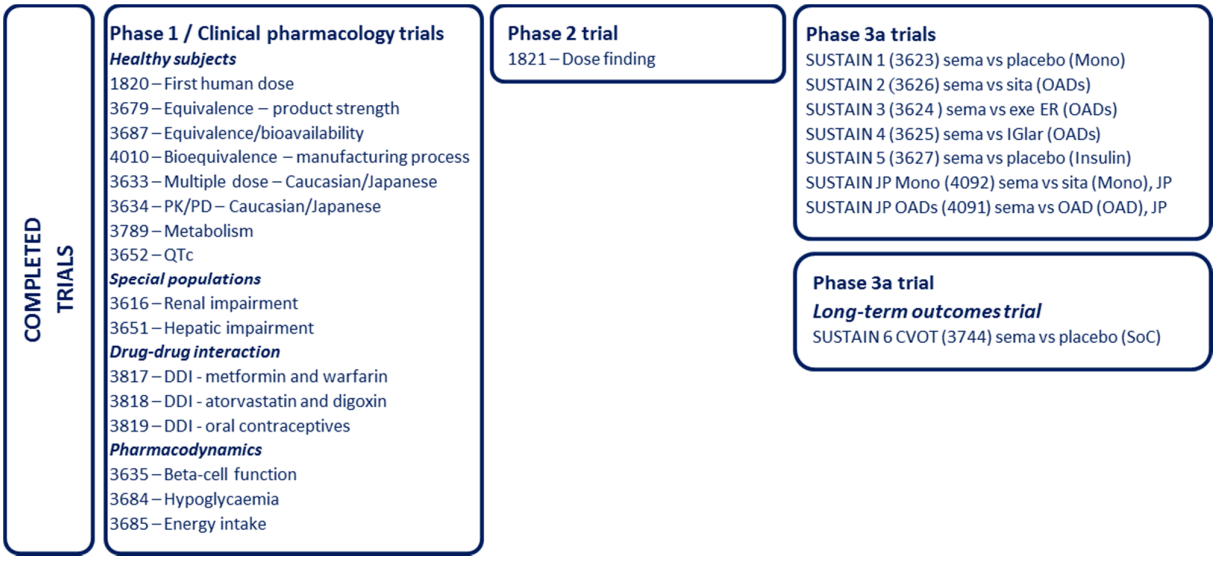
Overall, risk of embryotoxicity in humans cannot be entirely excluded, and consistent with other GLP-1 RAs semaglutide is not recommended for use during pregnancy, see Section 9.10.

3 Overview of clinical development of semaglutide s.c. once-weekly

Summary

- A comprehensive global clinical program was conducted for semaglutide. The trials were designed to provide results applicable to a broad T2D population including the elderly, patients with renal impairment, and patients at high cardiovascular risk.

The semaglutide application was based on 25 completed trials with semaglutide s.c. once-weekly including 16 phase 1 clinical pharmacology trials, one phase 2 dose-finding trial, and eight phase 3a trials (including the 2-year CVOT) (Figure 4). A total of 9,384 individuals, of whom 5,710 were exposed to semaglutide and 3,674 to comparators/placebo, were included in the clinical program. Approximately 1/3 of the total population was recruited from sites in the US. Details on the phase 3a trials are provided in Section 5 and Appendix 1.



Note: For the phase 3a trials, trial ID and background anti-glycemic treatments are indicated in parentheses.
Abbreviations: CVOT: cardiovascular outcomes trial; DDI: drug-drug interaction; Exe ER: exenatide extended release; IGlar: insulin glargine; JP: Japanese; Mono: monotherapy; OADs: oral anti-glycemic drugs; PD: pharmacodynamic; PK: pharmacokinetic; Sita: sitagliptin; SoC: standard-of-care.

Figure 4 Semaglutide development program: Overview of completed clinical trials

4 Clinical pharmacology

Summary

- Semaglutide has pharmacokinetic properties compatible with once-weekly administration with a median time to maximum concentration (t_{max}) of 1−3 days and an elimination half-life ($t_{½}$) of approximately 1 week.
- Semaglutide steady state exposure was dose-proportional, similar between injection sites, and the within- and between patient variability was low.
- All patients, irrespective of sex, age, race, ethnicity, body weight and renal or hepatic impairment should be dosed in accordance with the proposed dosing regimen for semaglutide.
- No clinically relevant pharmacokinetic drug-drug interactions were observed with semaglutide.
- Semaglutide did not prolong QTc intervals.
- Semaglutide lowered fasting and postprandial blood glucose by enhancing glucose-dependent stimulation of insulin secretion from the β-cells and by reducing glucagon secretion from the α-cells.
- During induced hypoglycemia, semaglutide did not alter the counter regulatory responses of increased glucagon.
- The mechanism of semaglutide-induced body weight loss was lowered appetite and energy intake. The semaglutide-induced weight loss was primarily from fat tissue.
- Semaglutide lowered postprandial lipid response.

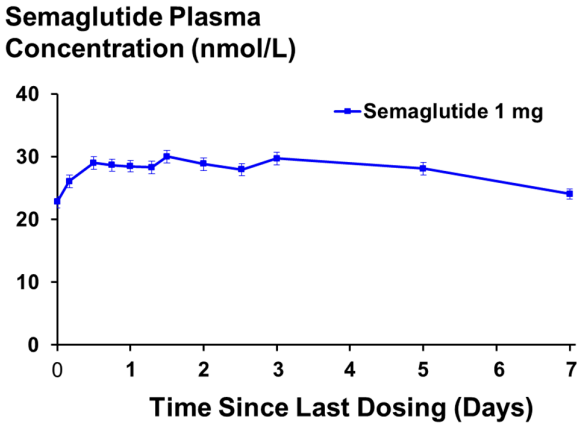
4.1 Pharmacokinetic and –dynamic properties of semaglutide

The pharmacokinetic (PK) and pharmacodynamic (PD) properties of semaglutide administered s.c. once-weekly were evaluated in a comprehensive clinical pharmacology program including 16 trials.

Pharmacokinetic properties of semaglutide

Semaglutide has pharmacokinetic properties compatible with once-weekly administration. The pharmacokinetic profile during a dosing interval at steady state was relatively flat with low fluctuations between trough and maximum concentrations and with a median time to maximum concentration (t_{max}) of 1 to 3 days after dosing (Figure 5). In addition, the elimination half-life ($t_{½}$) was approximately 1 week. The prolonged exposure to semaglutide is the result, in part, of the extensive binding of semaglutide to plasma albumin (>99%).

Steady-state exposure was achieved following 4 to 5 weeks of once-weekly administration. The steady state exposure of semaglutide was dose-proportional. In patients with T2D, the mean weekly steady state concentrations following s.c. administration of 0.5 mg and 1 mg semaglutide were approximately 65.0 ng/mL (16 nmol/L) and 123.0 ng/mL (30 nmol/L), respectively. The within- and between patient variability was low (less than 10% and 27%, respectively).



Note: Semaglutide mean (geometric) plasma concentration +/- standard error in patients with T2D (N=36).
Abbreviations: N: number of patients; T2D: type 2 diabetes mellitus.

Figure 5 Pharmacokinetic profile during a semaglutide 1 mg dosing interval at steady state in patients with T2D

Population-pharmacokinetic analyses of phase 3a data showed that exposure was similar among injection sites supporting that different injection sites (thigh, abdomen, and upper arm) can be used interchangeably. In addition, semaglutide steady state exposure was not influenced by the presence of anti-semaglutide antibodies, which appeared in 1−2 % of the patients in the phase 3a trials.

Based on dedicated trials in subjects with various degrees of renal and hepatic impairment and a population pharmacokinetic analysis, no dose adjustment is needed for semaglutide for any patients with T2D, irrespective of sex, age, race, ethnicity, body weight and renal or hepatic impairment . Consistent with other GLP-1 RAs, body weight was the only intrinsic factor assessed to be of importance for semaglutide exposure, with increasing body weight resulting in lower exposure. However, in the exposure range associated with semaglutide 0.5 mg and 1 mg, patients, independent of body weight, achieved a clinically relevant HbA_{1c} lowering effect.

As expected for a protein-based compound, semaglutide does not have any effect on the activity of drug metabolizing cytochrome P450 enzymes and drug transporters *in vitro* and, accordingly, the potential for classical pharmacokinetic drug-drug interactions is low. The minor delay of gastric emptying with semaglutide may influence the absorption of concomitantly administered oral medicinal products. However, no clinically relevant pharmacokinetic drug-drug interactions were observed between semaglutide and any of the orally administered compounds tested (metformin,

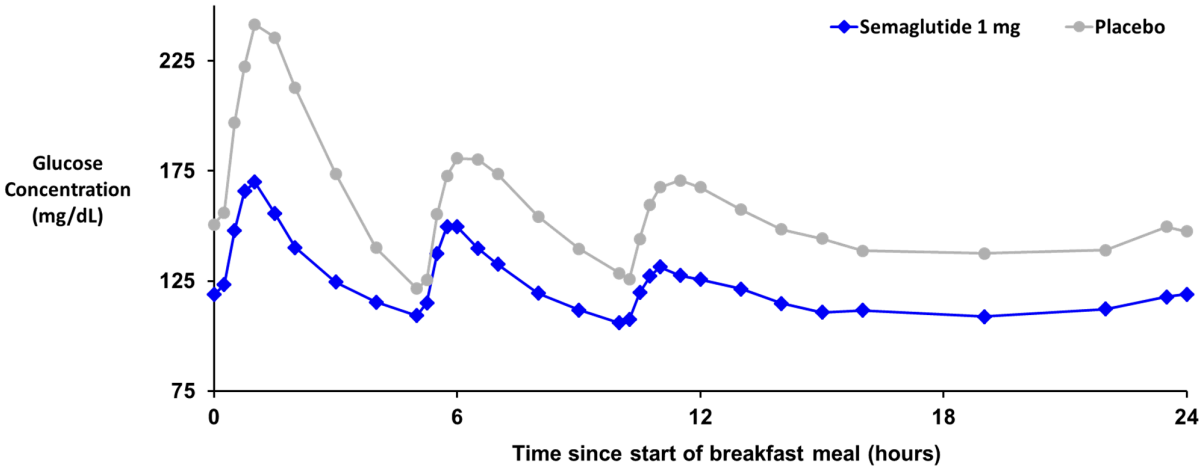
warfarin, digoxin, atorvastatin or oral contraceptive combination drug) and thus, no dose adjustments of the orally administered drugs are required.

Cardiac repolarization by QT interval evaluation

Semaglutide did not prolong QTc intervals at therapeutic nor at supra-therapeutic dose levels (1.5 mg steady state) as assessed in a dedicated thorough QTc trial, consistent with other drugs in the GLP-1 RA drug class.[69, 70]

Pharmacodynamic profile of semaglutide

The pharmacodynamic profile of semaglutide were evaluated in a dedicated series of studies, and were performed after 12 weeks of treatment (including 4-week dose escalations) at steady state with semaglutide 1 mg. Semaglutide treatment, as compared with placebo, lowered fasting and postprandial plasma glucose concentrations (Figure 6) by enhancing glucose-dependent stimulation of insulin secretion from the β-cells and by reducing glucagon secretion from the α-cell. This resulted in a substantial reduction in 24-hour glucose exposure in semaglutide-treated patients. At steady state, semaglutide 1 mg caused a minor delay of early postprandial gastric emptying, reducing the rate at which glucose appeared in the circulation postprandially.



Note: Mean plasma glucose profiles after standardized meals at steady state after 12 weeks of treatment with semaglutide 1 mg. N(semaglutide)=36; N(placebo)=38
Abbreviations: N: number of patients; sema: semaglutide; T2D: type 2 diabetes mellitus.

Figure 6 24-hour glucose profiles at steady state in patients with T2D

During induced hypoglycemia, semaglutide did not alter the counter regulatory responses of increased glucagon when compared with placebo, and did not impair the decrease of C-peptide.

Semaglutide lowered fasting triglycerides (12%) and VLDL cholesterol concentrations (21%), as compared to placebo. Fasting HDL, LDL and total cholesterol concentrations were similar with

semaglutide and placebo. The postprandial triglycerides, VLDL cholesterol and ApoB48 response to a high fat meal was reduced by 40% or more.

Semaglutide induced weight loss (4–5 kg after 12 weeks treatment), primarily from fat tissue (3-fold larger loss of fat mass versus lean body mass), as assessed by air displacement plethysmography.[71, 72] The mechanism of body weight loss was decreased appetite, leading to lower daily energy intake (24% decrease) while there was no evidence that semaglutide increased energy expenditure. In addition to a semaglutide-induced suppression of appetite in the fasting state and postprandially, semaglutide also improved perceived control of eating as it was associated with less food cravings and a relative lower preference for high fat foods. There were no indications of food aversion with semaglutide or difference versus placebo in nausea ratings during the meals being responsible for the markedly reduced energy intake with semaglutide.

To further assess glucose metabolism, including β-cell function, measurements of fasting glucose, insulin, glucagon and 7-point glucose profiles, β-cell function (HOMA-B and pro-insulin/insulin ratio) and insulin resistance (HOMA-IR) were performed in the phase 3a trials. The beneficial effects of semaglutide on glycemic metabolism, including β-cell function, and body weight observed in the clinical pharmacology program were confirmed in the phase 3a trials. In addition, data from the phase 2 trial showed that semaglutide lowered fasting glucose with onset after the initial dose.

4.2 Exposure-response analyses

Semaglutide 0.5 and 1 mg are the proposed maintenance doses for use in patients with T2D. Robust dose-response relationships for efficacy (HbA_{1c} and body weight) and tolerability (gastrointestinal adverse events), were established in patients with T2D in phase 3a trials (see Sections 6.2, 6.3 and 9.4). The relationships were supported by analyses using exposure-response models on data from four phase 3a trials (SUSTAIN 1–3 and SUSTAIN JP OADs) using the average semaglutide plasma concentration (C_{avg}) as the exposure variable.

The change from baseline in HbA_{1c} was exposure-dependent, and the relationship was similar in males and females and across subgroups of body weight, age, race, ethnicity, diabetes duration and renal function. A consistent increase in effect was observed across the concentration range associated with 0.5 mg and 1 mg semaglutide at steady state (~10–50 nmol/L). The increase in semaglutide concentrations associated with increasing the dose from 0.5 to 1 mg provides an additional improved glycemic response; on average an HbA_{1c} reduction of 0.27%-points.

5 Phase 3a program

Summary

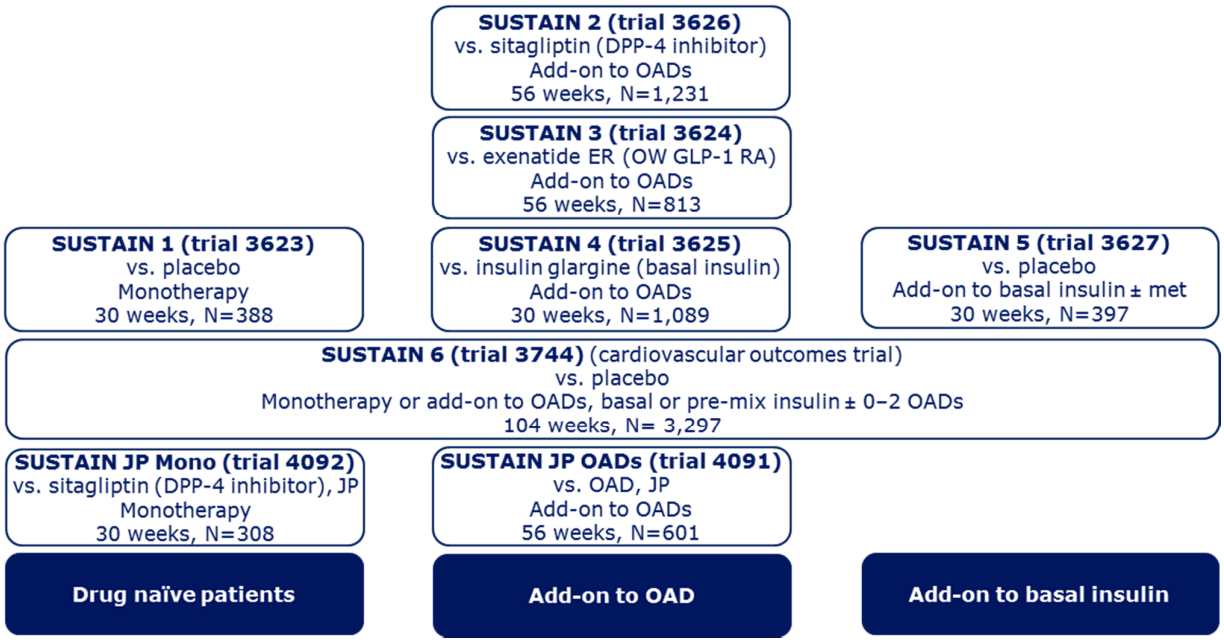
- The phase 3a clinical program covered use of semaglutide in a broad T2D population, with clinical characteristics covering the continuum of T2D care.
- Semaglutide was investigated versus placebo when administered as monotherapy and as combination therapy with basal insulin.
- Semaglutide was investigated versus relevant marketed anti-glycemic drugs (sitagliptin, exenatide ER and insulin glargine) when administered as combination therapy with oral anti-glycemic drugs.
- The semaglutide phase 3a program included a cardiovascular outcomes trial (CVOT) conducted to fulfill the regulatory requirement to assess cardiovascular safety of semaglutide compared to placebo. The design and execution of the trial were in accordance with guidelines and recommendations from FDA.[5]
- The analyses of glycemic efficacy were primarily based on the five key efficacy trials (SUSTAIN 1–5), according to pre-specified statistical analyses, and supported by data from SUSTAIN 6 (CVOT) and two Japanese trials.
- Evaluation of the effect of semaglutide on cardiovascular safety was primarily based on SUSTAIN 6 (CVOT).
- SUSTAIN 6 (CVOT) accounted for approximately 50% of the total exposure to semaglutide in the clinical development program, and was a key contributor to the safety analyses providing 2-year safety data.

5.1 Overview of phase 3a program

The trials in the semaglutide phase 3a program (denoted SUSTAIN) compared the therapeutic response to semaglutide to that of placebo and/or a specific active comparator drug, each trial thus providing independent evidence of the effect of semaglutide utilized in different treatment regimens appropriate for different stages of T2D (Figure 7). Semaglutide was investigated versus placebo when administered as monotherapy in drug-naïve patients and as combination therapy with basal insulin. Semaglutide as combination therapy with oral anti-glycemic drugs was investigated in head-to-head trials versus the most relevant active comparators available at the time of the program planning including sitagliptin, exenatide ER and insulin glargine, see Section 5.4 for details. In addition, a dedicated head-to-head trial versus dulaglutide, the currently most used OW GLP-1 RA, has recently been finalized as part of the semaglutide phase 3b program.[12]

The semaglutide phase 3a program included five pivotal controlled trials (SUSTAIN 1–5), referred to as the key efficacy trials, all with a primary objective to evaluate the effect of semaglutide on glycemic control. These efficacy data are supported by SUSTAIN 6 (CVOT) (see below) and two Japanese phase 3a trials (SUSTAIN JP Mono and SUSTAIN JP OADs) referred to as the 'Japanese trials'. In accordance with the requirements in the Japanese diabetes guideline[13] these trials were designed with the primary objective to evaluate the safety of semaglutide for treatment of T2D in Japanese patients. However, the major trial design features of the Japanese trials were identical to those of SUSTAIN 1–5.

The semaglutide phase 3a program also included a long-term (104-week) cardiovascular outcomes trial, referred to as SUSTAIN 6(CVOT).[5] SUSTAIN 6 (CVOT) was designed as a double-blind, placebo-controlled trial evaluating the cardiovascular safety of semaglutide versus placebo in patients with T2D and established cardiovascular disease or evidence of cardiovascular risk factors (see Section 7). Both semaglutide and placebo were used in addition to standard-of-care therapy and the trial had secondary endpoints related to long-term glycemic control, weight loss, and microvascular complications including nephropathy and diabetic retinopathy, as well as long-term safety. SUSTAIN 6 (CVOT) accounted for approximately 50% (2,932 PYE/ 5,644 PYE) of the total exposure to semaglutide in the clinical development program.



Abbreviations: Exe ER: exenatide extended release; DPP-4: dipeptidyl peptidase-4; GLP-1 RA: glucagon-like peptide-1 receptor agonist; JP: Japan; met: metformin; N: number of patients; OAD: oral anti-glycemic drug; OW: once-weekly.

Figure 7 Phase 3a program: Development program covers the continuum of T2D therapy

The trial design and results of several of the phase 3a trials are described in peer-reviewed, published journal articles: SUSTAIN 1[73] SUSTAIN 2[74, 75], SUSTAIN 4[76, 77], SUSTAIN 6 (CVOT),[78] and SUSTAIN JP Mono.[79]

5.2 Key features of the trial designs

All phase 3a trials were randomized, parallel group, multi-center trials. There was no washout or discontinuation of previous background medication prior to randomization. The trials were designed for complete follow-up on patients who discontinued treatment prematurely, ensuring that data collection continued in these patients for the full duration of the trials to minimize missing data, with patients who withdrew their informed consent or were lost to follow-up as the only exception.

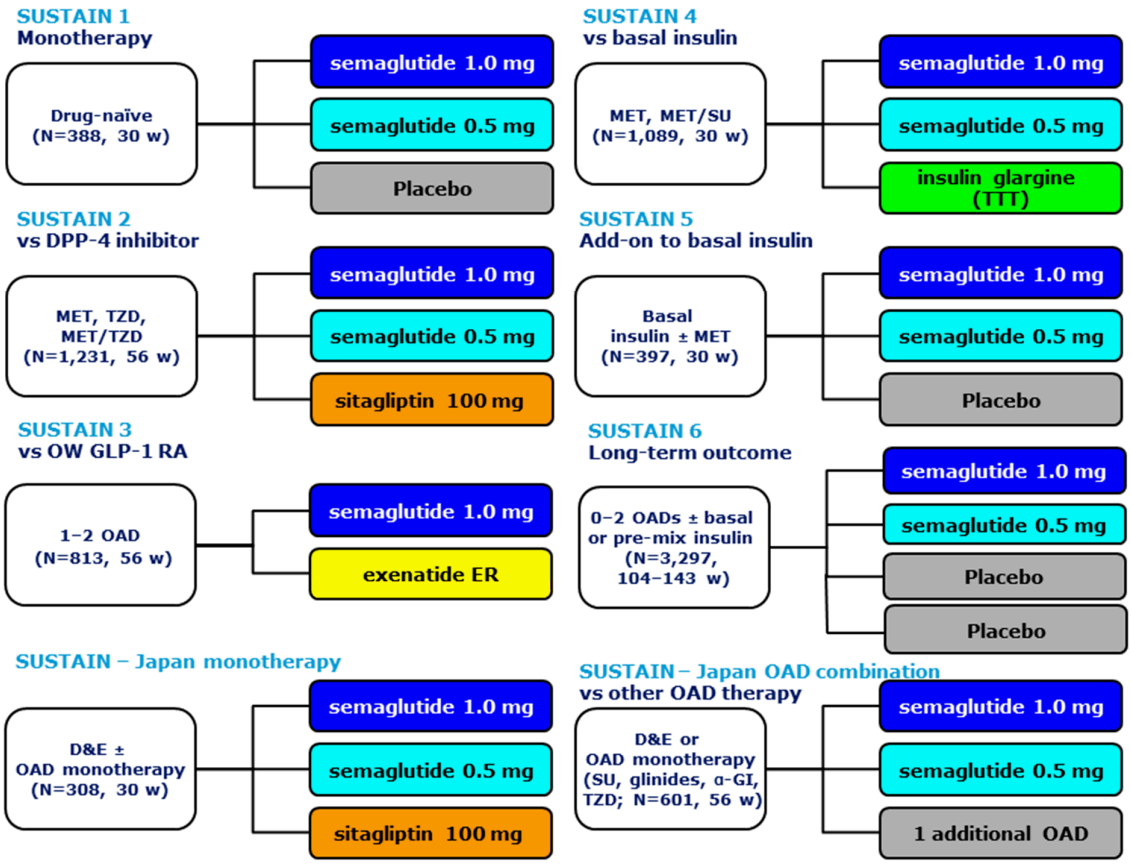
The main design and trial procedures were very similar and aligned across all phase 3a trials (except the CVOT), but differed in the required diabetes background medication, comparators, and length of treatment periods. An overview of the major trial design features of the phase 3a trials is provided in Figure 8 and designs are presented in detail in Appendix 1, Section 1.

Trial durations

The duration of treatment in the phase 3a trials ranged from 30 to 104 weeks. A 30 week maintenance treatment period, which is adequate to demonstrate the maximal treatment effect of semaglutide on glycemic control, was applied in three of the five key efficacy trials; SUSTAIN 1 (semaglutide vs. placebo [Mono]), SUSTAIN 4 (semaglutide vs. insulin glargine [OADs]) and SUSTAIN 5 (semaglutide vs. placebo [insulin]). To provide evidence of sustained efficacy on change in HbA_{1c} and to support the conclusions on reductions in body weight and long-term safety, SUSTAIN 2 (semaglutide vs. sitagliptin [OADs]) and SUSTAIN 3 (semaglutide vs. exenatide ER [OADs] had a 56-week treatment duration. The placebo-controlled CVOT (SUSTAIN 6) had a duration of treatment of 2 years (104 weeks) to evaluate persistency in effect, provide long-term safety exposure and to observe an adequate number of MACEs to fulfill the primary objective of the trial.

Semaglutide doses

The selection of doses used in the phase 3a program was determined by data from the phase 2 dose-finding trial. Doses were selected based on pre-defined criteria: i) the lowest dose had to be at least 0.5 %-point better than placebo on HbA_{1c} change from baseline, ii) the increments between the two doses had to support a clinically meaningful separation on glycemic control with a ΔHbA_{1c} $\geq$0.3 %-point difference between doses when evaluating data from patients that completed the treatment, iii) both doses had to be well-tolerated. The results and the model-estimated results predicted that the 1 mg semaglutide dose had the near maximal effect on HbA_{1c}. Based on these predicted responses both semaglutide 0.5 mg and 1 mg met the pre-specified criteria for an acceptable efficacy-tolerability ratio, supporting both doses for further evaluation in the phase 3a program.



Abbreviations: D&E: Diet and exercise; DPP-4: dipeptidyl peptidase-4; ER: extended release; GLP-1: glucagon-like peptide-1; MET: metformin; N: number of randomized patients; OAD: oral antiglycemic drugs; OW: once-weekly; SU: sulfonylurea; TTT: treat-to-target; TZD: thiazolidinediones; w: week; α-GI: alpha-glucosidase inhibitor.

Figure 8 Phase 3a program: Overview of trial designs

The two maintenance doses of semaglutide (0.5 and 1 mg) were tested in all phase 3a trials to provide comparative safety and efficacy, except in SUSTAIN 3, where only the highest maintenance dose of 1 mg was used to allow a direct comparison with the maximum exenatide ER dose of 2 mg.

To mitigate gastrointestinal side effects, all semaglutide-treated patients in the phase 3a program followed a fixed gradual dose-escalation regimen starting at 0.25 mg for 4 weeks before escalating to 0.5 mg as maintenance dose or for additional 4 weeks before escalating to 1 mg maintenance dose.

Blinding

The phase 3a trials were blinded to the extent possible, based on the nature of the comparators to ensure the best possible basis for unbiased interpretation.

Placebo-controlled trials (SUSTAIN 1, SUSTAIN 5 and SUSTAIN 6 [CVOT]) were double-blinded, consistent with standard of research and regulatory guidance. Double-blinding was obtained within volume of injection/dose groups (0.5 mg and 1 mg). No blinding of dose volume was performed (0.5 mg vs. 1 mg or corresponding volume of placebo); thus trial participants were blinded with respect to semaglutide vs. placebo/comparators, but not to which dose level (volume) they received. A double-blind trial design was attained in SUSTAIN 2 (semaglutide vs. sitagliptin [OADs]) via a double-dummy treatment scheme.

An open-label trial design was necessary for some trials. SUSTAIN 4 (semaglutide vs. insulin glargine [OADs]) was conducted as an open-label trial due to the complexity of blinding of insulin given the need to titrate insulin dose. Due to the complexity of preparing a placebo version of exenatide ER, the once-weekly GLP-1 RA comparator trial (SUSTAIN 3) was conducted as an open-label trial. Both Japanese trials used an open-label trial design in line with the Japanese guidelines.[13]

Trial governance

The SUSTAIN program was conducted by Novo Nordisk and was governed by internal and external committees as presented below.

An independent external data monitoring committee (DMC) was established for SUSTAIN 6 (CVOT) to monitor the safety of the patients and perform ongo ing evaluation of safety and effectiveness data. The DMC was composed of permanent members whose expertise covered relevant specialties including cardiology, endocrinology, gastroenterology , and statistics. The DMC received unblinded data from an external independent statistical consultant at predefined time points and *ad-hoc* in accordance with written guidelines. During SUSTAIN 6 (CVOT), the DMC provided recommendations on trial continuation, modification, or termination to the internal Novo Nordisk safety committee. These procedures ensured adequate monitoring of patients' safety including cardiovascular safety while maintaining MACE reports blinded to Novo Nordisk. The written guideline, i.e., the DMC charter, was developed in collaboration between the DMC and Novo Nordisk.

An independent external event adjudication committee (EAC) was constituted to perform ongoing blinded adjudication on selected medical events of special interest according to pre-defined diagnostic criteria in all semaglutide phase 3a trials, see Appendix 2. The purpose of the adjudication was to confirm events in a consistent manner according to standardized criteria using independent external medical experts. The EAC was composed of 18 permanent members covering required medical specialties, who were board certified within cardiology, neurology, oncology, endocrinology, gastroenterology, nephrology and ophthalmology. The following events were adjudicated: fatal events, acute coronary syndrome (myocardial infarction or unstable angina pectoris), cerebrovascular event (stroke or transient ischemic attack), hospitalization for heart failure, coronary revascularization procedures, pancreatitis, neoplasm (malignant or benign) and

thyroid disease if suspected to be a thyroid neoplasm or if requiring thyroidectomy. In addition, events of nephropathy and diabetic retinopathy were adjudicated in SUSTAIN 6 (CVOT). The EAC worked in accordance with written guidelines in the EAC charter. Adjudication was performed using common process for data and source document collection and common charter definitions for each type of event adjudicated. The EAC had no authorization to impact the trials including trial conduct, trial protocol or amendments.

An independent committee of external thyroid experts was responsible for monitoring calcitonin during the trials at regular intervals. The committee provided recommendations to the investigators with regard to further investigation and treatment of individual patients with clinically relevant abnormal calcitonin values. The Calcitonin Monitoring Committee worked in a blinded manner.

An internal Novo Nordisk Safety Committee was responsible for the overall safety surveillance across all semaglutide clinical trials. The Safety Committee worked in a blinded manner.

5.3 Trial population

The phase 3a trials studied 8,093 patients of whom 4,792 patients received at least one dose of semaglutide (Table 4). A total of 3,301 patients were included in comparator groups including 1,906 in placebo groups and 1,395 in active comparator groups (Exe ER: 405; IGlar: 360; sitagliptin: 510, other OAD: 120).

Table 4 Trials in phase 3a program: Number of patients randomized and exposed

	Total		Semaglutide	
	Randomized	Exposed	Randomized	Exposed
SUSTAIN 1-5 (Key efficacy trials)	3,918	3,899	2,473	2,465
SUSTAIN 6 (CVOT)	3,297	3,286	1,648	1,642
Phase 3a program incl. SUSTAIN 6 (CVOT), SUSTAIN JP Mono and SUSTAIN JP OAD	8,124	8,093	4,806	4,792

Exposure was extensive as the trial duration for individual patients was set to a minimum of 30 weeks and up to 2 years allowing for a robust efficacy and safety evaluation. A total of 1,321 patients were exposed to semaglutide for 18 months or longer.

The total phase 3a exposure to semaglutide was 5,644 patient years of exposure (PYE); 2,712 PYE in the combined SUSTAIN 1–5 and the Japanese trials, and 2,932 PYE in SUSTAIN 6 (CVOT).

No patients from the United States (US) were enrolled in SUSTAIN 2 nor in the two Japanese trials. Across the remaining phase 3a trials, patients from the US constituted between 32.0% and 45.7% of the patients (27.8% in average across all trials) (Table 6). Patients from the US represented 92.7% of patients from the region 'North America' (US+Canada).

Altogether, the semaglutide exposure is large enough to evaluate the semaglutide efficacy and safety profile in the target populations and exceeds the exposure requirements in guidance documents.[80-82]

Patient population in phase 3a program

The completed phase 3a trials, including SUSTAIN 6 (CVOT), cover the spectrum of potential use scenarios of semaglutide in adult patients with T2D, from treatment initiation in patients who are drug-naïve to treatment intensification in patients treated with metformin, SU and/or insulin. Patient selection criteria were chosen to reflect real-life scenarios and were sufficiently broad to allow enrolment of patients with comorbidities representative for T2D (see Appendix 1, Section 2 for a complete overview of inclusion and exclusion criteria).

An important strength of the semaglutide program is the heterogeneity of the population studied, which encompassed a broad range of patients in terms of age, race, regions, duration of diabetes, comorbidities, and level of HbA_{1c} control at baseline. The phase 3a program (incl. SUSTAIN 6 [CVOT]) included a broad T2D population with an age span including patients up to 89 years and a wide range of renal function (normal as well as mild, moderate and severe impairment). The majority of patients were overweight (BMI≥27 kg/m^2) or obese (BMI of ≥30 kg/m^2) at baseline and common comorbidities were well-represented. None of the trials enrolled pediatric or adolescent patients (<18 years of age). In line with other GLP-1 RAs, patients with a personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2) were excluded from all trials.

Patient population in SUSTAIN 6 (CVOT)

The effect of semaglutide on cardiovascular outcomes was investigated in a T2D population (>50 years) with established cardiovascular disease or evidence of cardiovascular risk factors (Table 5). Patient selection criteria applied in SUSTAIN 6 (CVOT) were sufficiently broad to cover the continuum of T2D care (no upper HbA_{1c} limit) and allow enrolment of patients with T2D at high cardiovascular risk excluding only patients unlikely to complete the trial due to pre-existing clinical conditions (e.g., patients with chronic heart failure New York Heart Association (NYHA) class IV, continuous renal replacement therapy, end-stage liver disease, or treatment-requiring malignant neoplasms).The SUSTAIN 6 (CVOT) key inclusion and exclusion criteria are shown in Table 5; see Appendix 1, Section 2 for a complete overview of inclusion and exclusion criteria.

Table 5 SUSTAIN 6 (CVOT): Key inclusion and exclusion criteria

Key inclusion criteria
• Men and women with type 2 diabetes • Established cardiovascular disease (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic heart failure of NYHA class II-III, or chronic kidney disease [eGFR < 60 mL/min/1.73 m^2]) and age ≥ 50 years. OR Cardiovascular risk factors (persistent micro-albuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction or an ankle-brachial index <0.9) and age ≥ 60 years. • Anti-glycemic drug naïve, or treated with 1 or 2 OAD(s), or treated with human NPH insulin or long-acting insulin analogue or pre-mixed insulin, alone or in combination with 1 or 2 OAD(s). • HbA_{1c} ≥7.0%.
Key exclusion criteria
• Type 1 diabetes. • Use of a GLP-1 RAs (exenatide, liraglutide or other), or pramlintide or insulin other than basal and pre-mixed insulin within 3 months prior to screening and dipeptidyl peptidase 4 (DPP-4) inhibitors within 1 month prior to screening. • A familial or personal history of multiple endocrine neoplasia type 2 or medullary thyroid cancer. • Acute coronary or cerebrovascular event within 3 months prior to randomization.

Abbreviations: DPP-4: dipeptidyl peptidase 4; eGFR: estimated glomerular filtration rate; GLP-1 RAs: glucagon-like peptide-1 receptor agonists; HbA_{1c}: glycosylated hemoglobin; NPH: neutral protamine Hagedorn; NYHA: New York Heart Association; OADs: oral antiglycemic agents.

Baseline characteristics in phase 3a program including SUSTAIN 6 (CVOT)

Demographics, medical history, and concomitant illness were collected at screening in all trials. Within all trials, patients randomized to semaglutide or placebo/active comparators were well-matched with respect to demographics and baseline characteristics. Consistent with the intended treatment cascade of the T2D population, the mean diabetes duration and baseline HbA_{1c} levels differed for the phase 3a trials; patients in SUSTAIN 1 (semaglutide vs. placebo [Mono]) had the shortest disease duration and lower HbA_{1c} levels while patients in SUSTAIN 5 (semaglutide vs. placebo [insulin]) had the longest disease duration and higher baseline HbA_{1c} levels (Table 6). The mean HbA_{1c}, duration of diabetes and mean age were higher for the SUSTAIN 6 (CVOT) population as compared to the remaining phase 3a trials (phase 3a pool). The phase 3a program included a sizeable number of elderly patients (baseline age of 75 years or above); 477 patients (phase 3a pool: 156 patients; SUSTAIN 6 [CVOT]: 321 patients) of whom 259 patients were exposed to semaglutide. In SUSTAIN 6 (CVOT), a substantial proportion (1598 patient, 48.5%) of the patients enrolled was 65 years of age or above, yielding a sufficient number of elderly patients based on current guideline recommendations.[81, 82] In SUSTAIN 6 (CVOT), 83% of patients had clinical evidence of cardiovascular disease and a total of 17% of semaglutide-treated patients had chronic heart failure characterized as NYHA class II or III at baseline, see Section 7.4 for details. SUSTAIN 6 (CVOT) included patients with different degrees of renal impairment (70% of patients had some degree of renal impairment) and was the only phase 3a trial that allowed patients with

Table 6 Trials in phase 3a program: Demographics and baseline characteristics

Trial/ Characteristic	Key efficacy trials					CVOT	Japanese trials	
	SUSTAIN 1 N: 387	SUSTAIN 2 N: 1,225	SUSTAIN 3 N: 809	SUSTAIN 4 N: 1,082	SUSTAIN 5 N: 396	SUSTAIN 6 N: 3,297	SUSTAIN JP Mono N: 308	SUSTAIN JP OADs N: 600
Sex (%, men/women)	54/ 46	51/ 49	55/ 45	53/ 47	56/ 44	61/ 39	76/ 24	71/ 29
Age (years) (min-max)	53.7 (18−88)	55.1 (23−83)	56.6 (20−83)	56.5 (22−82)	58.8 (19−86)	64.6 (50−89)	58.3 (22−83)	58.5 (26−83)
Patients from US (%)	124 (32.0%)	None	313 (38.7%)	495(45.7%)	180 (45.5%)	1,137 (34.5%)	NA	NA
Race (%, White/ Black or Afr.Am/ Asian)	64/ 8/ 21	69/ 5/ 25	84/ 7/ 2	77/ 9/ 11	77.5/ 5/ 17	83/ 7/ 8	0/ 0/ 100	0/ 0/ 100
Ethnicity (%, Hisp or Lat/ not Hisp or Lat)	30/ 70	17/ 83	24/ 76	20/ 80	12/ 88	15.5/ 84.5	0/ 100	0/ 100
HbA_{1c} (%) (min-max)	8.05 (6.40-10.30)	8.07 (5.90-11.40)	8.35 (6.50−11.20)	8.17 (5.50-11.70)	8.37 (6.80-11.10)	8.70 (5.90−17.90)	8.15 (6.70-11.20)	8.09 (6.70−13.10)
Diabetes duration (years) (min-max)	4.18 (0.10-34.50)	6.58 (0.30-39.20)	9.21 (0.30-54.00)	8.57 (0.20-59.90)	13.32 (0.44-39.58)	13.90 (0.10−53.90)	7.97 (0.15-41.89)	8.85 (0.13−41.71)
Body weight (kg) (min-max)	91.93 (39.80-185.3)	89.48 (43.6-167.0	95.79 (49.90-198.3)	93.45 (43.00-187.8)	91.70 (47.50−165.6)	92.09 (40.7-216.8)	69.34 (39.10-129.4)	71.53 (39.50−142.0)
BMI (kg/m^2) (min-max)	32.93 (16.35−71.80)	32.46 (19.00-56.44)	33.76 (21.05-72.84)	33.01 (19.15-62.46)	32.18 (19.48-51.64)	32.80 (17.63−77.66)	25.43 (17.15-42.89)	26.41 (16.31−53.47)
Normal renal function: eGFR ≥90 mL/min/1.73 m^2 N (%))	247 (63.8)	803 (65.6)	518 (64.0)	652 (60.3)	201 (50.8)	990 (30)	202 (65.6)	412 (68.7)
Mild renal impairment: eGFR 60−<90 mL/min/1.73 m^2 (N (%))	121 (31.3)	418 (34.1)	290 (35.8)	378 (34.9)	160 (40.4)	1,368 (41.5)	106 (34.4)	176 (29.3)
Moderate renal impairment: eGFR 30−<60 mL/min/1.73 m^2 (N (%))	19 (4.9)	3 (0.2)	NA	52 (4.8)	35 (8.8)	832 (25.2)	NA	12 (2.0)
Severe renal impairment: eGFR 15−<30 mL/min/1.73 m^2 (N (%))	NA	NA	NA	NA	NA	95 (2.9)	NA	NA
End stage renal impairment: eGFR <15 mL/min/1.73 m^2 (N (%))	NA	NA	NA	NA	NA	12 (0.4)	NA	NA

Abbreviations: Afr.Am: African American; BMI: Body mass index; CVOT: Cardiovascular outcomes trial; eGFR: estimated glomerular filtration rate; FAS: full analysis set; Hisp or Lat: Hispanic or Latino; JP: Japan; Mono: monotherapy; N: Number of patients in FAS; OADs: oral antiglycemic agents; NA: Not applicable.

severe renal impairment (95 patients, 2.9%) and end-stage renal disease (12 patients, 0.4%) to be enrolled.

Microvascular complications were present at baseline in a high proportion of patients enrolled in SUSTAIN 6 (CVOT); approximately 45% had pre-existing diabetic nephropathy (mainly based on chronic renal failure or micro-albuminuria), 30% had pre-existing diabetic retinopathy (mainly non-proliferative retinopathy), and 41% had pre-existing peripheral diabetic neuropathy.

The program represented a global population. Adequate exposure to semaglutide across races and ethnic groups was ensured by including patients from 45 countries. The majority of patients were White and of non-Hispanic or Latino ethnicity (Table 6). Patients of Hispanic or Latino ethnicity comprised up to 30% of the trial population and the most prevalent other racial groups such as African-American, Asian and native races were represented. Approximately 28% of the total population was recruited from sites in the US. In general, the baseline characteristics of the US trial population were consistent with the baseline characteristics of the non-US trial population. The racial distribution of patients differed in the US and non-US populations in accordance with the respective racial compositions of the regions in which the trials were conducted.

5.4 Anti-glycemic treatment

Background treatment

Semaglutide was evaluated as monotherapy in drug-naïve patients and in combination with the recommended and most frequently used anti-glycemic drugs, including metformin, sulfonylurea (SU), and basal insulin (Table 7). The clinical development program did not include dedicated clinical phase 3a trials investigating semaglutide as add-on to metformin or sulfonylurea (both as monotherapy), however these were addressed as part of the pre-defined analyses in SUSTAIN 2 (94% on metformin monotherapy) and SUSTAIN 6 (CVOT), respectively. In addition, a head-to-head trial versus dulaglutide, both administered as add-on to metformin, has been finalized after the NDA submission as part of the semaglutide phase 3b program.[12]

In SUSTAIN 6 (CVOT), semaglutide was evaluated as add-on to standard-of-care. Investigators were instructed to administer best-practice standard of care treatment in addition to trial product, with the objective to provide optimal treatment to manage the patient's diabetes and cardiovascular risk. Hence, SUSTAIN 6 (CVOT) included a mix of background treatments that covered the T2D treatment cascade.

Table 7 Trials in phase 3a program: Background anti-glycemic treatment at baseline

Trial	N	No background treatment	Metformin monotherapy	Metformin + SU	SU monotherapy	Basal insulin +/- OADs	Other (TZD)
SUSTAIN 1	387	99.7%	0%	0%	0%	0%	0.3%
SUSTAIN 2	1,225	0.1%	94.2%	0.2%	0%	0%	5.6% (a:5.4%)
SUSTAIN 3	809	0.1%	49.2%	45.1%	2.7%	0.1%	2.7% (a: 2.3%)
SUSTAIN 4	1,082	0%	48.2%	51.4%	0.2%	0%	0.2%
SUSTAIN 5	396	0%	0%	0%	0%	100%	0%
SUSTAIN 6 (CVOT)	3,297	1.6%	11.8%	22.1%	3.7%	58.0%	2.8% (a,b: 2.3%)
SUSTAIN JP Mono	308	100%	0%	0%	0%	0%	0%
SUSTAIN JP OADs	600	28.5%	0%	0%	28.3%	0%	43.2% (a:14.2%)

a) pioglitazone or pioglitazone hydrochloride. **b**) rosiglitazone.
Note: For the evaluation of efficacy in subgroups, the following treatment groups were combined: SU monotherapy, insulin monotherapy and combination therapy, and 'other'.
Abbreviations: CVOT: cardiovascular outcomes trials; FAS: full analysis set, JP: Japan; Mono: monotherapy; N: number of patients in FAS; OADs: oral anti-glycemic drugs; SU: sulfonylurea; TZD: thiazolidinediones.

Evaluation of the effect of semaglutide as add-on to SGLT-2 inhibitors was not part of the phase 3a program as no SGLT-2 inhibitor product was marketed at the time of design and initiation of the program (a few patients in SUSTAIN 6 (CVOT) had SGLT-2 inhibitors added as part of their standard-of-care treatment). A phase 3b trial evaluating semaglutide versus placebo as add on to a SGLT-2 inhibitor is currently ongoing. In addition, a dedicated head-to-head trial versus an SGLT-2 inhibitor (canagliflozin) is currently ongoing as part of the semaglutide phase 3b program.

Background medications were to be maintained at the stable, pre-trial dose and frequency during the treatment period in all trials except in SUSTAIN 6 (CVOT), where standard-of-care therapies could be adjusted during the trial as clinically indicated based on investigator assessment. Hence, other anti-glycemic, lipids- and blood pressure-lowering medications were administered and intensified in combination with semaglutide/placebo in SUSTAIN 6 (CVOT) reflecting a real-world clinical situation.

Rescue medication

In the phase 3a trials (excluding SUSTAIN 6 [CVOT]), patients with unacceptable hyperglycemia were to be offered treatment intensification (rescue medication), at the discretion of the investigator in accordance with ADA/EASD guidance.[83] Unacceptable hyperglycemia was identified based on predefined criteria related to fasting plasma glucose (FPG) and rescue medication was to be

initiated if FPG > 270 mg/dL from randomization to end of week 5; FPG > 240 mg/dL from week 6 to end of week 11 or FPG > 200 mg/dL from week 12 to end-of-trial. Treatment intensification was to be administered as add-on to randomized treatment; GLP-1 RAs, DPP-4 inhibitors and pramlintide were not allowed. The most common medications initiated or intensified during the trials were insulin, biguanides and SU. In SUSTAIN 6 (CVOT), patients were on a background of standard-of-care, and thus no rescue criteria were defined.

Among the treatment completers in phase 3a trials, the proportion of patients initiating rescue medication was generally lower with semaglutide (0.0−5.4%) than with comparators (1.4−20.2%) (Table 9). The proportion of time without rescue medication relative to the on-treatment period ranged from 95% to 100% with semaglutide and from 88% to 99% with comparator products (Table 8), in line with the limited use of rescue mediation in the semaglutide treatment groups.

Table 8 Trials in phase 3a pool: Total patient years of observation and time without rescue treatment

	SUSTAIN						
	1 Sema 0.5mg /1mg /PBO	**2** Sema 0.5mg /1mg/ Sita	**3** Sema 1mg Exe ER	**4** Sema 0.5mg /1mg / IGlar	**5** Sema 0.5mg /1mg / PBO	**JP Mono** Sema 0.5mg / 1mg / Sita	**JP OAD** Sema 0.5mg / 1mg /OAD
PYE on-treatment	80/82/81	435/431/453	414/408	225/219/235	84/82/84	69/63/70	271/257/136
PYE on-treatment without rescue medication	78/79/71	418/424/397	394/378	219/216/232	83/81/75	68/63/68	271/256/130
% patients on rescue	4.7/3.8/20.2	5.4/2.2/19.7	5.4/9.6	3.9/2.5/1.4	2.3/0.8/14.3	1.0/0.0/4.9	0.0/0.0/5.8
Proportion of time without rescue, %	97/97/88	96/99/88	95/93	98/99/99	99/99/90	99/100/97	100/100/96

Notes: FAS on-treatment. Total patient years of observation for the on-treatment without rescue mediation observation period as compared to on-treatment period. For placebo (PBO), pooled data are provided.
Abbreviations: Exe ER: exenatide extended release; IGlar: insulin glargine; JP: Japan; mono: mono-therapy; OAD: anti-glycemic drugs; PBO: placebo; pts: patients; PYO: patient years of exposure; sema: semaglutide; sita. sitagliptin.

Comparator products

Semaglutide as combination therapy with oral anti-glycemic drugs was investigated in head-to-head trials with the most relevant active comparators available at the time of the program planning. The maximum allowed doses of comparator products were used, based on product labelling, in SUSTAIN 2 and SUSTAIN JP Mono (sitagliptin 100 mg once-daily) and SUSTAIN 3 (exenatide ER 2 mg once-weekly). In SUSTAIN 4, target levels of fasting blood glucose (FPG) (71- <100 mg/dL) were not reached with insulin glargine once-daily, despite up-titration from 10 IU to a mean dose of 29.2 IU. This likely reflects clinical practice of titrating insulin with caution to balance efficacy versus risk of hypoglycemia and undesirable weight gain. The overall mean insulin dose reported in this trial was consistent with that reported in trials comparing other weekly GLP-1 RAs and insulin glargine.[84, 85]

5.5 Patient disposition

The phase 3a program was conducted within the target population of more than 8,100 randomized patients (Table 4). All efforts were to be made to keep the patients on treatment during the trials. However, in case of a potential safety concern (including pregnancy and pancreatitis), unacceptable intolerability, or at request of the patient, the trial product could be discontinued. However patients were to remain in the trial after premature discontinuation of trial product unless consent was withdrawn. The proportion of patients completing the pre-planned treatment periods in the individual trials were high ranging from 79.4 to 93.2% (Table 9), i.e., a low proportion of patients discontinued treatment prematurely. The primary reasons for premature treatment discontinuation across trials were categorized as "adverse events" or "other reasons". "Other reasons" included a variety of reasons not related to adverse events or protocol deviations. The differences in discontinuation rates between semaglutide and placebo/comparators treatment groups were mainly due to a higher number of gastrointestinal adverse events leading to premature treatment discontinuation with semaglutide; see Section 9.4 for further details. Among the treatment completers in phase 3a trials, the proportion of patients initiating rescue medication was generally lower with semaglutide (0.0−5.4%) than with comparators (1.4−20.2%) (Table 9).

Patients were to be encouraged to stay in the trial irrespective of degree of adherence to randomized treatment e.g., lack of adherence to visit schedule, missing assessments or trial product discontinuation. In the individual trials, the numbers and proportions of patients completing the trials were high (91.4−98.4%) demonstrating a high degree of retention in the trials. The primary efficacy analysis was performed based on data collected while on-treatment without rescue medication. The broad data collection provides the opportunity to analyze phase 3a trials using various analysis populations and data-sets (i.e., observation periods), thereby adding robustness to the trial conclusions. In SUSTAIN 6 (CVOT), the vital status at end-of-trial was known for 99.6% of patients (vital status unknown for 13 patients [6 with semaglutide and 7 with placebo]), indicating that the results are both robust and reliable.

Table 9 Trials in phase 3a program: Patient disposition

Trial / Patients	Key efficacy trials					CVOT	Japanese trials	
	SUSTAIN 1	**SUSTAIN 2**	**SUSTAIN 3**	**SUSTAIN 4**	**SUSTAIN 5**	**SUSTAIN 6**	**SUSTAIN JP Mono**	**SUSTAIN JP OADs**
	Total Sema 0.5 /1 mg / PBO	Total Sema 0.5 mg / 1 mg / Sita	Total Sema 1 mg / Exe ER	Total Sema 0.5 mg / 1 mg / IGlar	Total Sema 0.5 mg / 1 mg / PBO	Total Sema 0.5/1 mg PBO 0.5/1 mg	Total Sema 0.5 mg / 1 mg / Sita	Total Sema 0.5 mg / 1 mg / OAD
FAS (a)	387 128/130/129	1,225 409/409/407	809 404/405	1,082 362/360/360	396 132/131/133	3,297 826/822/ 824/825	308 103/102/103	600 239/241/120
Premature treatment discontinuation (%)	12.1 13.3/12.3/10.9	11.9 13.0/14.9/7.9	20.6 20.3/21.0	12.0 13.5/15.3/7.2	10.9 10.6/12.2/9.8	20.0 19.9/22.6/ 18.3/19.3	6.8 2.9/14.7/2.9	9.3 6.3/14.1/5.8
- *Gastrointestinal adverse events*	1.6 2.3/2.3/0.0	4.2 4.6/7.6/0.2	3.3 4.5/2.2	2.5 2.8/4.7/0.0	1.8 1.5/3.8/0.0	4.3 5.7/9.4/1.2/1.0	3.6 1.0/9.8/0.0	4.2 2.9/7.5/0.0
- *Other adverse events (b)*	3.1 3.9/3.1/2.3	2.8 3.4/2.4/2.7	5.0 5.2/4.9	2.2 2.5/2.8/1.4	2.5 3.0/3.8/0.8	5.6 6.2/5.0/4.6/6.7	1.6 1.9/1.0/1.9	3.2 2.9/3.3/3.3
- *Protocol violation (in- or exclusion criteria (c)*	1.8 3.1/1.5/0.8	1.1 1.0/1.0/1.5	4.4 3.7/5.2	2.5 3.3/3.6/0.6	0.8 0.8/0.0/1.5	-	0.3 0.0/1.0/0.0	0.0 0.0/0.0/0.0
- *Other reason (d)*	5.7 3.9/5.4/7.8	3.8 3.9/3.9/3.4	7.6 6.7/8.4	4.8 5.0/4.2/5.3	5.8 5.3/4.6/7.5	10.0 8.0/8.3/12.4/11.6	1.3 0.0/2.9/1.0	2.0 0.4/3.3/2.5
Withdrawals (%)	6.7 7.0/5.4/7.8	5.4 5.6/5.1/5.6	8.5 7.9/9.1	5.8 6.6/5.2/5.5	3.8 3.0/3.0/5.3	0.5 0.2/0.6/ 0.5/0.5	1.6 0.0/2.9/1.9	3.5 2.5/4.1/4.1
Use of rescue medication (%)	9.6 4.7/3.8/20.2	9.1 5.4/2.2/19.7	7.5 5.4/9.6	2.6 3.9/2.5/1.4	5.8 2.3/0.8/14.3	NA	1.9 1.0/0.0/4.9	1.2 0.0/0.0/5.8
Completed treatment without rescue medication (%)	78.3 82.0/83.8/69.0	79.0 81.7/82.9/72.5	71.8 74.3/ 69.4	85.4 82.6/82.2/91.4	83.3 87.1/87.0/75.9	NA	91.2 96.1/85.3/92.2	89.5 93.7/85.9/88.3
Completed treatment (%)	87.9 86.7/87.7/89.1	88.1 87.0/85.1/92.1	79.4 79.7/79.0	88.0 86.5/84.7/92.8	89.1 89.4/87.8/90.2	80.0 80.1/77.3/ 81.7/80.7	93.2 97.1/85.3/97.1	90.7 93.7/85.9/94.2
Completed trial (%) (e)	92.5 92.2/94.6/90.7	94.5 94.4/94.6/94.4	91.4 92.1/90.7	93.7 92.5/94.5/94.0	95.7 96.2/96.2/94.7	98.0 98.3/98.7/ 97.6/97.6	98.4 100/97.1/98.1	96.3 97.5/95.9/95.0

a) A total of 20 randomized patients in phase 3a trials excluding the CVOT (similarly distributed across trials) were not exposed to trial product and thus not included in the FAS. **b**) Events of pancreatitis are included under other adverse events. **c**) Protocol violation (in- or exclusion criteria)' is included in 'Other reasons' in SUSTAIN 6 (CVOT). **d**) Events of pregnancies are included under other reasons **e)** Completed trial includes patients with a follow-up visit. In SUSTAIN 6 (CVOT) trial completers were defined as patients who attended the end-of-trial follow-up visit (final visit) or died during the trial. **Abbreviations**: NA: Not applicable.

6 Glycemic control and body weight

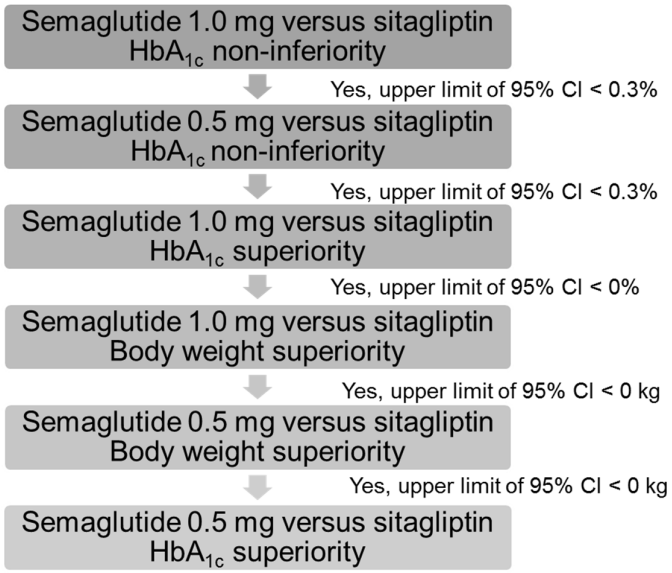
Summary

- Evaluation of the glycemic efficacy of semaglutide was performed in all eight phase 3a trials. Key conclusions are based on the five key efficacy trials (SUSTAIN 1–5) and supported by data from SUSTAIN 6 (CVOT) and the two Japanese trials.
- Semaglutide provided consistent and durable improvements in HbA_{1c} in all trials when administered as monotherapy or when used with other anti-glycemic drugs.
- HbA_{1c} reductions obtained with semaglutide were significantly greater and superior to placebo (as monotherapy or in combination with basal insulin) and to the active comparators sitagliptin, exenatide ER and insulin glargine, all well-established in current T2D treatment for lowering of HbA_{1c} (SUSTAIN 1–5).
- The mean HbA_{1c} levels achieved at end-of-treatment (SUSTAIN 1–5), of 6.60−6.96% with semaglutide 0.5 mg and 6.46−6.81% with semaglutide 1 mg, are lower than what has previously been seen in a large clinical trial program with T2D glucose lowering therapies.[1-4]
- Mean reductions in HbA_{1c} at end-of-treatment of up to 1.45 %-points were achieved with semaglutide 0.5 mg and 1.85 %-points with semaglutide 1 mg from mean baseline levels of 8.05% to 8.37%.
- Superior glycemic efficacy of each dose of semaglutide versus comparator was demonstrated and the results were supported by pre-specified sensitivity analyses.
- Significantly more patients with semaglutide versus comparators achieved the ADA treatment targets in all trials. With semaglutide 0.5 mg and 1 mg, an HbA_{1c} <7% was achieved for up to 74% and 79% of patients, respectively.
- Overall, sustained and consistent treatment effects of semaglutide 0.5 mg and 1 mg on glycemic efficacy were seen across all subgroups investigated.
- Semaglutide significantly reduced body weight both as monotherapy and in combination therapy, compared with placebo or active comparators; sitagliptin, exenatide ER and insulin glargine.
- Mean reductions in body weight of up to 4.28 kg (4.9%) with semaglutide 0.5 mg and 6.42 kg (7.3%) with semaglutide 1 mg were obtained at end-of-treatment.
- The reduction in body weight was sustained for up to 104 weeks.
- Superior reductions in body weight of each dose of semaglutide versus comparators were demonstrated and supported by all sensitivity analyses.
- Significantly more patients with semaglutide versus comparators achieved a weight loss response of ≥5% and ≥10%.

6.1 Statistical methods for evaluation and analyses of glycemic control and body weight

The primary endpoint for assessing glycemic efficacy in the five key efficacy trials (SUSTAIN 1–5) was change from baseline in HbA_{1c} at end-of-treatment. Change from baseline in body weight (kg) at end-of-treatment was a confirmatory secondary endpoint in SUSTAIN 1–5 and SUSTAIN 6 (CVOT). HbA_{1c}, body weight and other efficacy endpoints were collected and analyzed similarly across all the phase 3a trials including the CVOT in which time to first MACE was the primary endpoint.

Each key efficacy trial was sufficiently powered to confirm the effect, and potential benefits of each dose of semaglutide on HbA_{1c} and body weight endpoints. In all the key efficacy trials (SUSTAIN 1–5) the family-wise type 1 error rate was controlled in the strong sense (5%, two-sided) for HbA_{1c} and body weight endpoints across the two doses of semaglutide using a pre-specified hierarchical testing scheme (SUSTAIN 2 shown as example in Figure 9). The hierarchical tests constitute a closed testing procedure; therefore, no adjustment of the significance level was performed.[86, 87] The statistical testing hierarchy was built on the general principle that glycemic efficacy should be established before testing for added benefits in terms of superiority. Consequently, added benefits could only be concluded if semaglutide was effective in reducing HbA_{1c}. For controlled trials including an active comparator, the alternative hypothesis of non-inferiority as the first step was consistently tested against a non-inferiority margin of 0.3%-point for the HbA_{1c} treatment difference. Based on the established HbA_{1c} efficacy of the active comparators a non-inferiority margin of 0.3%-point was considered to be sufficiently narrow to robustly confirm the glycemic efficacy of semaglutide as recommended by FDA guidance.[88]



Abbreviations: CI: confidence interval; HbA_{1c}: glycosylated hemoglobin.

Figure 9 SUSTAIN 2: Hierarchical testing strategy

Efficacy was evaluated in the phase 3a trials as the effect of initiating and continuing treatment with semaglutide throughout the planned treatment period of the trial. Accordingly, an efficacy estimand (*de jure* effect) was pre-specified in statistical analysis plans in line with the intention in the protocols. The primary estimand was defined as the treatment difference between semaglutide and comparator, assuming that all randomized patients remained on trial product without initiation of rescue medication. For treatment of individual patients an efficacy estimand is considered to provide important information on the glycemic effects of semaglutide for both patients and prescribers as it provides the effect a patient can expect if he/she initiates and continues treatment with semaglutide.[89] This information is, together with premature treatment discontinuation rate and semaglutide safety profile, informative for deciding on an optimal treatment for individual patients.

With the exception of SUSTAIN 6 (CVOT), all efficacy analyses were based on all randomized and exposed patients using the on-treatment without rescue medication observation period. Hence, all efficacy evaluations are based on measurements that were collected prior to an eventual onset of rescue medication; and thereby avoid confounding by rescue medications (see Table 9 for proportion of patients on rescue medication). In this analysis, data collected after initiation of rescue medication or premature treatment discontinuation were set to missing and imputed based on the missing at random assumption (MAR). Supportive analyses were performed based on the in-trial observation period, thereby including all data collected during trial regardless of treatment adherence or rescue medication status. In SUSTAIN 6 (CVOT) the effect of semaglutide on glycemic control and body weight was evaluated primarily based on all randomized patients using the in-trial observation period in line with the pre-specified analysis of the primary MACE endpoint and standards for long-term outcomes trials with a standard-of-care design.[5]

Continuous endpoints, including HbA_{1c} and body weight, were analyzed in a mixed model for repeated measurements (MMRM) adjusted for treatment, country (SUSTAIN 1–5), stratification (if applicable) and baseline value as a continuous covariate, all nested within visit. An unstructured covariance matrix was assumed for measurements within the same patient. The properties of the MMRM are well-understood and described comprehensively in the literature.[89] In this model the mechanism for missing data is assumed to be missing at random (MAR). Thus, the interpretation of missing data concerns what the outcomes would have been, had they been measured under the assumption that these patients had continued treatment without initiating rescue medication in line with the intention of the efficacy estimand.

Because any assumption regarding missing data is unverifiable, a series of pre-specified sensitivity analyses were performed to investigate the robustness of the conclusions on the effect on HbA_{1c} and body weight endpoints. These included standard ways historically used to analyze data from diabetes trials, i.e., a complete case analysis, a per-protocol analysis for testing HbA_{1c} non-inferiority and an analysis using last-observation carried forward to impute missing data (Table 10). As a conservative sensitivity analysis, a comparator-based multiple imputation analysis was performed using the method of Koch[90] for testing non-inferiority.

Table 10 SUSTAIN 1–5: Pre-planned and *post-hoc* sensitivity analyses of efficacy endpoints

Model	Population	Observation period
Pre-planned analyses		
Primary MMRM	FAS	On-treatment without rescue medication
LOCF		
Comparator-based multiple imputation, non-inferiority		
Comparator-based multiple imputation, superiority		
Per-protocol	Patients who: -not violated inclusion criteria -not fulfilled any exclusion criteria -had at least 23 weeks of trial product exposure	
Complete-case	Patients in FAS with non-missing data for the primary endpoint	
In-trial MMRM	FAS	In-trial
***Post-hoc* analysis**		
In-trial retrieved dropout	FAS	In-trial

Note: FAS includes all randomized patients exposed to at least one dose of trial product.
Abbreviations: FAS: full analysis set; LOCF: Last observation carried forward: MMRM: mixed model for repeated measurements.

Finally, an in-trial sensitivity analysis was pre-specified which also included data collected after initiation of anti-glycemic rescue medication. Interpretation of HbA_{1c} results from the in-trial analyses may be complicated by effective alternative anti-glycemic drugs used as rescue medication. This is particularly the case if use of rescue is imbalanced across treatment groups. In general, each analysis has its own limitations, but collectively the analyses sufficiently evaluated the sensitivity of the HbA_{1c} and body weight analysis results to variation in the method for handling missing data, analysis method, analysis population and data foundation.

An additional sensitivity multiple imputation -based analysis for FAS using the in-trial observation period (referred as an in-trial retrieved dropout analysis) was made *post-hoc*, based on discussion with FDA at the pre-NDA meeting. The analysis imputed missing data on the primary HbA_{1c} endpoint at end-of-treatment based on information from the subgroup of patients with off-treatment data available. It is hereby assumed, that the likely values of what the missing data would have been if available, are appropriately described by information from patients who at the primary endpoint visit are similar in terms of randomized treatment and treatment completion status.

6.2 HbA_{1c}

6.2.1 Change in HbA_{1c}

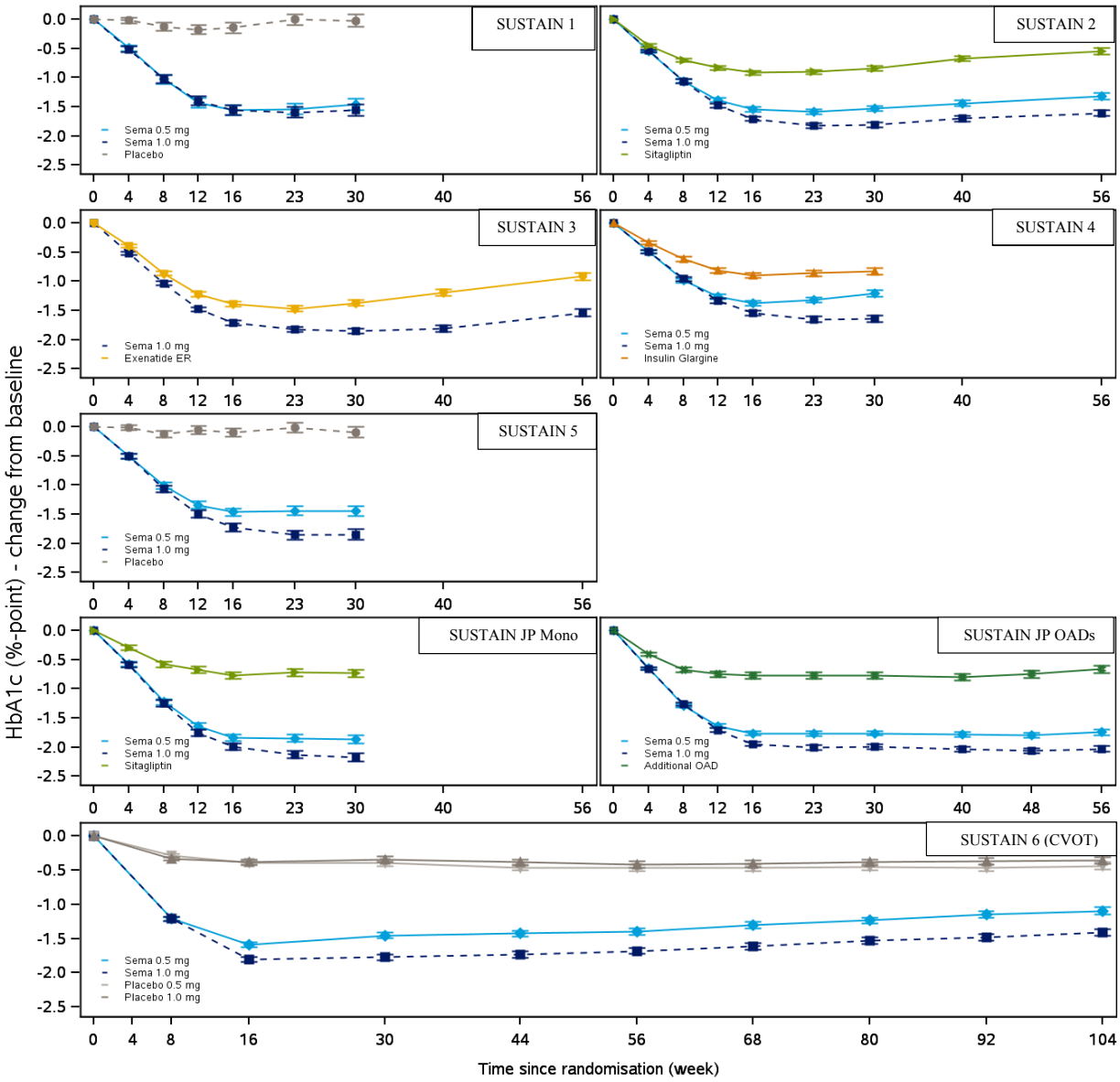
Semaglutide 0.5 mg and 1 mg consistently reduced HbA_{1c} across drug-naïve patients on semaglutide monotherapy, patients uncontrolled on OADs treated with semaglutide as add-on to 1−2 OADs and in patients with long-standing T2D uncontrolled on basal insulin treated with semaglutide as add-on to basal insulin (Figure 10). The reduction in HbA_{1c} with semaglutide was most pronounced during the initial 5−6 months of treatment with the nadir being reached after approximately 16−30 weeks of treatment in all trials. In all phase 3a trials, HbA_{1c} reductions were sustained during the entire treatment period of up to 56 weeks, albeit HbA_{1c} slightly increased between week 30 and week 56 for the trials with a treatment period beyond week 30, but remained below the baseline and close to the nadir level. The attenuation was seen both with semaglutide and comparators and likely reflects the progression of the disease and/or adherence to treatment. End-of-treatment mean HbA_{1c} levels achieved with semaglutide in SUSTAIN 1–5 were below the target HbA_{1c} of 7% (Table 11), as recommended by the ADA.[7]

Table 11 Trials in the phase 3a program: Estimated HbA_{1c} (%) at end-of-treatment

Trial Duration	N	Baseline HbA_{1c}	Mean (SE)		
			Semaglutide 0.5 mg	Semaglutide 1 mg	Comparator
SUSTAIN 1 30 weeks	387	8.05%	6.60% (0.10)	6.50% (0.10)	8.03% (0.10), Placebo
SUSTAIN 2 56 weeks	1,225	8.07%	6.76% (0.05)	6.46% (0.05)	7.53% (0.05), Sitagliptin
SUSTAIN 3 56 weeks	809	8.35%	NA	6.81% (0.06)	7.43% (0.06), Exenatide ER
SUSTAIN 4 30 weeks	1,082	8.17%	6.96% (0.05)	6.53% (0.05)	7.34% (0.05), Insulin glargine
SUSTAIN 5 30 weeks	396	8.37%	6.92% (0.09)	6.52% (0.09)	8.27% (0.09), Placebo
SUSTAIN 6 (CVOT),104 weeks	3,297	8.70%	7.61% (0.05)	7.29% (0.05)	8.26% (0.05), Placebo 0.5 mg 8.34% (0.05), Placebo 1 mg
SUSTAIN JP Mono, 30 weeks	308	8.15%	6.28% (0.07)	5.97% (0.07)	7.41% (0.07), Sitagliptin
SUSTAIN JP OADs, 56 weeks	600	8.09%	6.35% (0.05)	6.06% (0.05)	7.43% (0.07), OADs

Notes: Estimates from a MMRM based on the FAS using the 'on-treatment without rescue medication' data for SUSTAIN 1-5 and Japanese trials and the in-trial observation period for SUSTAIN 6 (CVOT). Mean estimates are adjusted according to observed baseline distribution in the FAS.
Abbreviations: CVOT: cardiovascular outcomes trial; FAS: full analysis set. JP: Japan; MMRM: mixed model for repeated measurements; N: number of patients in FAS; OADs: oral anti-glycemic drugs; SE: standard error.

The effects of semaglutide on HbA_{1c} reduction in SUSTAIN 1–5 were supported by data from SUSTAIN 6 (CVOT) and the two Japanese trials (Table 11). In SUSTAIN 6 (CVOT), mean baseline HbA_{1c} was relatively high (8.7%), reflecting that many patients had poor glycemic control.



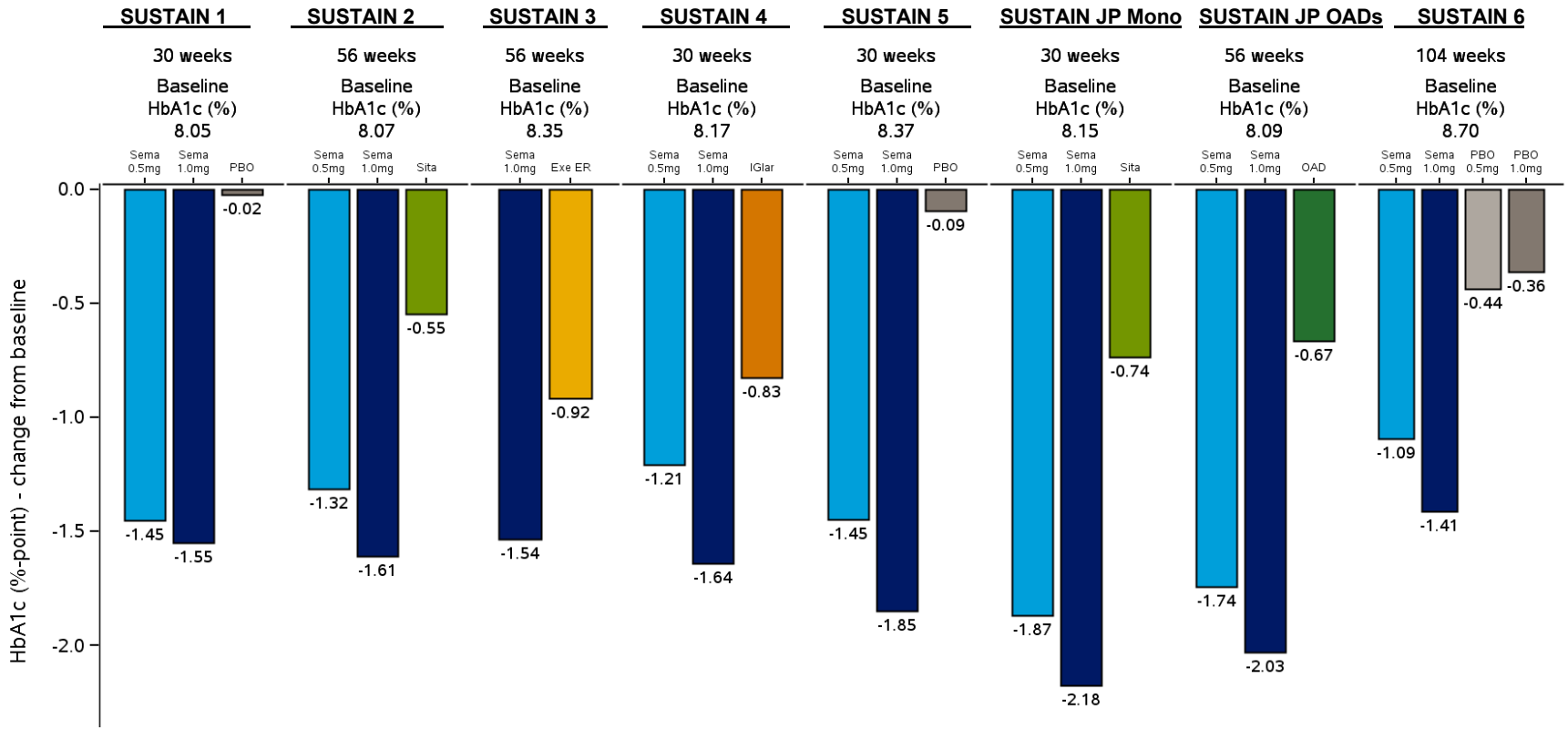
Notes: Estimates are from a MMRM based on the FAS using the 'on-treatment without rescue medication' data for SUSTAIN 1-5 and Japanese trials and the in-trial observation period for SUSTAIN 6 (CVOT). Mean estimates are adjusted according to observed baseline distribution in the FAS. Error bars are+/- 1×SEM.
Abbreviations: CVOT: cardiovascular outcomes trial; ER extended release; JP: Japan; Mono: monotherapy; OAD: oral anti-glycemic drug; SEM: standard error of the mean; sema: semaglutide.

Figure 10 Trials in the phase 3a program: Estimated HbA_{1c} (%-point) by treatment week

and that no upper limit was defined for baseline HbA_{1c}. Investigators were instructed to follow recommendations on standard-of-care treatment for anti-glycemic therapy added to semaglutide or placebo throughout the treatment period, with the aim of achieving similar glycemic control in the two treatment groups based on individualized HbA_{1c} targets. In spite of the recommendations and dedicated efforts to optimize glycemic control for all patients, the placebo group did not achieve the same level of control on standard-of-care therapy as achieved with semaglutide (Figure 10 and Figure 11).

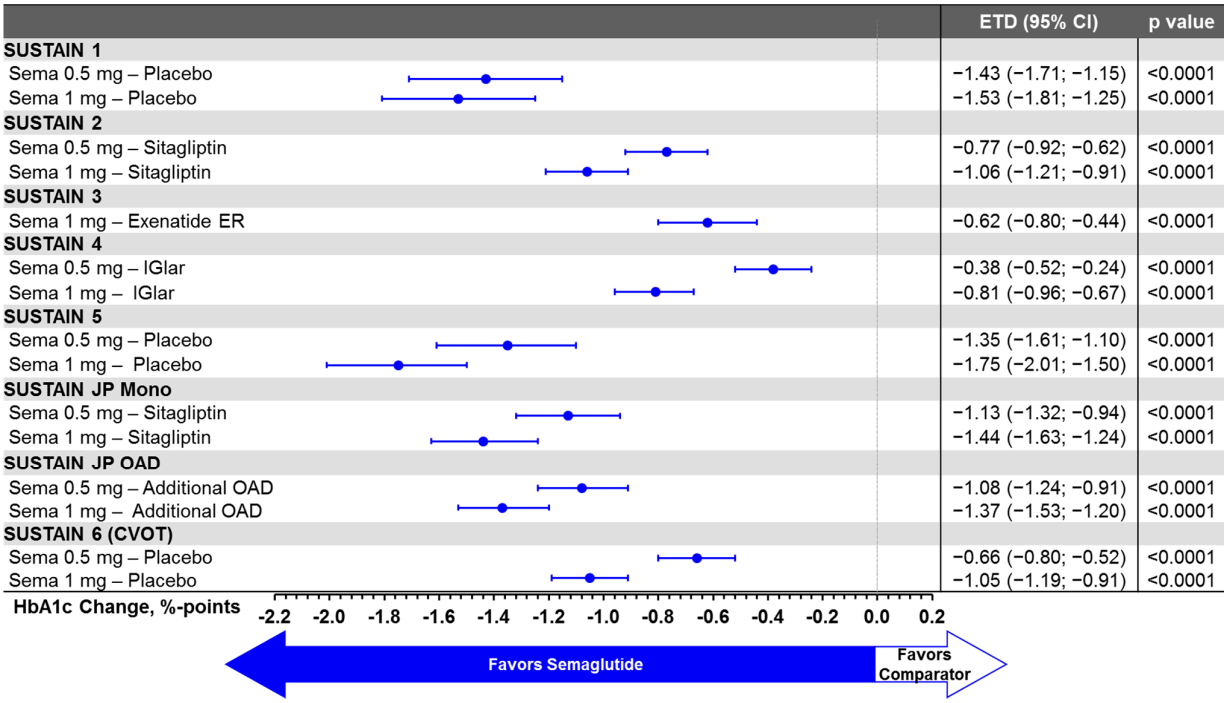
The reduction in HbA_{1c} with placebo and standard-of-care in SUSTAIN 6 (CVOT) is in line with reductions reported with placebo in other recent CVOTs with GLP-1 RAs[14], DPP-4 inhibitors[15-18] and the SGLT-2 inhibitor empagliflozin[19] which used similar recommendations for standard-of-care treatment. The reduction in HbA_{1c} in SUSTAIN 6 (CVOT) was sustained during the entire treatment period of 104 week, although some attenuation was seen during the second year of treatment consistent with findings in the other CVOTs and likely reflecting progression of disease and/or adherence to therapy (Figure 10). Less attenuation was observed in placebo-treated patients, where treatment intensification was used to a greater extent.

In the individual trials semaglutide 0.5 mg and 1 mg were evaluated versus placebo (as mono-therapy or combination therapy with insulin) and the active comparators sitagliptin, exenatide ER, or insulin glargine. Comparators were used at maximum recommended doses; sitagliptin 100 mg OD, exenatide ER 2 mg OW, and insulin glargine was titrated based on pre-breakfast plasma glucose. Across the 5 key efficacy trials (SUSTAIN 1–5), semaglutide 0.5 mg and 1 mg each significantly reduced HbA_{1c} from baseline to end-of-treatment more than the trial-specific comparators (Figure 11 and Figure 12). Superiority of semaglutide 0.5 mg and 1 mg was confirmed in all five key efficacy trials (SUSTAIN 1–5) and supported by SUSTAIN 6 (CVOT) and the 2 Japanese trials. Across all trials the estimated treatment difference between semaglutide 1 mg and comparators were greater than 0.6%.



Notes: Estimates are from a MMRM based on the FAS using the 'on-treatment without rescue medication' data for SUSTAIN 1–5 and Japanese trials and the in-trial observation period for SUSTAIN 6 (CVOT). Mean estimates are adjusted according to observed baseline distribution in the FAS.
Abbreviations: CVOT: cardiovascular outcomes trial; Exenatide ER: exenatide extended release; FAS: full analysis set; IGlar: insulin glargine; JP: Japan; MMRM: mixed model for repeated measurements; Mono: monotherapy; OAD: oral anti-glycemic drug; PBO: placebo; Sita: sitagliptin.

Figure 11 Trials in the phase 3a program: Estimated change from baseline in HbA_{1c} (%−point).

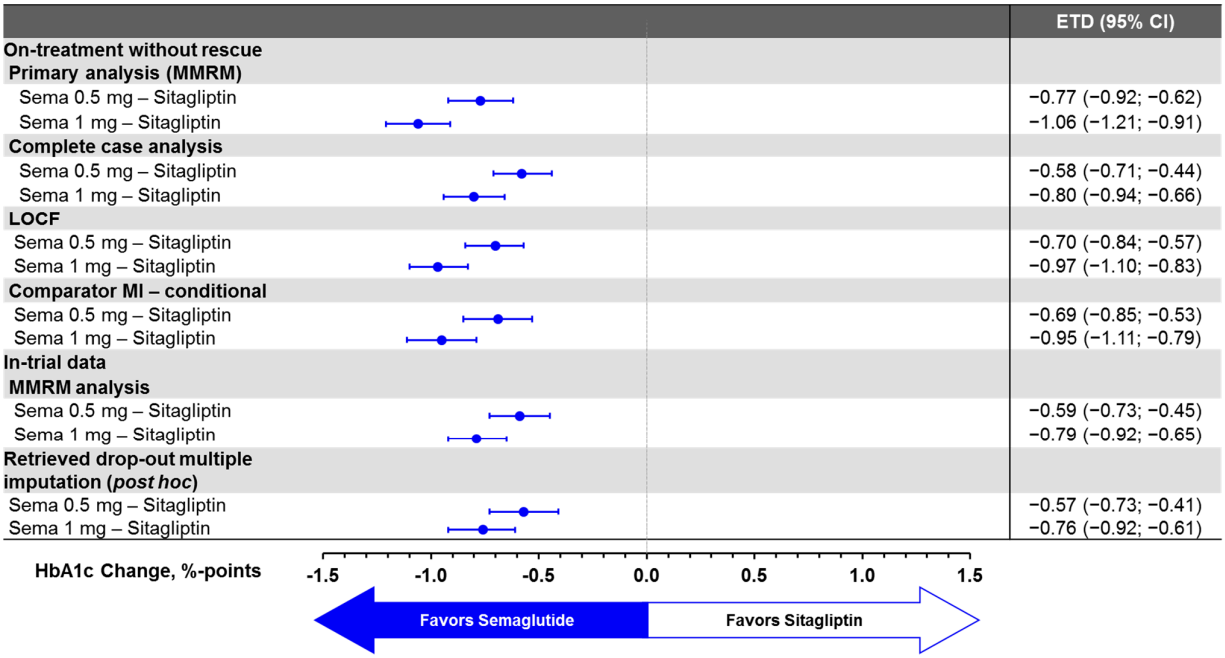


Notes: Estimates are from a MMRM based on the FAS using the 'on-treatment without rescue medication' data for SUSTAIN 1–5 and Japanese trials and the in-trial observation period for SUSTAIN 6 (CVOT). Mean estimates are adjusted according to observed baseline distribution in the FAS. Background treatment in SUSTAIN 6 (CVOT) was standard-of-care.
Abbreviations: CI: confidence interval; CVOT: cardiovascular outcomes trial; ETD: estimated treatment difference; Exenatide ER: exenatide extended release; IGlar: insulin glargine; JP: Japan; Mono: monotherapy; OAD: oral anti-glycemic drug; PBO: placebo; Sita: sitagliptin.

Figure 12 Trials in the phase 3a program: Estimated treatment differences (ETD) versus comparator products in HbA_{1c} (%−point) (primary analysis)

The conclusions of superior glycemic efficacy for both doses of semaglutide versus comparator from SUSTAIN 1–5 based on the primary MMRM analysis were supported by all statistical sensitivity analyses (see Table 10) showing significant and clinical relevant treatment differences (see example from SUSTAIN 2 in Figure 13).

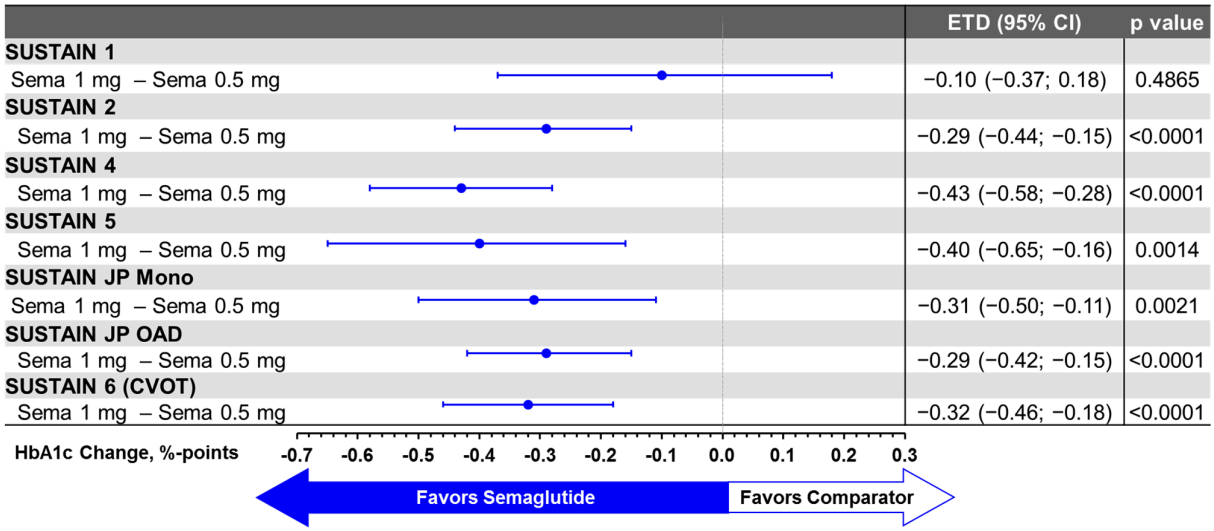
The magnitude of the reduction in HbA_{1c} with semaglutide increased with increasing baseline HbA_{1c} levels in all trials. Overall, larger reductions in HbA_{1c} were achieved with semaglutide across all ranges of baseline HbA_{1c} than with placebo or active comparators. Across all intervals of baseline HbA_{1c}, greater reductions in HbA_{1c} were achieved with semaglutide 1 mg than with 0.5 mg. These findings are supported by the exposure-response analysis (data not shown).



Notes: Estimated treatment differences and associated confidence intervals are from statistical analyses of HbA_{1c} (%) at week 56. Comparator multiple imputations were performed simulating sequentially all missing data from the comparator group using a conditional approach including as independent variables intermediate HbA_{1c} values. Retrieved drop-out multiple imputations were performed simulating missing data by treatment group from patients off treatment at week 56.
Abbreviations: CI: confidence interval; ETD: estimated treatment difference; LOCF: last observation carried forward; MI: multiple imputations; MMRM: mixed model for repeated measurements.

Figure 13 SUSTAIN 2: Preplanned and *post-hoc* sensitivity analyses of primary HbA_{1c} analyses

A larger reduction in HbA_{1c} was achieved with semaglutide 1 mg than with 0.5 mg across trials (Figure 11 and Figure 14) that tested both doses, with the smallest difference between semaglutide doses in the monotherapy trial (SUSTAIN 1). The dose-response of semaglutide 0.5 mg and 1 mg on HbA_{1c} change from baseline to end-of-treatment was evaluated *post-hoc* for all phase 3a trials, except SUSTAIN 3 where only the semaglutide 1 mg dose was tested. A significantly larger reduction in HbA_{1c} from baseline to end-of-treatment was achieved with semaglutide 1 mg versus 0.5 mg in all trials, except in SUSTAIN 1.



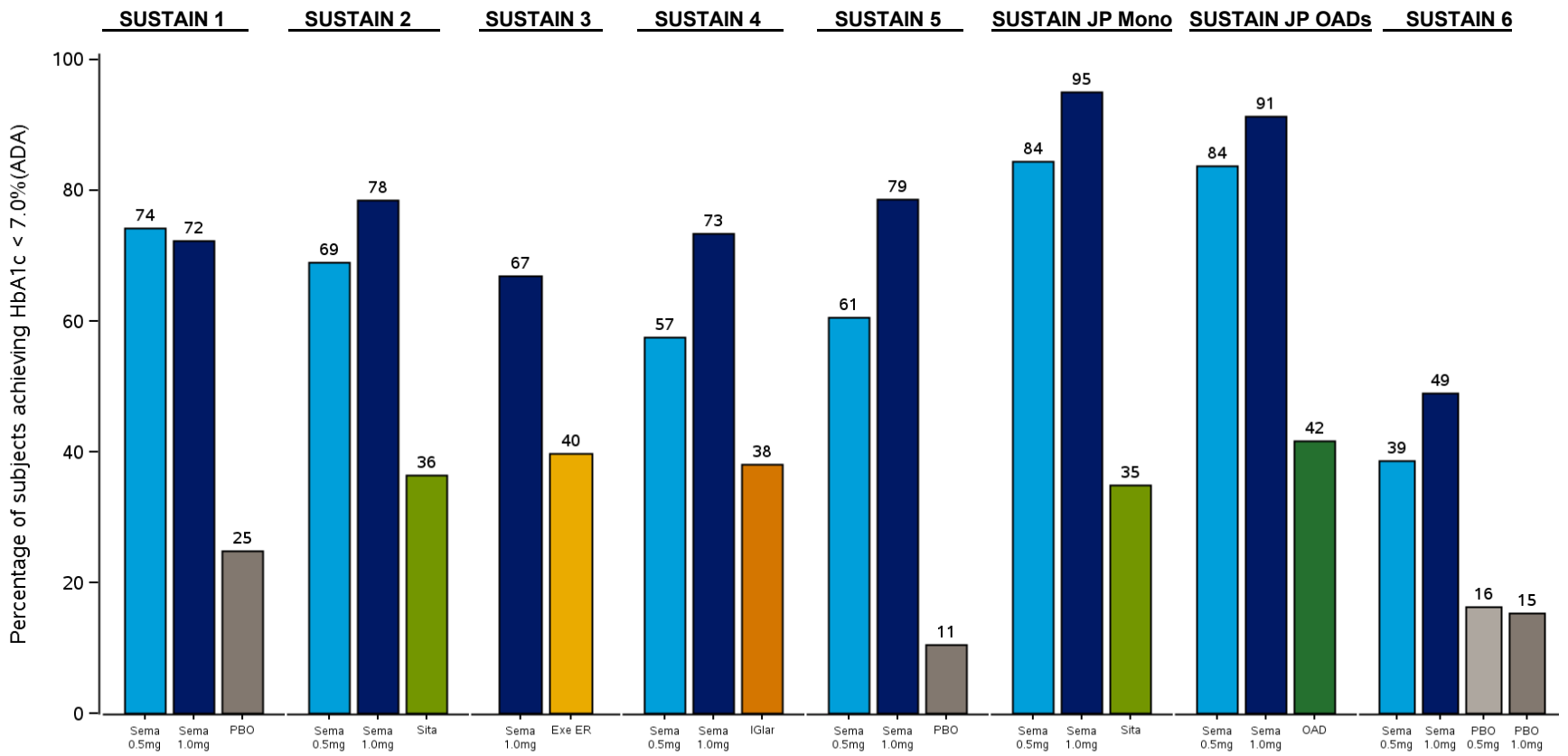
Notes: Estimates from a MMRM based on the FAS using the 'on-treatment without rescue medication' data for SUSTAIN 1–5 and Japanese trials and the in-trial observation period for SUSTAIN 6 (CVOT). Mean estimates are adjusted according to observed baseline distribution in the FAS. Background treatment in SUSTAIN 6 (CVOT) was standard-of-care.
Abbreviations: CI: confidence interval; CVOT: cardiovascular outcomes trial; ETD: estimated treatment difference; FAS: full analysis set; JP: Japan; MMRM: mixed model for repeated measurements; Mono: monotherapy; OADs: oral antiglycemic drugs.

Figure 14 Trials in phase 3a program excl. SUSTAIN 3: Estimated treatment differences (ETDs) from *post-hoc* analyses of HbA_{1c} (%-point change) of semaglutide 1 mg versus 0.5 mg

6.2.2 HbA_{1c} targets

In line with the reduction observed in mean HbA_{1c} with semaglutide, significantly greater proportions of patients with semaglutide than with comparators achieved the pre-defined treatment targets of HbA_{1c} <7% (ADA target[8, 20])(Figure 15) at end-of-treatment (at weeks 30, 56 or 104). The proportion of patients achieving target glycemic levels with semaglutide are the highest obtained in a T2D clinical development program.[1-4]

Reductions in HbA_{1c} were accompanied by relevant reductions in fasting plasma glucose and post-prandial glucose increments.



Note: Percentages are based on the FAS using the 'on-treatment without rescue medication' data for SUSTAIN 1–5 and Japanese trials and the in-trial observation period for SUSTAIN 6 (CVOT). Missing data are imputed from the MMRM on the continuous scale and subsequently dichotomized.
Abbreviations: ADA: American Diabetes association; CVOT: cardiovascular outcomes trial; JP: Japan;
MMRM: mixed model for repeated measurements; Mono: monotherapy.

Figure 15 Trials in phase 3a program: Proportion of patients reaching ADA HbA_{1c} target < 7.0% at end-of-treatment.

6.2.3 HbA_{1c} reduction in subpopulations

The treatment difference in HbA_{1c} reduction with semaglutide (0.5 mg and 1 mg) versus comparator products was consistent across subpopulations of major demographic factors (age, sex, race and ethnicity), relevant disease factors at baseline (duration of diabetes, body weight, BMI, and renal function), background diabetes treatment (metformin monotherapy, metformin + SU, other) and region (Africa, Asia+Australia, Europe, North America [US+Canada] and South America). The estimated mean change from baseline and estimated treatment differences (ETD) between semaglutide and comparator were similar across and within the different subpopulations, supporting the applicability of the data from the phase 3a trials across a very broad population with T2D. Results from the population pharmacokinetic analysis showed higher semaglutide exposure in patients with a lower body weight (see Section 4.2), however, the HbA_{1c} response was consistent across different levels of baseline body weight and BMI.

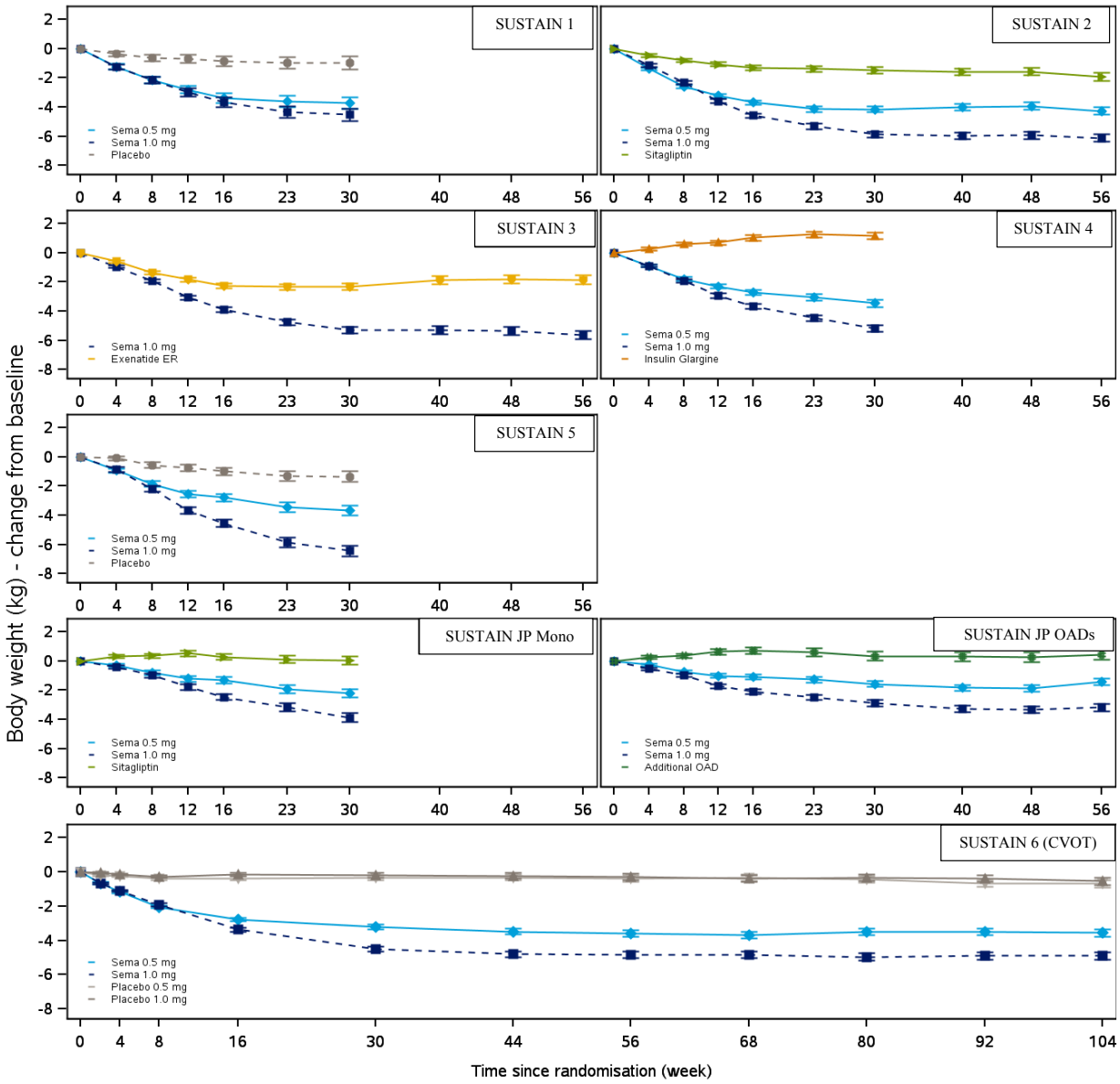
6.3 Body weight

In the semaglutide development program there was no specific focus on lifestyle modification other than general recommendations consistent with recommended standard of care. Semaglutide monotherapy or in combination with anti-glycemic drugs provided clinically relevant, sustained and consistent weight loss across all phase 3a trials (Figure 16).

The weight loss with semaglutide was already evident after 4 weeks of treatment and reached nadir after 30 weeks. The reduction was maintained after long-term treatment of up to 104 weeks in SUSTAIN 6 (CVOT), supporting the persistency in the effect. The weight loss achieved at end-of-treatment with semaglutide in the phase 3a trials (range 0.5 mg: -1.43 to-4.28 kg corresponding to 2.3−4.9%; 1 mg: -3.18 to -6.42 kg corresponding to 4.8−7.3%) (Figure 17) was clinically relevant according to recent ADA standards of care.[8]

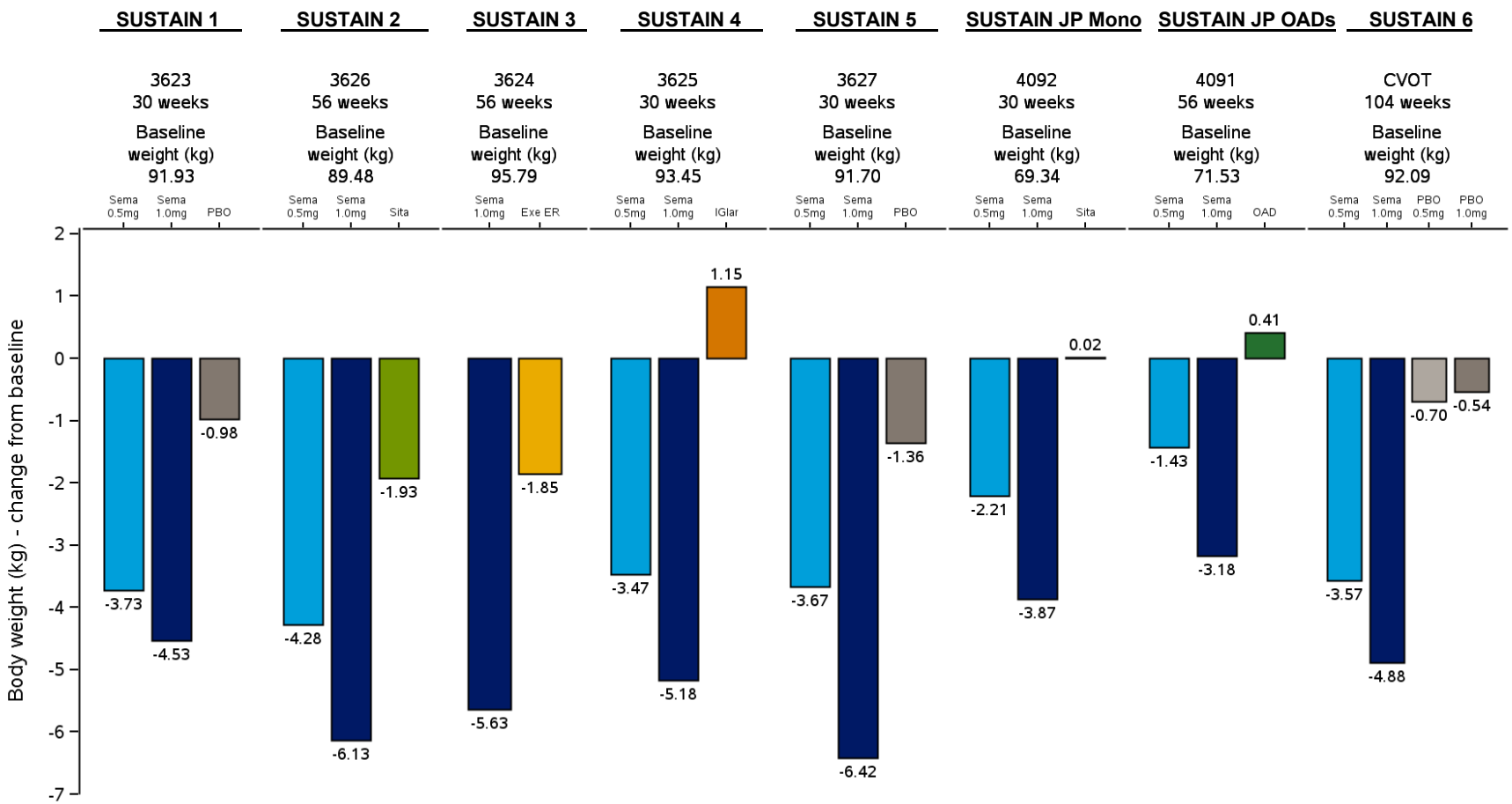
Methods for evaluation and analyses of data related to body weight are described in Section 6.1. The reductions in body weight achieved with semaglutide at end-of-treatment in all phase 3a trials were significantly greater than with placebo (when administered as monotherapy or in combination therapy with insulin) and the active comparators sitagliptin, exenatide ER and insulin glargine (Figure 17). Superiority of semaglutide 0.5 mg and 1 mg on weight loss was demonstrated for all phase 3a trials (Figure 18). A range of sensitivity analyses (see Table 10) confirmed the superiority of semaglutide over placebo and active comparators in weight loss in the individual trials, giving similar results as the MMRM analysis, thereby confirming the robustness of the primary analyses.

A weight loss of ≥5% was achieved for significantly more patients with semaglutide 0.5 mg (37−46%) and 1 mg (45−66%) versus placebo (7−11%) and active comparators (4−18%) in SUSTAIN 1–5 where statistical tests were performed. In line with this, a weight loss of ≥10% was achieved for significantly more patients with semaglutide 0.5 mg (7−13%) and 1 mg (13−26%) versus placebo (2−3%) and active comparators (1−4%) in SUSTAIN 1–5.



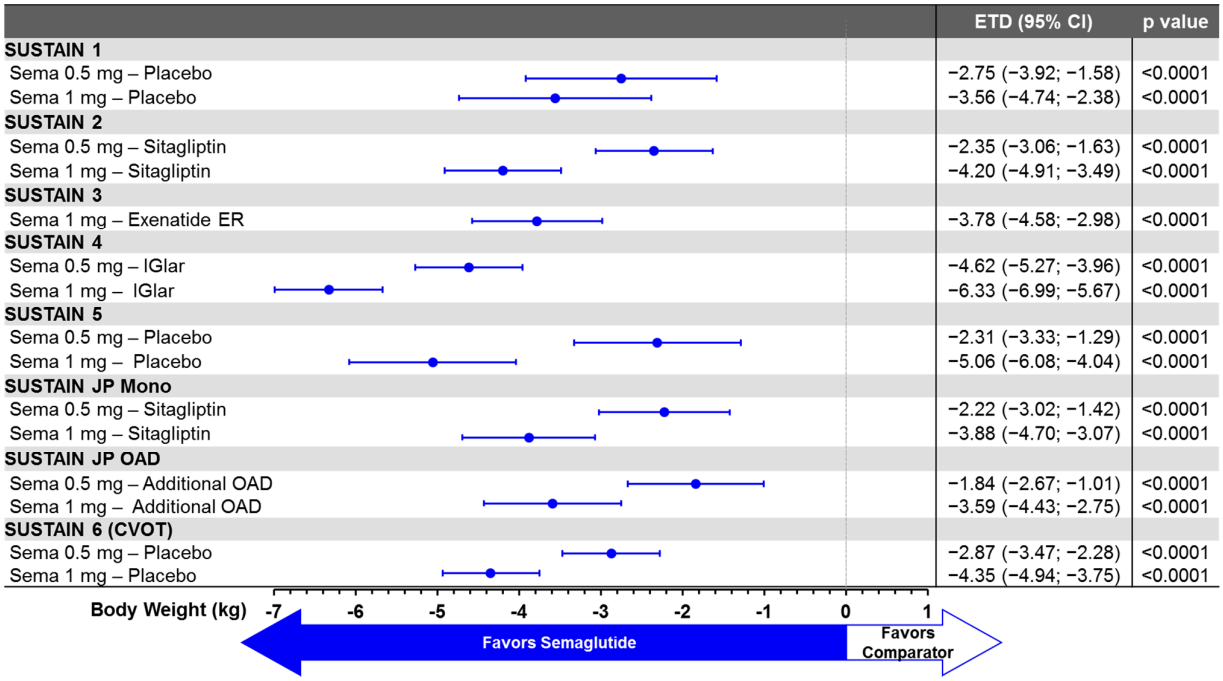
Notes: Estimates are from a MMRM based on the FAS using the 'on-treatment without rescue medication' data for SUSTAIN 1-5 and Japanese trials and the in-trial observation period for SUSTAIN 6 (CVOT). Mean estimates are adjusted according to observed baseline distribution in the FAS.
Abbreviations: CVOT: cardiovascular outcomes trial; ER: extended release; JP: Japan; MMRM: mixed model for repeated measurements; Mono: monotherapy; OAD: oral anti-glycemic drug; sema: semaglutide.

Figure 16 Trials in phase 3a program: Estimated body weight (kg) by treatment week



Notes: : Estimates are from a MMRM based on the FAS using the 'on-treatment without rescue medication' data for SUSTAIN 1-5 and Japanese trials and the in-trial observation period for SUSTAIN 6 (CVOT). Mean estimates are adjusted according to observed baseline distribution in the FAS.
Abbreviations: CVOT: cardiovascular outcomes trial; Exe ER: exenatide extended release; IGlar: insulin glargine; Mono: monotherapy; OAD: oral anti-glycemic drug; PBO: placebo; sema: semaglutide; Sita: sitagliptin.

Figure 17 Trials in phase 3a program: Estimated change from baseline in body weight (kg).



Notes: Estimates are from a MMRM based on the FAS using the 'on-treatment without rescue medication' data for SUSTAIN 1–5 and Japanese trials and the in-trial observation period for SUSTAIN 6 (CVOT). Mean estimates are adjusted according to observed baseline distribution in the FAS. Background treatment in SUSTAIN 6 (CVOT) was standard-of-care.
Abbreviations: CI: confidence interval; CVOT: cardiovascular outcomes trial; ETD: estimated treatment difference; ER: extended release; IGlar: insulin glargine; JP: Japan; Mono: montherapy; OAD: oral anti-glycemic drug.

Figure 18 Trials in phase 3a program: Estimated treatment differences (ETDs) in body weight (kg)

The weight loss obtained, as well as proportion of patients with weight loss ≥5%, were higher with semaglutide 1 mg than with 0.5 mg in all trials (Figure 16, Figure 17 and Figure 18). This is consistent with the exposure-response analysis showing a linear increase in change from baseline in body weight with increasing semaglutide exposure in the investigated exposure range of approximately 10–50 nmol/L. The linear relationship between exposure and body weight change indicates that higher exposure than achieved with 1 mg may lead to larger weight loss, i.e., the effect did not appear to level-off at the highest exposures.

Reductions in body weight with semaglutide were accompanied by significant and sustained reductions in BMI and waist circumference in all phase 3a trials.

6.4 Discussion and conclusions on glycemic control and body weight

Semaglutide provided consistent and sustained improvements in glycemic control across all treatment regimens investigated including monotherapy and as combination therapy with widely used OADs and insulin. The mean HbA_{1c} levels achieved at end-of-treatment (SUSTAIN 1–5), of

6.46−6.81% with semaglutide 1 mg and 6.60−6.96% with semaglutide 0.5 mg, are lower than what has previously been seen in a large clinical trial program with T2D glucose lowering therapies.[1-4] The reductions in HbA_{1c} achieved with semaglutide were clinically relevant with mean reductions in HbA_{1c} of 1.54−1.85 %-points with semaglutide 1 mg and 1.21−1.45 %-points with semaglutide 0.5 mg. The reductions in HbA_{1c} obtained with semaglutide were superior across trials versus placebo or widely used active comparators sitagliptin, exenatide ER, and insulin glargine. In addition, the reductions in HbA_{1c} with semaglutide corresponded to significantly more patients with semaglutide versus comparators achieve the ADA-defined treatment target of HbA_{1c} <7%. With semaglutide 1 mg, HbA_{1c} <7% was achieved for up to 79% of patients; exceeding the levels obtained in other T2D clinical development programs.[1-4] The improvement in glycemic control for the overall population as well as across the subgroups was achieved with a low risk of hypoglycemia. The superiority of semaglutide was confirmed by all statistical sensitivity analyses performed. The effects of semaglutide on HbA_{1c} were sustained throughout the trial of up to 104 weeks.

Consistent treatment effects of semaglutide 0.5 mg and 1 mg on glycemic efficacy were seen across all subgroups and subpopulations investigated, thus supporting a broad use of semaglutide. The sustained effect of semaglutide on HbA_{1c} is supported by a lower proportion of patients with semaglutide who initiated other glucose-lowering treatment during the trials versus placebo and comparator products.

Overweight and obesity are a well-known risk factors for hyperglycemia, T2D and cardiovascular disease.[8,9] A moderate weight loss of 5% can improve glycemic control and cardiovascular risk factors in patients with T2D,[10] and thereby may have a beneficial effect on T2D and cardiovascular disease. Accordingly, current ADA treatment guidelines recommend that patients with T2D achieve modest weight loss (5–7%) to improve glycemic control and reduce cardiovascular risk.[8, 11] Weight gain or modest weight loss despite lifestyle intervention has been associated with patient frustration, reduced motivation and potentially decreased compliance with medication.[91] Semaglutide provided clinically meaningful weight loss, and the reduction in body weight was sustained for up to 104 weeks. Superior body weight loss was achieved and maintained consistently across all eight phase 3a trials for semaglutide compared with placebo or active comparators (sitagliptin, exenatide ER, and insulin glargine). Correspondingly, with semaglutide 1 mg, up to 66% of patients achieved a weight loss of ≥5% with no specific focus on lifestyle modification other than general recommendations consistent with recommended standard-of-care. The magnitude of the change from baseline in body weight in SUSTAIN 1–5 was 4.5 to 6.4 kg with semaglutide 1 mg and 3.5 to 4.3 kg with semaglutide 0.5 mg. This reduction is greater than what has been previously reported with GLP-1 RAs for treatment of T2D.[1-4] However, direct comparisons with these trials should be made with caution due to the differences in study design and patient populations between individual trials. The demonstration of superior weight loss with semaglutide across a heterogeneous T2D population is encouraging, given the high proportion of patients with T2D who are overweight or

obese, conditions that are linked to an increased risk of comorbidities, including cardiovascular complications.[83, 92]

Hence, both superior glycemic control and weight loss were demonstrated for semaglutide when used as monotherapy in drug-naïve patients and combination therapy with other anti-glycemic agents. The combination of strong glycemic control and large body weight reduction with a low potential for hypoglycemia, administered as a once-weekly injection, is a promising finding given that a high proportion of patients with diabetes are overweight or obese and many other treatments are either weight-neutral or associated with weight gain accompanied by hypoglycemia and/or the need to be injected daily.[93, 94] When compared to basal insulin (insulin glargine), semaglutide also demonstrated a benefit-risk profile that indicates it may be an effective alternative treatment option with superior glycemic control and weight loss in addition to a lower risk of hypoglycemia. Hence, semaglutide may be beneficial in overcoming barriers in relation to treatment intensification, i.e. weight gain, hypoglycemia and multiple injections. In comparison to a currently marketed once-weekly GLP-1 RA (exenatide ER 2 mg), semaglutide 1 mg once-weekly demonstrated superior glycemic control and weight loss in addition to reduced immunogenicity.

7 Cardiovascular safety

Summary

- Evaluation of the effect of semaglutide on cardiovascular risk was primarily based on the dedicated cardiovascular outcomes trial (CVOT) SUSTAIN 6.
- A total of 254 first MACE were accrued during the 2-year treatment period. This amount of data is substantially larger than what is generally accepted to be needed to firmly evaluate the primary non-inferiority hypothesis (margin 1.8) of cardiovascular safety.
- Cardiovascular safety of semaglutide was established in SUSTAIN 6 (CVOT) based on 3-component MACE with an estimated hazard ratio for semaglutide versus placebo of 0.74 $[0.58; 0.95]_{95\%CI}$. The cardiovascular safety was supported by all three components of the MACE endpoint; non-fatal stroke, non-fatal myocardial infarction and cardiovascular death.
- The 2-year cumulated incidence of MACE was 6.2% with semaglutide and 8.4% with placebo.
- Non-inferiority of semaglutide versus placebo was confirmed with a margin of 1.8 (pre-planned) as well as 1.3 (*post-hoc)* with the upper bound of the 95% CI being below 1.0.
- The cardiovascular safety of semaglutide was supported by results based on preplanned analyses using a broader definition of MACE including the 3-component MACE, revascularization (coronary and peripheral), unstable angina pectoris requiring hospitalization and hospitalization for heart failure. In line with the results for the primary MACE analysis, cardiovascular safety of semaglutide was established with a hazard ratio of 0.74 $[0.62; 0.89]_{95\%CI}$) and the upper bound of the confidence interval below 1.
- A total of 21 patients had EAC-confirmed MACE in the 7 phase 3a trials (excluding SUSTAIN 6 (CVOT)). The proportions of patients with MACE were similar with semaglutide (0.5 mg: 8 patients [0.6%], 1 mg: 5 patients [0.3%]) and comparator products (8 patients [0.5%]).
- Blood pressure and blood lipids were reduced with semaglutide versus placebo or the active comparators sitagliptin, exenatide ER and insulin glargine.
- A small, persistent increase in resting pulse rate (1 to 6 beats/minutes) was observed with semaglutide in the phase 3a trials, consistent with the GLP-1 RA class effects.

7.1 Background

Diabetes has been identified as an independent risk factor for cardiovascular (CV) disease, and alongside smoking, obesity, dyslipidaemia and hypertension account for most of the risk for heart disease and stroke worldwide.[95] Atherosclerotic CV disease is the leading cause of morbidity and mortality in patients with diabetes[8]; the risk of CV disease is 2-4 times greater for patients with T2D compared to the general population,[96,97] and death from CV causes is the most common cause of death in patients with T2D.[98] CV complications represent a major burden for patients, prescribers and society in general as the most common comorbidity in T2D, underscoring the need for therapies that do not increase the cardiovascular risk.

7.2 Statistical methods for evaluation and analyses of cardiovascular safety

In 2008, the US Food and Drug Administration (FDA) issued a guidance for industry for evaluation of cardiovascular safety associated with new diabetes drugs requiring sponsors to show that new anti-glycemic agents are not associated with an unacceptable increase in cardiovascular risk.[5] Accordingly, the semaglutide phase 3a program included a CVOT conducted to assess the cardiovascular safety of semaglutide compared to placebo. The design and execution of SUSTAIN 6 (CVOT) was in accordance with recommendations from FDA.

The trial was designed to rule out an excess cardiovascular risk of 80% or more for semaglutide as compared to placebo. SUSTAIN 6 (CVOT) was a long-term, multi-center, multi-national, randomized, double-blind, placebo-controlled trial that randomized 3,297 patients with T2D and high cardiovascular risk (see definition in Table 5). Semaglutide was evaluated versus placebo on a background of standard-of-care therapies using two maintenance dose levels of semaglutide (0.5 mg and 1 mg once-weekly) and volume-matched placebo (randomized 1:1:1:1). The randomization of patients was stratified to ensure even distribution within strata according to the following 3 stratification variables: cardiovascular disease status at baseline (established cardiovascular disease, or evidence of cardiovascular risk factors), insulin treatment at baseline (none, basal insulin, pre-mixed insulin), and renal impairment (eGFR<30 mL/min/ 1.73m^2 at baseline [presence or absence]). By trial selection criteria, patients with severe renal impairment are always included in the "established cardiovascular disease" stratum. This resulted in a total of 9 strata.

The primary endpoint was time from randomization to first occurrence of an adjudicated 3-component composite MACE defined as cardiovascular death, non-fatal myocardial infarction (including silent MIs), or non-fatal stroke. Deaths of unknown cause were included as presumed cardiovascular deaths in the statistical analyses in line with guideline recommendations.[5, 99, 100] SUSTAIN 6 (CVOT) had as a secondary objective to serve as a long-term safety and efficacy trial in the semaglutide development program, and thereby the trial differed from typical post-approval CVOTs as both efficacy and safety parameters were assessed frequently throughout the trial. Patients were to stay on treatment for the entire duration of the trial, and temporary treatment discontinuations (i.e., 'drug-holidays') were not allowed. During the trial, efforts were made to track outcomes and vital status for all patients, including those who discontinued trial medication.

These characteristics combined with the treatment duration of 2 years for all patients enabled assessment of long-term safety and effectiveness of semaglutide in a clinically relevant high cardiovascular-risk population.

A blinded, independent, external event adjudication committee (EAC) prospectively adjudicated potential MACEs reported in all phase 3a trials, including the cardiovascular outcomes trial, in accordance with a predefined set of diagnostic criteria as agreed upon with the FDA (see Appendix 2 for details). Identification of events to be sent for adjudication and adjudication of events were performed blinded to treatment assignment and included all fatal events as well as events suspected to be stroke, transient ischemic attach (TIA), myocardial infarction (MI), hospitalization for heart failure, unstable angina pectoris (UAP) requiring hospitalization, and revascularization procedures.

SUSTAIN 6 (CVOT) was designed to be both *time* and *event* driven. All patients were to be treated for a minimum of 104 weeks for evaluation of long-term safety. In addition, at least 122 first MACEs were required in order to ensure 90% power for the test of non-inferiority on the primary endpoint with a margin of 1.8 based on an assumption of a true hazard ratio of 1.0 (i.e., no difference between pooled semaglutide versus pooled placebo). In case fewer than 122 first MACEs were collected during the 104 weeks period, the trial would have been extended to accrue the 122 first MACEs. However, as the actual MACE rate was higher than the rate used in the power calculations and the target of 122 patients with MACEs would be achieved during the 2–year treatment period, the time requirement became the defining factor for the trial duration. Accordingly the trial duration was fixed for all patients to 104 weeks followed by a 5-week follow-up period. A total of 254 first MACEs were accrued during the 2-year treatment period. Hence, the number of patients with MACEs was more than twice as high as originally planned. The number of MACEs in SUSTAIN 6 (CVOT) is therefore substantially larger than what is generally accepted to be sufficient to firmly evaluate the primary non-inferiority hypothesis (margin 1.8) of cardiovascular safety.[5]

The statistical analysis plan (SAP) was discussed and commented upon by FDA prior to unblinding and database lock (DBL). No interim analysis was performed in SUSTAIN 6 (CVOT). The primary endpoint was, in line with the assumption of no effect on cardiovascular risk, analyzed based on pooled data from semaglutide 0.5 mg and 1 mg versus pooled placebo (0.5 mg and 1 mg) using a stratified Cox proportional hazards model based on data from all randomized patients (full analysis set: FAS) in line with the intention-to-treat (ITT) principle. As a supportive analysis the primary analysis model was repeated comparing the effect on first MACE for each dose level. All EAC-confirmed events that occurred after randomization until the follow-up visit and reported prior to DBL were included in the statistical analyses. Patients who did not experience an event between randomization and the follow-up visit were censored at last date of contact. Statistical analyses were performed using a predefined hierarchy. The pre-specified hierarchical testing strategy included a test for non-inferiority (margin 1.8) on the primary MACE endpoint (pooled semaglutide versus

pooled placebo) as a first step, followed by tests of superiority versus placebo for each dose of semaglutide on body weight and HbA_{1c} endpoints.

The strength of evidence for establishing cardiovascular safety was evaluated by the totality of evidence including the magnitude and direction of the estimated hazard ratios for the primary MACE outcome and supporting endpoints. The extent of uncertainty as measured by the 95% confidence interval for the primary MACE endpoint was compared to the non-inferiority margin of 1.3 in line with the 2008 FDA guidance for evaluating cardiovascular safety in new antiglycemic therapies.[5] Finally, the strength of statistical evidence for cardiovascular safety was evaluated by calculating the *post-hoc* p-value for the non-inferiority hypotheses with margin 1.3 for the primary MACE endpoint.

Pre-specified sensitivity analyses were performed to investigate the robustness of the result for the primary endpoint. These included analyses that investigated the impact of exposure to trial product based on pre-defined criteria (Table 12).

Table 12 SUSTAIN 6 (CVOT): Pre-planned and *post-hoc* sensitivity analyses of primary MACE endpoint

Model	Population	Observation period
Pre-planned analyses		
Primary analysis, stratified Cox model	FAS	In-trial
Stratified Cox model with treatment as four levels		
Un-stratified Cox model		
Stratified Cox model	FAS, excluding patients with a CV event within 90 days prior to randomization	
Stratified Cox model	SAS (a)	On-treatment (7 day window) (b)
		On-treatment (30 day window) (c)
		On-treatment (42 day window) (c)
***Post-hoc* analyses**		
Stratified Cox model	FAS	In trial, adding a MACE for all patients lost to follow-up in the semaglutide group and none in the placebo group.
		In-trial, excluding MACEs classified as 'undetermined' cause of death
		In-trial, including additional MACEs for acute coronary syndrome and cerebrovascular events that the EAC were unable to adjudicate.

a) The SAS population includes all exposed patients and evaluated according to treatment actual received. **b**) The 42 day ascertainment window represented the planned follow-up period in the trials (i.e., 5+1 weeks). **c**) The 7 and 30 day ascertainment windows were included in the statistical analysis plan (SAP) after discussion with the FDA.
Abbreviations: EAC: event adjudication committee: FAS: full analysis set; MACE: major adverse cardiovascular event: SAS: safety analysis set.

Furthermore, the impact of different ascertainment windows (7, 30 and 42 days) following treatment discontinuation was assessed. In addition, *post-hoc* analyses were performed to further evaluate the robustness of the results.

7.3 Baseline cardiovascular status in SUSTAIN 6 (CVOT)

Of the 3,297 patients randomized into SUSTAIN 6 (CVOT), the majority (83.0%) were enrolled based on established cardiovascular disease at baseline, while 17.0% were enrolled based only on evidence of cardiovascular risk factors (Table 13, see definitions in Table 5).

Baseline cardiovascular history and complications were well-balanced across groups and were consistent with what would be expected in a population with a long duration of diabetes and a high prevalence of cardiovascular disease. Frequent cardiovascular-related conditions at baseline were hypertension (92.8% of patients), ischemic heart disease (60.5%) prior myocardial infarction (32.5%) prior ischemic stroke (11.6%), and a prior hemorrhagic stroke (3.3%). A total of 24% of the patients had chronic heart failure characterized as NYHA class I, II, or III at baseline.

The population was treated for T2D and cardiovascular risk factors in accordance with the standard-of-care approach in SUSTAIN 6 (CVOT) and use of concomitant cardiovascular and anti-glycemic medication was consistent with what would be expected in a population with a long duration of diabetes and a high prevalence of cardiovascular disease. A high proportion of patients received treatment with statins (72.8%), anti-hypertensive medications (93.5%) and anti-platelet agents (76.3%) and had well-controlled levels of blood lipids and blood pressure.

Table 13 SUSTAIN 6 (CVOT): Cardiovascular history and complications at screening

	Semaglutide		Placebo	
	N	(%)	N	(%)
Number of patients	1,648		1,649	
Established cardiovascular disease, age≥50 years	1,353	(82.1)	1,382	(83.8)
Evidence of cardiovascular risk factors, age≥60 years	295	(17.9)	267	(16.2)
Ischemic heart disease	988	(60.0)	1,006	(61.0)
Stable angina pectoris	231	(14.0)	251	(15.2)
Asymptomatic (silent) cardiac ischemia	136	(8.3)	149	(9.0)
Unstable angina	125	(7.6)	117	(7.1)
Non-ST-elevation myocardial infarction (a)	180	(10.9)	184	(11.2)
ST-segment elevation myocardial infarction (a)	202	(12.3)	197	(11.9)

Abbreviations: N: number of patients; SD: standard deviation; %: proportion of patients.

table is continued on next page

	Semaglutide		Placebo	
	N	(%)	N	(%)
Myocardial infarction (a)	530	(32.2)	542	(32.9)
PCI performed (b)	490	(29.7)	522	(31.7)
CABG performed (b)	288	(17.5)	289	(17.5)
Stroke	230	(14.0)	261	(15.8)
Ischemic stroke	178	(10.8)	205	(12.4)
Hemorrhagic stroke	52	(3.2)	56	(3.4)
Transient ischemic attack	98	(5.9)	94	(5.7)
Heart failure	381	(23.1)	396	(24.0)
NYHA class I	91	(5.5)	97	(5.9)
NYHA class II	241	(14.6)	240	(14.6)
NYHA class III	44	(2.7)	49	(3.0)
Left ventricular diastolic dysfunction	354	(21.5)	316	(19.2)
Left ventricular hypertrophy	508	(30.8)	471	(28.6)
Hypertension	1,543	(93.6)	1,516	(91.9)
Systolic BP (mmHg), mean (SD)	136.0	(17.47)	135.3	(16.82)
Diastolic BP (mmHg), mean (SD)	76.99	(10.00)	77.10	(10.04)
Lipids				
LDL-cholesterol (mg/dL), mean (SD)	89.67	(36.84)	90.08	(38.13)
HDL-cholesterol (mg/dL), mean (SD)	45.45	(12.72)	45.21	(12.61)

a) The number of patients with myocardial infarction also includes patients with STEMIs and Non-STEMIs tabulated under ischemic heart disease. **b**) Only evaluated in patients with ischemic heart disease.
Abbreviations: BP: blood pressure; CABG: coronary artery bypass graft surgery; N: number of patients; NYHA: New York Heart Association; PCI: Percutaneous Coronary Intervention; SD: standard deviation %: proportion of patients.

7.4 Cardiovascular outcomes

7.4.1 3-component MACE (primary endpoint)

A total of 254 patients had an EAC-confirmed MACE during SUSTAIN 6 (CVOT); fewer with semaglutide (108 patients, 6.6%) than with placebo (146 patients, 8.9%). The primary analysis was time to first EAC-confirmed MACE. Cardiovascular safety of semaglutide was established with an estimated hazard ratio for semaglutide versus placebo of 0.74 $[0.58; 0.95]_{95\%CI}$ (Table 14).

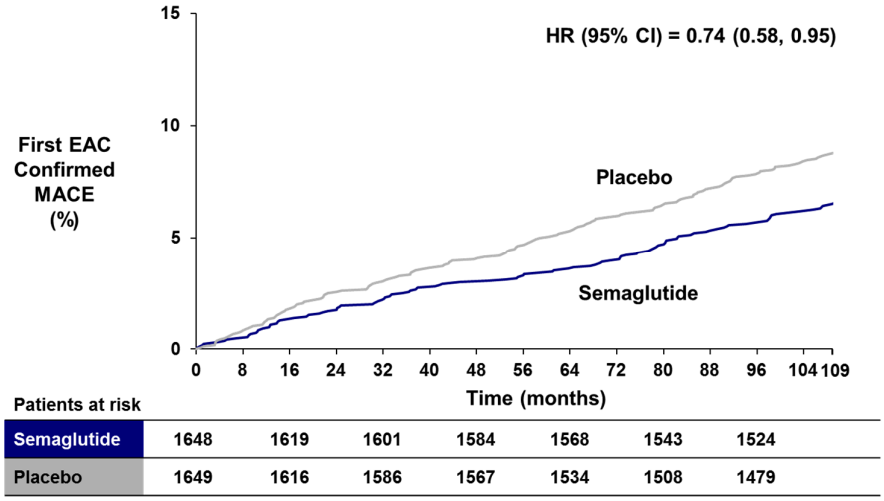
The 2-year cumulated incidence was 6.2% with semaglutide and 8.4% with placebo, corresponding to an absolute risk difference of 2.2% and a relative risk difference of 26%. Non-inferiority of semaglutide versus placebo was confirmed with a margin of 1.8 (pre-planned) as well as 1.3 (*post-hoc*) with the upper bound of the 95% confidence interval being below 1.0. The estimated risk of experiencing a first MACE within any certain time from randomization was lower with semaglutide than with placebo. The semaglutide and placebo Kaplan-Meier curves separated shortly after trial

initiation and the lines continued to separate throughout the trial, suggestive of a constant treatment effect over time in favor of semaglutide (Figure 19).

Table 14 SUSTAIN 6 (CVOT): First EAC-confirmed MACE

	Semaglutide		Placebo	
	N	(%)	N	(%)
Number of patients	1,648		1,649	
MACEs	108	(6.6)	146	(8.9)
Cardiovascular death (a)	44	(2.7)	46	(2.8)
Non-fatal myocardial infarction (b)	47	(2.9)	64	(3.9)
Non-fatal stroke	27	(1.6)	44	(2.7)
Hazard ratio (semaglutide/placebo)			0.74 [0.58; 0.95]$_{95\% CI}$	
Test for non-inferiority (H_0: HR ≥ 1.8 (pre-planned)			p <0.0001	
Test for non-inferiority (H_0: HR ≥ 1.3 (*post-hoc*)			p < 0.0001	
Test for risk reduction (H_0: HR ≥ 1.0 (*post-hoc*)			p = 0.0167	

a) including undetermined cause of death; **b**) including silent myocardial infarctions.
Notes: FAS in-trial. Time from randomization to first occurrence of a MACE (cardiovascular death, non-fatal MI or non-fatal stroke) was analyzed using the pre-specified Cox proportional hazard analysis using the two-sided Wald test, with treatment (semaglutide, placebo) as fixed factor and stratified by all possible combinations of the three stratification factors used in the randomization procedure (9 levels).
Abbreviations: EAC: event adjudication committee; HR: hazard ratio; MACE: major adverse cardiovascular event; N: number of patients; %: proportion of patients.

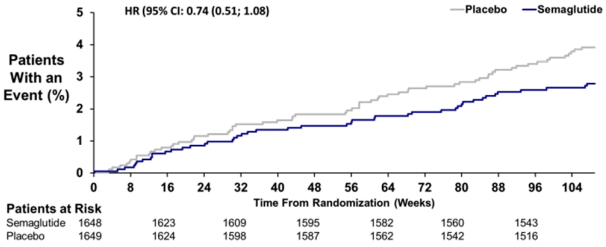


Notes: FAS in-trial. Kaplan-Meier estimates for cumulative proportion of patients with EAC-confirmed MACE. Estimated HR from stratified Cox proportional hazards model.
Abbreviations: CI: confidence interval; EAC: event adjudication committee; FAS: full analysis set; HR: hazard ratio; MACE: major adverse cardiovascular event.

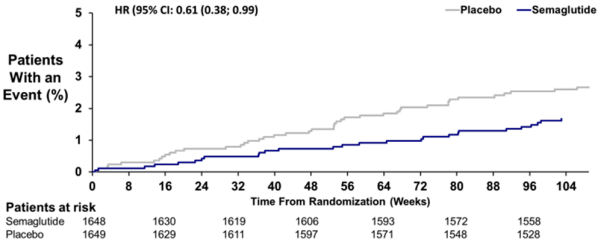
Figure 19 SUSTAIN 6 (CVOT): Plot of time to first EAC-confirmed MACE, semaglutide versus placebo

This risk difference was due to fewer events of non-fatal stroke and myocardial infarctions with no difference in cardiovascular deaths. The MACE components, events of non-fatal MI and non-fatal stroke had hazard ratios below 1.0 and generally followed the same pattern as that seen for overall MACEs, with a HR: 0.61 [0.38; 0.99]$_{95\%\ CI}$ for non-fatal stroke and a HR: 0.74 [0.51; 1.08]$_{95\%CI}$ for non-fatal myocardial infarction compared with placebo (Figure 20). The overall number of cardiovascular deaths was low in this trial (semaglutide: 44 deaths; placebo: 46 deaths), and cardiovascular deaths occurred at similar frequency with semaglutide and placebo (HR of 0.98 [0.65; 1.48]$_{5\%CI}$) with no clustering over time.

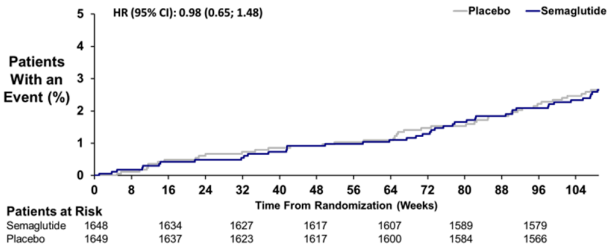
Non-fatal myocardial infarction



Non-fatal stroke



Cardiovascular death



Notes: FAS in-trial. Kaplan-Meier estimates for cumulative proportion of patients with EAC-confirmed event(s).
Abbreviations: CV: cardiovascular; CVOT: cardiovascular outcomes trial; EAC: event adjudication committee; FAS: full analysis set; sema. semaglutide.

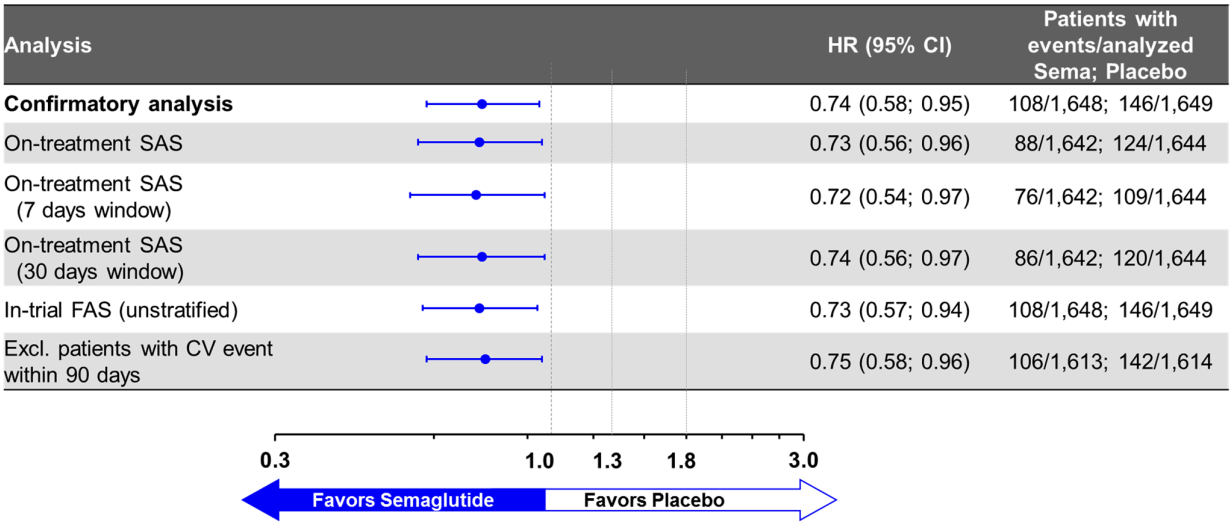
Figure 20 SUSTAIN 6 (CVOT): Kaplan Meier plot of time to first EAC-confirmed non-fatal myocardial infarction, non-fatal stroke or cardiovascular death

The cardiovascular safety of semaglutide was established for each semaglutide dose with upper bounds of the confidence intervals below 1.3. Time to first MACE analyses for semaglutide 0.5 mg and 1 mg compared with their volume-matched placebo groups, provided similar results as the primary analysis with a hazard ratio of 0.71 [0.49; 1.02]$_{95\%CI}$) for semaglutide 1 mg and a hazard ratio of 0.77 [0.55; 1.08]$_{95\%CI}$) for semaglutide 0.5 mg. The finding of similar results across two independent analyses (by dose) further supports the robustness of the primary analysis.

In support of the results from the primary analysis, the number and rate of all MACEs, including both first and recurrent events, was also lower with semaglutide (129 events and 3.8 events per 100 PYO) than with placebo (165 events, 4.9 events per 100 PYO).

Sensitivity analyses of 3-component MACE

The results of the pre-specified and *post-hoc* sensitivity analyses (Table 12) consistently supported the outcome and robustness of the primary analysis with hazard ratios that ranged from 0.72 to 0.75 (Figure 21, pre-planned analyses). All sensitivity analyses had confidence intervals with an upper bound below 1.0, supporting the robustness of the result from the primary analysis.



Notes: Summary of pre-planned analyses of time to first EAC-confirmed MACE. Estimated HRs and associated CIs are from the Cox proportional hazards model with treatment as fixed factor and , if not otherwise mentioned , stratified by all possible combinations of the three stratification factors used in the randomization procedure (in total 9 levels).
Abbreviations: CI: confidence interval; CV: cardiovascular; CVOT: cardiovascular outcomes trial; EAC: event adjudication committee; FAS: full analysis set; HR: estimated hazard ratio; MACE: major adverse cardiovascular event; SAS: safety analysis set; sema. semaglutide.

Figure 21 SUSTAIN 6 (CVOT): Forest plot of pre-planned sensitivity analyses of time to first EAC-confirmed MACE

EAC confirmation rates did not differ between semaglutide and placebo across reporting methods (see details in Appendix 2). Overall, the EAC confirmation rate of adjudicated possible cardiovascular events was highest among events identified by investigators. Evaluation of MACEs based solely on investigator-reported adverse events revealed similar conclusions as the primary analysis of EAC-confirmed first cardiovascular events.

The potential impact of cardiovascular events that the EAC received but could not adjudicate due to insufficient information and deaths with undetermined cause on the primary MACE endpoint was addressed in *post-hoc* sensitivity analyses. The cause of death was classified as 'undetermined' by the EAC for 33 of 90 patients classified as cardiovascular death (semaglutide: 13 patients; placebo: 20 patients) (see details in Appendix 2). Per the pre-specified analysis plan, these patients contributed to the primary analysis of MACEs as cardiovascular deaths. A *post-hoc* statistical

sensitivity analysis was performed excluding those events from the analysis, yielding a similar result as the primary analysis (HR: 0.77 $[0.59; 1.00]_{95\%CI}$). The EAC was unable to adjudicate a total of 30 potential events (semaglutide: 12 events; placebo: 18 events) of myocardial infarction or stroke due to insufficient information (see Appendix 2). A *post-hoc* statistical sensitivity analysis was performed where these events were included in the analyses and counted as EAC-confirmed MACEs, yielding a hazard ratio of 0.74 $[0.58; 0.94]_{95\%CI}$. Hence, both analyses confirmed the robustness of the primary analysis. Differences between semaglutide and placebo in the proportion of patients with investigator-reported cardiovascular adverse events were overall consistent with the findings and conclusions based on corresponding EAC-confirmed cardiovascular events, adding to the validity and robustness of the adjudication process and primary analyses.

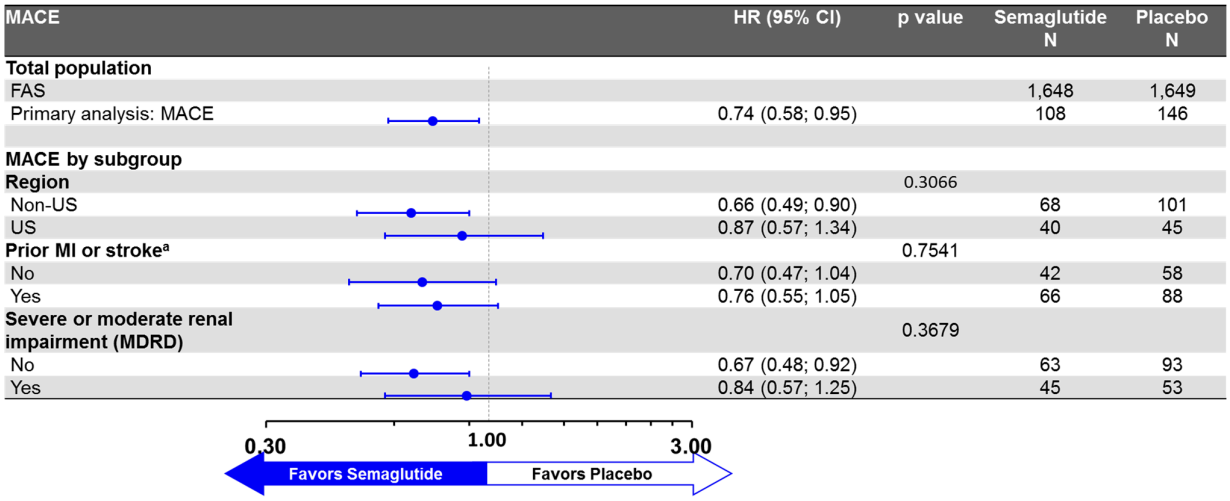
A modified composite MACE endpoint, i.e., non-fatal MI, non-fatal stroke and all-cause death was a secondary endpoint in SUSTAIN 6 (CVOT) evaluating the impact on deaths classified by the EAC as non-cardiovascular related. For the modified MACE endpoint, a hazard ratio of 0.77 $(0.61; 0.97)_{95\%CI}$ was consistent with the results of the primary MACE analysis.

A total of 98% of patients completed SUSTAIN 6 (CVOT) (see Section 5.5). An analysis of a highly unlikely scenario was performed as a *post-hoc* sensitivity analysis to evaluate the potential impact of missing follow-up information on the non-inferiority margin of 1.3. In the analysis, the 24 semaglutide-treated patients who were non-completers (withdrew from the trial or were lost to follow-up) and without a MACE were assumed to experience a MACE at time of censoring. Placebo-treated non-completers without a MACE were assumed not to experience MACEs, resulting in 132 events with semaglutide and an unchanged 146 events with placebo. The analysis provided a hazard ratio of 0.89 with a 95% confidence interval of [0.71; 1.13], with the upper value still below the 1.3 limit supporting the robustness of non-inferiority of semaglutide versus placebo for 1.3 non-inferiority margin. Given that this extreme scenario still maintained the conclusion of excluding the *post-hoc* 1.3 non-inferiority margin for semaglutide compared to placebo for the primary MACE endpoint, other imputation methods would also show non-inferiority with margin 1.3.

7.4.2 3-component MACE in subpopulations

Pre-specified analyses of the primary endpoint on time to first MACE evaluated the consistency of the treatment effect between semaglutide and placebo across multiple subpopulations based on age, sex, race, ethnicity, region, baseline BMI, baseline HbA_{1c}, duration of diabetes, chronic heart failure class II-III, evidence of cardiovascular disease, renal status and insulin treatment at baseline (Appendix 3, Figures 1–4). Additional subpopulations were examined *post-hoc* using the same methods as for the pre-specified analyses: previous myocardial infarction or stroke, pre-existing diabetic retinopathy, baseline body weight, geographical area, baseline use of statins, baseline use of angiotensin-converting enzyme (ACE)-inhibitor/angiotensin-receptor (AR) blocker and baseline use of acetylsalicylic acid (Appendix 3, Figures 5 and 6). Interpretation of results from analyses of subpopulations should be made with caution, since spurious findings can arise when multiple

subgroups are analyzed. Nonetheless, consistent effects on MACEs were seen across subpopulations including the US versus non-US population and in patients with renal impairment (Figure 22), confirming the cardiovascular safety of semaglutide across these populations. Of note, consistent effects were seen when semaglutide was administered to patients without previous myocardial infarction or stroke, i.e., as primary prevention (HR: 0.70 $[0.47; 1.04]_{95\%CI}$) as well as in patients with a previous myocardial infarction or stroke (secondary prevention) (HR: 0.76 $[0.55; 1.05]_{95\%CI}$) (Figure 22).



a) *Post-hoc* analysis.
Notes: FAS in-trial. Estimated HRs and associated CIs and p-value for interaction is from the un-stratified Cox proportional hazards model with an interaction between treatment and subgroup as fixed factor.
Abbreviations: CI: confidence interval; FAS: full analysis set; HR: hazard ratio; MACE: major adverse cardiovascular events; MI: myocardial infarction; MDRD: modification of diet in renal disease estimated glomerular filtration rate.

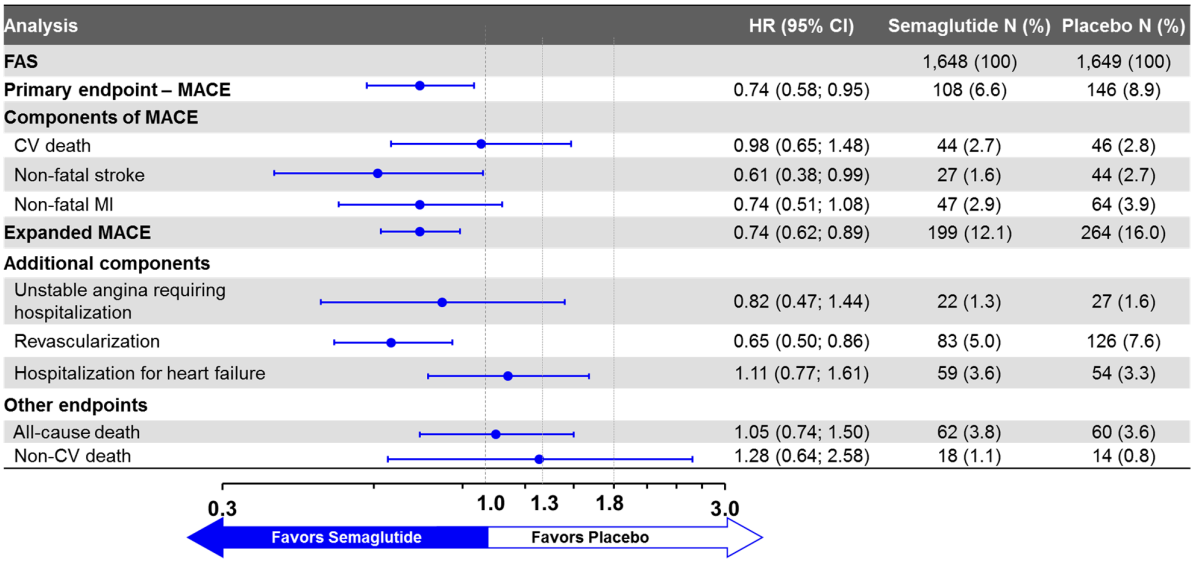
Figure 22 SUSTAIN 6 (CVOT): Selected subgroup analysis of 3-component MACE

7.4.3 Expanded MACE and individual components of expanded MACE

The establishment of cardiovascular safety of semaglutide was supported by results based on preplanned analyses using a broader definition of MACE (expanded MACE). This expanded MACE endpoint included the 3-component MACE discussed above, as well as revascularization (coronary and peripheral), unstable angina pectoris (UAP) requiring hospitalization and hospitalization for heart failure (additional 209 patients with events). In line with the results for the primary MACE analysis, cardiovascular safety of semaglutide was established based on time to first expanded MACE (HR: 0.74 $[0.62; 0.89]_{95\%CI}$) with an upper bound of the confidence interval below 1 (Figure 23).

For the expanded MACE endpoint, all four individual cardiovascular components closely related to atherosclerotic disease; events of non-fatal myocardial infarction, non-fatal stroke,

revascularization, and unstable angina requiring hospitalization, had point estimates with hazard ratios below 1 (Figure 23).



Notes: FAS in-trial. Estimated hazard ratios and associated confidence intervals are from a Cox proportional hazard model with treatment (semaglutide, placebo) as fixed factor and stratified by all possible combinations of the three stratification factors used in the randomization procedure (in total 9 levels).
Abbreviations: CI: confidence interval; CV: cardiovascular; FAS: full analysis set; HR: hazard ratio; MACE: major adverse cardiovascular events; MI: myocardial infarction; N: number of patients; % proportion of patients with events.

Figure 23 SUSTAIN 6 (CVOT): Forest plot of time to first expanded cardiovascular composite outcomes and individual components, semaglutide versus placebo

There was no evidence of an effect of semaglutide on hospitalization for heart failure (HR of 1.11 $[0.77; 1.61]_{95\%CI}$). All-cause mortality, including cardiovascular deaths and non-cardiovascular deaths, were similar with semaglutide and placebo. The number of non-CV deaths was low in both groups (Figure 23).

7.4.4 3-component MACE in phase 3a pool

A total of 21 patients had EAC-confirmed MACEs in the 7 phase 3a trials (excluding SUSTAIN 6 [CVOT]). The proportions of patients with MACEs were similar with semaglutide (0.5 mg: 8 patients [0.6%], 1 mg: 5 patients [0.3%]) and comparator products (8 patients [0.5%]).

7.5 Intensification of cardiovascular medication in SUSTAIN 6 (CVOT)

In SUSTAIN 6 (CVOT), co-morbidities and cardiovascular risk factors were to be treated in accordance with standard-of-care based on individual requirements and at investigator's discretion. At baseline, the population was generally well-treated with regards to cardiovascular risk factors. During the 2-year trial period, semaglutide-treated patients had less intensification (i.e., additional

medication or increased dose of medication) with cardiovascular medication than placebo-treated patients. *Post-hoc* statistical analyses of cardiovascular medication added during the trial showed fewer additions for semaglutide versus placebo with regards to anti-hypertensive drugs (0.5 mg and 1 mg), diuretics (0.5 mg and 1 mg), anti-thrombotic medication (0.5 mg) and lipid-lowering drugs (1 mg). Thus, it is unlikely that the observed effect of semaglutide on cardiovascular safety could be attributed to an imbalance in cardiovascular medication received during the trial period.

7.6 Cardiometabolic parameters

T2D and obesity are associated with numerous metabolic abnormalities that contribute to the development of cardiovascular disease, including hypertension and hyperlipidemia. Semaglutide may effect these factors directly, as well as indirectly via weight loss.[101]

7.6.1 Blood pressure

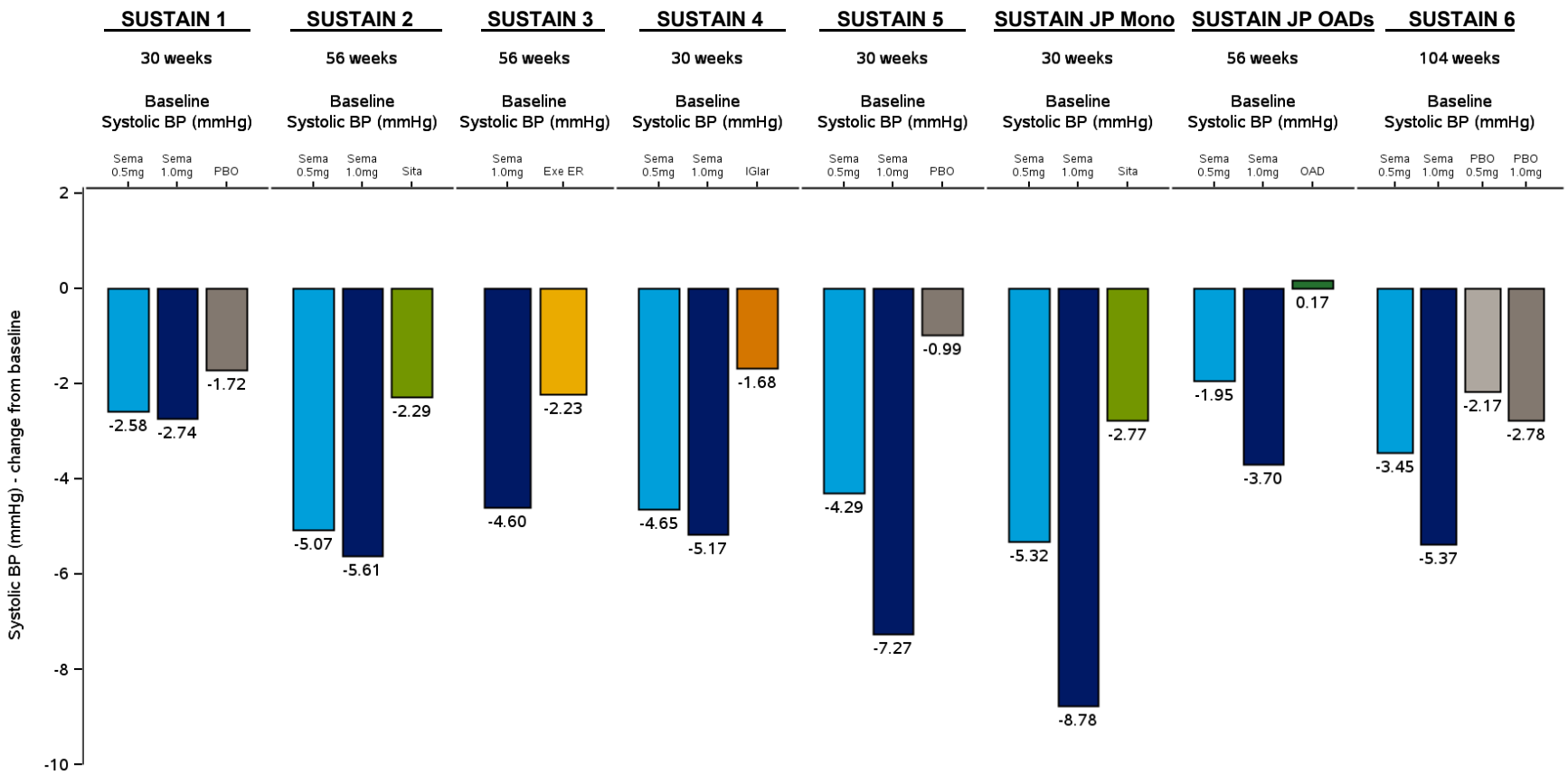
Lowering of blood pressure is of clinical relevance in patients with T2D who often have hypertension.[21-23] In the semaglutide development program including SUSTAIN 6 (CVOT), hypertension was to be treated according to local practice and no general treatment target or guidelines were reinforced.

Semaglutide treatment decreased systolic blood pressure (SBP) progressively during the initial 23 to 30 weeks of treatment, after which the mean blood pressures levels remained stable. The reduction in SBP was significantly greater with semaglutide than with comparators in all trials, except in SUSTAIN 1 where the reduction was significant greater only with 1 mg than with placebo (Figure 24). A larger decrease in SBP was consistently seen with semaglutide 1 mg than with semaglutide 0.5 mg, indicating a dose-dependent effect. There was a non-significant reduction in diastolic blood pressure with semaglutide as compared to placebo and active comparators.

These changes in SBP and diastolic blood pressure (DBP) are consistent with findings for other GLP-1 RAs. The general decrease in blood pressure with semaglutide was not associated with more adverse events related to hypotension or syncope.

7.6.2 Pulse rate

In concordance with the GLP-1 RA class, resting pulse rate was increased with semaglutide and the increase was non-dose related for the doses studied in the development program. An increase in resting pulse rate of 1 to 6 beats/minutes during treatment was seen across trials in the phase 3a program, consistent with observations for liraglutide (increase of 2 to 3 beats/min) [102-105] and other GLP-1 RAs.[22, 23] The underlying mechanism of the increase in pulse rate remains to be determined, but a study indicates that the GLP-1 receptors are present on myocytes of the sino-atrial node in non-human primates and humans.[106] The increase in pulse rate with semaglutide (1 mg: 2.11 beats/min) was not significantly different than the increase observed with exenatide ER (2 mg: 1.08 beats/min), with an estimated treatment difference of 1.03 beats/min $[-0.19;2.25]_{95\%CI}$. No clinical consequences of increased pulse rate (e.g., increased angina pectoris, hospitalization for



Note: Estimates from a MMRM based on the FAS using the 'on-treatment without rescue medication' data for SUSTAIN 1–5 and Japanese trials and the in-trial observation period for SUSTAIN 6 (CVOT). Mean estimates are adjusted according to observed baseline distribution in the FAS.
Abbreviations: BP: blood pressure; CVOT: cardiovascular outcomes trial; Exe ER: exenatide extended release;
FAS: full analysis set; IGlar: insulin glargine; JP: Japan; MMRM: mixed model for repeated measurements;
Mono: monotherapy; OAD: oral anti-glycemic drug; PBO: placebo; Sita: sitagliptin.

Figure 24 Trials in phase 3a program: Estimated change from baseline in systolic blood pressure (mmHg).

heart failure, palpitations or discontinuation of treatment due to tachycardia) were identified in the semaglutide development program. Furthermore, there was no increase in hospitalization for heart failure, MACE or increased mortality in SUSTAIN 6 (CVOT), all of which are hypothetically related to increased oxygen demand resulting from small increases in resting heart rate [107-109] (Section 7.4). Hence, based on the results obtained in SUSTAIN 6 (CVOT) as well as in the liraglutide CVOT (LEADER[14]), the increase in pulse rate does not seem to be associated with cardiovascular harm or result in an increased cardiovascular risk.

Semaglutide was not associated with increased reporting of arrhythmias in phase 3a trials including SUSTAIN 6 (CVOT). This is supported by data from the thorough QTc trial designed and conducted in accordance with recommendations in guidelines[110-112] Semaglutide administered at therapeutic and supra-therapeutic dose levels (up to 1.5 mg at steady state) did not prolong QTc intervals, consistent with trials within the GLP-1 drug class, where data have not indicated a QT-prolonging effect.[69, 70]

In the thorough QTc trial performed in healthy subjects, an increase in the PR-interval was found (estimated treatment difference of semaglutide 1 mg versus placebo across 11 time-points: 3.53 msec $[-1.08; 8.15]_{90\% CI}$ to 9.22 msec $[4.96; 13.47]_{90\% CI}$). This is in line with previous findings for GLP-1 RAs.[113] However, the PR prolongation has not been associated with increased risk of 2nd or 3rd degree AV-blocks nor related symptoms (syncope). This was confirmed in the phase 3a trials including SUSTAIN 6 (CVOT); no imbalances were identified with respect to any form of AV-block (1st – 3rd degree) or potential consequences of these (syncope) as evaluated by adverse events and centralized reading of ECGs. These data indicate no clinical consequences in patients with T2D of the PR interval prolongation seen in healthy subjects.

7.6.3 Lipids

Overall, improvements in the fasting blood lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, free fatty acids and VLDL) were seen with semaglutide treatment across phase 3a trials, especially with the 1 mg dose. Improvements were, however, modest and of uncertain clinical relevance.

7.7 Discussion and conclusions on cardiovascular safety

SUSTAIN 6 (CVOT) was a placebo-controlled, global, multicenter trial performed in a clinically distinct subpopulation (i.e., patients with T2D and at high cardiovascular risk) compared to the other phase 3a trials. The trial was well-conducted with high retention rates and vital status known at end-of-trial for nearly all patients, thus allowing robust conclusions to be drawn. Potential MACEs were evaluated by an external independent event adjudication committee. In accordance with regulatory guidelines on cardiovascular outcomes trials[5, 114] and in line with recommendations provided by the FDA, the trial was designed as a cardiovascular outcomes trial (CVOT) to demonstrate non-inferiority for the primary endpoint ‘time to first MACE’ (1.8 margin). A test of the 1.3 non-inferiority margin was not predefined as part of the confirmatory hierarchical testing

procedure. In SUSTAIN 6 (CVOT), patients were followed for a duration of 2 years. However, considering the number of MACEs accrued as well as the magnitude and robustness of the MACE hazard ratio and 95% confidence interval, the data obtained in SUSTAIN 6 (CVOT) is considered sufficient to demonstrate cardiovascular safety of semaglutide.

Cardiovascular safety of semaglutide was established in SUSTAIN 6 (CVOT) with an estimated hazard ratio for semaglutide versus placebo of 0.74 $(0.58; 0.95)_{95\%CI}$. Non-inferiority of semaglutide versus placebo for time to first MACE was confirmed with a margin of 1.8 (pre-planned) as well as 1.3 (*post-hoc*) with the upper bound of the 95% confidence interval being below 1.0. The conclusion based on the 3-component MACE was supported by the expanded MACE composite endpoint, and similar results were observed for each dose of semaglutide (0.5 mg and 1 mg) further supporting cardiovascular safety.

The primary analysis of cardiovascular safety of semaglutide was substantiated by a series of pre-specified statistical sensitivity analyses. These included several 'on treatment' analyses which resulted in similar hazard ratio point estimates ranging from 0.72 to 0.75 with upper confidence intervals below 1.0, all supporting cardiovascular safety. Furthermore, the findings were consistent across a variety of relevant subpopulations including baseline demographics and prognostic disease characteristics.

Treatment with semaglutide also resulted in significant reductions in SBP and improvements in lipid levels. In SUSTAIN 6 (CVOT) clinical relevant reductions in SBP were obtained with semaglutide (1 mg: -5.37 mmHg; 0.5 mg: -3.45 mmHg) in a population in which 94% of patients were receiving anti-hypertensive therapy at baseline. Reductions appeared to be dose-related and were significantly greater with semaglutide than with placebo even though fewer patients initiated new anti-hypertensive therapy with semaglutide than with placebo. Hypertension is an independent risk factor for cardiovascular disease and mortality and represents a common comorbidity in patients with T2D. Hypertension may also contribute to microvascular complications such as renal disease and retinopathy.[115, 116] Consequently, blood pressure control is an essential aspect in the management of T2D[117] and the reductions observed with semaglutide are clinically relevant.

8 Microvascular complications

Summary

- The analysis of time to first EAC-confirmed composite microvascular event (composite of nephropathy and retinopathy events) resulted in an estimated hazard ratio of 0.86 $[0.66; 1.12]_{95\%CI}$, corresponding to an estimated 14% lower risk with semaglutide versus placebo.
- Semaglutide reduced the risk of new or worsening nephropathy (composite endpoint). In SUSTAIN 6 (CVOT) time to first event analysis showed a hazard ratio (semaglutide vs. placebo) below 1 (HR: 0.64 $[0.46; 0.88]_{95\%CI}$ (p=0.0054), corresponding to an estimated 36% lower risk with semaglutide relative to placebo. The most pronounced effect was observed on the component 'new onset of persistent macro-albuminuria' (HR of 0.54 $[0.37; 0.77]_{95\%CI}$, p=0.0008).
- An increased risk of diabetic retinopathy complications (composite endpoint) was observed in SUSTAIN 6 (CVOT) (HR: 1.76 $[1.11; 2.78]_{95\%CI}$), see Section 10.5. The increased risk was observed in patients with pre-existing diabetic retinopathy.

8.1 Composite endpoint of microvascular complications

T2D is associated with a high risk of microvascular complications such as nephropathy and retinopathy.

In SUSTAIN 6 (CVOT), a combined microvascular endpoint looking at events indicating progression of microvascular disease or treatment thereof was included. The combined microvascular endpoint was a composite of new or worsening nephropathy and diabetic retinopathy complications. The combined microvascular composite endpoint, new or worsening nephropathy and diabetic retinopathy complications were pre-specified as secondary endpoints.

Time-to-first-event analyses were performed for these microvascular endpoints using a Cox proportional hazards model similar to that used for the primary analysis of MACEs with treatment as a factor based on the FAS. The analyses were based on first EAC-confirmed microvascular events.

Microvascular complications were evaluated based on components/criteria related to both treatments and diagnoses of events of new or worsening nephropathy and diabetic retinopathy (see Table 15). Due to opposite directional effects of treatment on the two components of the composite microvascular endpoint (diabetic retinopathy complications and new or worsening nephropathy), the results for the composite endpoint are described briefly, followed by a more in-depth description

of the results for the two components. Details on new or worsening nephropathy are presented in Section 8.2 and diabetic retinopathy complications are presented in Section 10.5.

Table 15 SUSTAIN 6 (CVOT): Microvascular composite endpoints and components

	Nephropathy composite	Diabetic retinopathy composite
Components/ criteria	• New onset of persistent macro-albuminuria (a,b) • Persistent doubling of serum creatinine and eGFR ≤45 mL/min/1.73 m^2 per MDRD (b) • Need for continuous renal replacement therapy (in the absence of an acute reversible cause) • Death due to renal disease	• Need for treatment with retinal photocoagulation • Need for treatment with intravitreal agents • Vitreous hemorrhage • Diabetes-related blindness (c)

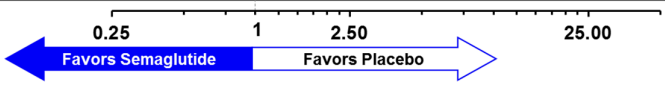
a) Macro-albuminuria was defined either as a 24-hour urine collection > 300 mg or as an elevated ratio in a spot sample > 300 mg albumin/ g creatinine. **b**) To confirm *persistent* macro-albuminuria or *persistent* doubling of serum creatinine, a confirmatory measurement was to be performed. **c**) Diabetes-related blindness was defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of less than 20 degrees, in the better eye with best correction possible). Note that the definition of 'diabetes-related blindness', does not mean it was a permanent loss of vision and could include a temporary reduction in visual acuity).
Abbreviations: eGFR: estimated glomerular filtration rate; MDRD: modification of diet in renal disease.

The analysis of time to first EAC-confirmed microvascular event counted first events fulfilling any of the 8 criteria defining the microvascular composite (Table 15). Likewise, the analysis of time to first EAC-confirmed nephropathy event counted first events fulfilling any of the 4 nephropathy criteria and the analysis of time to first EAC-confirmed retinopathy event counted first events fulfilling any of the 4 retinopathy criteria (Table 15). It should be noted that, a single EAC-confirmed event could simultaneously fulfil more than one of the criteria defining nephropathy or retinopathy events. Thus, a single event could count in more than one of the analyses of the individual components of the microvascular composite. Note that the composite microvascular endpoint combines with equal weighting events of unequal clinical severity, unequal clinical relevance and unequal expected frequency and, thus, results should be interpreted considering these limitations.

The analysis of time to first EAC-confirmed microvascular event resulted in an estimated hazard ratio of 0.86 $[0.66; 1.12]_{95\%CI}$, corresponding to an estimated risk reduction of 14% with semaglutide versus placebo. The difference between the treatment groups was largely due to a reduced risk of 'new onset of persistent macro-albuminuria' (Figure 25).

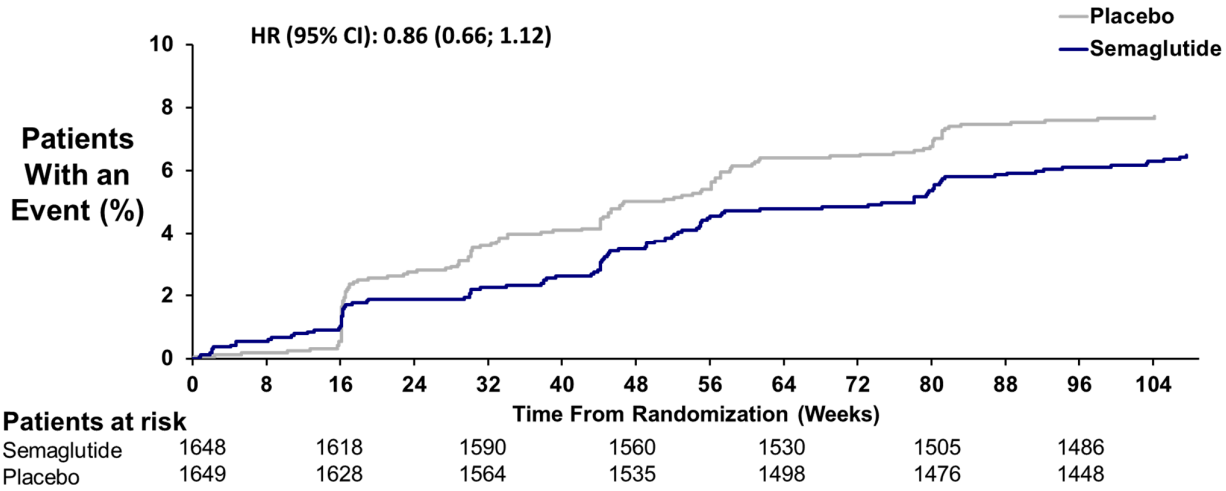
Events had onset throughout the entire observation period, with clustering of events at times of scheduled assessment of albumin, creatinine and creatinine clearance and funduscopy/fundus photography (Figure 26). The treatment difference occurred early and continued throughout the 2-year period.

Primary Analysis Component	Semaglutide N (%)	Placebo N (%)	HR (95% CI)
Microvascular composite	105 (6.4)	125 (7.6)	0.86 (0.66; 1.12)
New or worsening nephropathy	62 (3.8)	100 (6.1)	0.64 (0.46; 0.88)
Macroalbuminuria	44 (2.7)	81 (4.9)	0.54 (0.37; 0.77)
Doubling of serum creatinine	18 (1.1)	14 (0.8)	1.28 (0.64; 2.58)
Need for continuous renal replacement therapy	11 (0.7)	12 (0.7)	0.91 (0.40; 2.07)
Renal death	0 (0.0)	0 (0.0)	-
Diabetic retinopathy complications	50 (3.0)	29 (1.8)	1.76 (1.11; 2.78)
Need for retinal photocoagulation	38 (2.3)	20 (1.2)	1.91 (1.11; 3.28)
Need for intravitreal agent	16 (1.0)	13 (0.8)	1.23 (0.59; 2.56)
Vitreous hemorrhage	16 (1.0)	7 (0.4)	2.29 (0.94; 5.57)
Onset of diabetes-related blindness	5 (0.3)	1 (0.1)	5.01 (0.59; 42.88)



Notes: FAS in-trial. Time from randomization to first event was analyzed using a Cox proportional hazards model with treatment (semaglutide, placebo) as factor as fixed factor. Microvascular composite is the composite of the nephropathy and retinopathy endpoints. Doubling of serum creatinine was defined as persistent doubling of serum creatinine and eGFR $\leq$ 45 mL/min/1.73m^2 per MDRD.
Abbreviations: CI: confidence interval; EAC: event adjudication committee; eGFR: estimated glomerular filtration rate; HR: hazard ratio; MDRD: modification of diet in renal disease; N: number of patients; %: proportion of patients with event.

Figure 25 SUSTAIN 6 (CVOT): Forest plot of treatment contrasts for time to first EAC-confirmed microvascular composite endpoint and its components



Notes: FAS in-trial. Kaplan-Meier estimates for cumulative proportion of patients with nephropathy.
Abbreviations: CVOT: cardiovascular outcomes trial; EAC: event adjudication committee; FAS: full analysis set; sema: semaglutide.

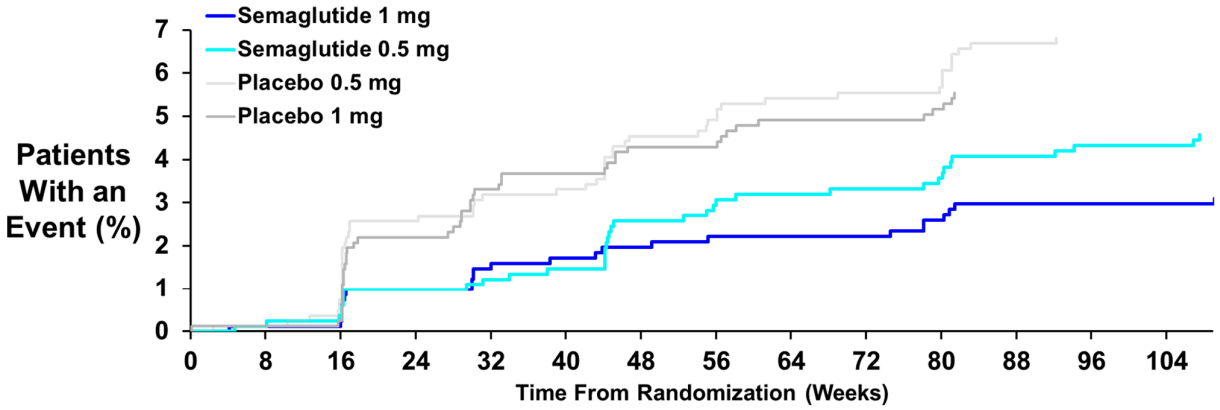
Figure 26 SUSTAIN 6 (CVOT): Kaplan-Meier plot of time to first occurrence of EAC-confirmed microvascular complications

8.2 Nephropathy

Nephropathy is a highly prevalent microvascular complication in patients with diabetes and T2D is the leading cause of end-stage kidney disease requiring renal replacement therapy. Reducing levels of blood glucose and blood pressure are essential in delaying the deterioration of renal function.

New or worsening nephropathy was evaluated by the EAC based on components/criteria related to both treatments and diagnoses of events (see Table 15). To ensure that transient and/or reversible changes in albuminuria or in renal function were not included in the analyses, the EAC Charter (Appendix 2, Section 2) required confirmatory measurements for nephropathy events (i.e., 'new onset of persistent macro-albuminuria' and 'persistent doubling of serum creatinine and eGFR ≤45 mL/min/ 1.73m^2') and excluded acute reversible causes for 'need for continuous renal replacement therapy'.

In SUSTAIN 6 (CVOT), the incidence and rate of new or worsening nephropathy (first events and recurrent events) were lower with semaglutide (62 patients with 68 events) than with placebo (100 patients with 106 events) (Figure 25).



Patients at Risk

Sema 0.5 mg	826	815	807	790	778	767	758
Sema 1 mg	822	815	798	790	785	774	767
Placebo 0.5 mg	824	812	785	770	753	741	726
Placebo 1 mg	825	817	785	775	765	757	745

Notes: FAS in-trial. Kaplan-Meier estimates: Analysis of time from randomization to first occurrence of new or worsening nephropathy. Patientswere censored at their planned end-of-trial visit, last direct patient-site contact or all-cause death of the patient, whichever came first.
Abbreviations: CVOT: cardiovascular outcomes trial; EAC: event adjudication committee; FAS: full analysis set; sema. semaglutide.

Figure 27 SUSTAIN 6 (CVOT): Kaplan-Meier plot of time to first occurrence of EAC-confirmed new or worsening nephropathy

Events had onset throughout the entire observation period, but as expected, events tended to cluster at time points of scheduled assessment of albumin and creatinine (Figure 27). The time to first event appeared dose-related (Figure 27). Time to first event analysis of the nephropathy endpoint showed a hazard ratio (semaglutide versus placebo) below 1 (HR: 0.64 $[0.46; 0.88]_{95\%CI}$, p=0.0054), with the most pronounced effect on the component 'new onset of persistent macro-albuminuria' (HR of 0.54 $[0.37; 0.77]_{95\%CI}$, p=0.0008) (Figure 25).

From the earliest stages of micro-albuminuria, it usually takes 10-20 years to develop end-stage renal disease (ESRD).[118] In SUSTAIN 6 (CVOT), the majority (approximately 72%) of the patients had normal renal function or only mild renal impairment at baseline, which together with a relatively short trial duration of 2 years may explain that the risk reduction in the nephropathy endpoint was driven by the component 'new onset of persistent macro-albuminuria'. A US consensus report[119] states that, although there are limitations, albuminuria is a clinically useful tool for predicting prognosis of progression of renal disease and for monitoring response to therapy. Furthermore, recent meta-analyses have demonstrated that the risk of ESRD significantly correlates with increasing urinary albumin to creatinine ratio (UACR)[120] and that for various interventions (pharmacological and dietary), the placebo-adjusted treatment effect on albuminuria significantly correlates with a subsequent reduced risk of ESRD.[121] Thus, in view of these data, the estimated risk reduction with semaglutide relative to placebo for 'new onset of persistent macro-albuminuria' in SUSTAIN 6 (CVOT) may be clinically relevant, although additional clinical data would be required to confirm and substantiate the effect.

Recent studies have shown that GLP-1 receptors are expressed in the renin-secreting cells of the juxtaglomerular apparatus in the kidney[106] and in the renal vasculature (including afferent arterioles)[122] and an anti-inflammatory effect has also been suggested.[123] Furthermore, short-term GLP-1 treatment has been shown to decrease angiotensin II levels and induce natriuresis in subjects with[124] or without T2D[125] and to reduce renin activity in subjects without diabetes.[126] These findings may support an additional effect of semaglutide on progression of renal disease besides the effect of improved glycemic control.

9 Clinical safety (excluding CV safety and diabetic retinopathy)

Summary

- The evaluation of the safety profile of semaglutide (0.5 mg and 1 mg) was based both on data from the 7 completed phase 3a trials of 30 to 56 weeks duration and data from the 2-year SUSTAIN 6 (CVOT) phase 3a trial.
- Semaglutide was well-tolerated when administered alone or in combination with other glucose lowering medicinal products for up to 2 years.
- The safety profile of semaglutide was overall consistent with other molecules within the GLP-1 RA class with gastrointestinal events, reduced appetite and weight decrease, and hypoglycemia (when combined with insulin or SU) as events evaluated to be causally related to semaglutide.
- Gastrointestinal events (mainly nausea, vomiting and diarrhea) were the most frequently reported adverse events during treatment with semaglutide and were the type of events most often leading to premature treatment discontinuation. Events were mainly mild or moderate in severity and of short duration. The majority of events occurred during dose escalation, and proportion of patients with events as well as number of events appeared to be dose-related.
- Events of cholelithiasis were reported more frequently with semaglutide than with comparator products, although the absolute risk was low (1-2%).
- A causal relationship between development of pancreatitis and treatment with semaglutide was not supported. EAC-confirmed events were few (below 1%) and mainly classified as 'acute mild pancreatitis' as per revised Atlanta classification.
- EAC-confirmed events of neoplasms in the SUSTAIN trials were distributed across several tissue types with estimated hazard ratios for semaglutide versus comparators/placebo on either side of unity and with no observed clustering within specific organ sites for either treatment group. No MTC cases were reported.
- The safety profile was consistent across subgroups of sex, age, race, ethnicity, body weight, hypertension, cardiovascular comorbidities, renal function, hepatic function, region, and anti-glycemic background medication, thus supporting the safe use of semaglutide across these groups.
- Except for diabetic retinopathy complications in SUSTAIN 6 (CVOT), no relevant differences were found between the safety profile in the less comorbid population in the phase 3a trials (excl. CVOT) compared to the more vulnerable and comorbid population in SUSTAIN 6 (CVOT).

9.1 Safety methodology

Safety methods

The safety of semaglutide was studied in the large semaglutide development program (5,710 semaglutide-treated patients) including patients across the T2D disease spectrum and with the most commonly associated comorbidities.

The evaluation of the safety profile of semaglutide (0.5 mg and 1 mg) was based both on data from the seven completed phase 3a trials of 30 to 56 weeks duration as well as data from the 2-year cardiovascular outcomes phase 3a trial. The phase 3a program covered the intended target populations, represented the majority of the overall exposure to semaglutide and enabled a focus on the comparison of the safety profile of semaglutide to placebo and active comparators. Unlike post-approval cardiovascular outcomes trials with selective safety reporting, full adverse event reporting was performed throughout SUSTAIN 6 (CVOT). A total of 2,687 patients (1,321 with semaglutide) were exposed for at least 18 months in SUSTAIN 6 (CVOT).

In all phase 3a trials including SUSTAIN 6 (CVOT), patients were to remain in the trial regardless of treatment adherence or addition of rescue medication to randomized treatment with continued collection of data. Hence, all patients were followed for the entire duration of the trials regardless of treatment adherence and, thus, the amount of missing data was low. This allows a comprehensive safety evaluation as patients were followed for the complete trial duration, unless they withdrew their consent. Accordingly, safety was evaluated based on exposed patients using both the on-treatment observation period (i.e., treatment-emergent events) and the in-trial observation period (including the period after discontinuation of trial medication). For the majority of safety assessments, the primary focus was on the period where patients were considered exposed to trial product (i.e., the on-treatment observation period). Due to a potential long latency and diagnostic lead time, the evaluation of cardiovascular and microvascular disorders, neoplasms and fatal events focused primarily on data from the entire trial period regardless of treatment adherence (i.e., the in-trial observation period).

The safety evaluation was based on standard safety parameters including investigator-reported adverse events including serious adverse events and deaths, clinical laboratory assessments (including anti-semaglutide antibodies), vital signs, ECGs and physical examinations. Based on the safety profiles of marketed GLP-1 RAs and common diabetic comorbidities, specific adverse events were selected as being of special interest for further in-depth data collection and assessments.

Areas of special interest were chosen based on:

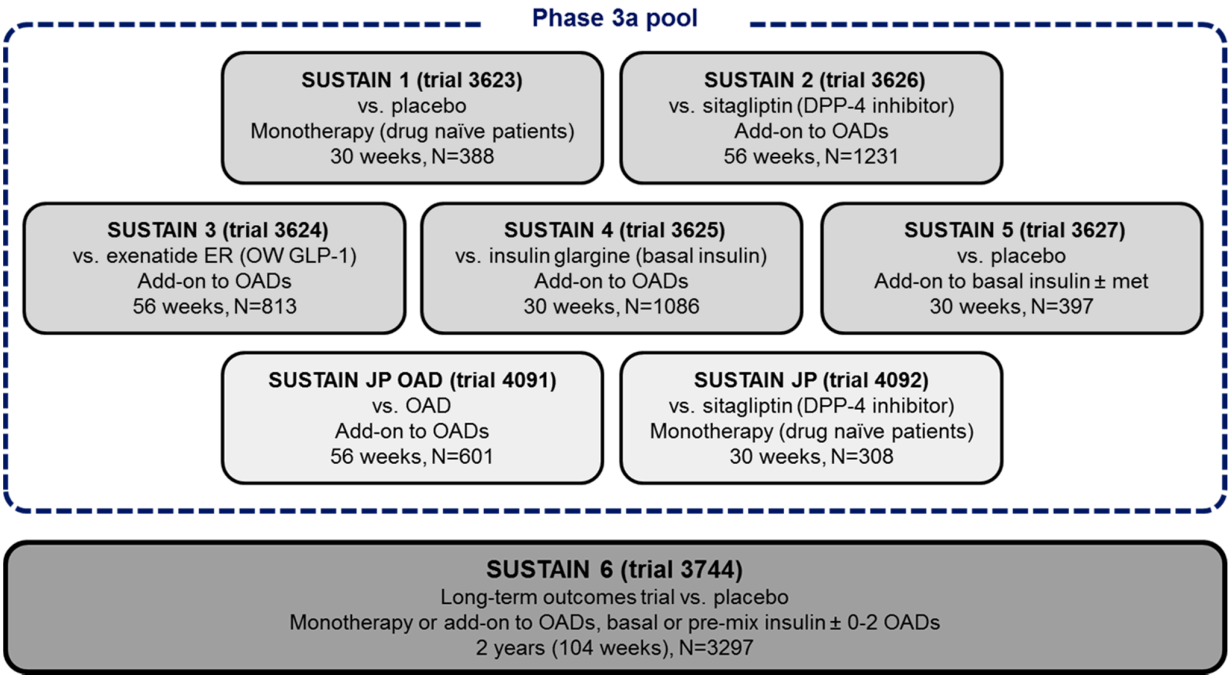
- observations relevant to the GLP-1 RA class: Gastrointestinal tolerability, cardiovascular safety including effects on pulse rate and PR interval, exocrine pancreas safety (pancreatitis and pancreatic cancer) including pancreatic enzyme elevations, thyroid safety including C-cell pathology and calcitonin elevations, and altered renal function.

- important safety parameters for the disease or population being treated: cardiovascular outcome assessments, neoplasms, acute gallstone disease, episodes of hypoglycemia and microvascular complications including diabetic retinopathy and nephropathy.
- general drug development safety concerns: adverse events leading to treatment discontinuation, hepatic safety, immunogenicity including antibody formation, allergic reactions and injection site reactions, medication errors, events of suspected transmission of an infectious agent via a medicinal product, rare events, and pregnancy.

Adverse events were analyzed based on either standardized MedDRA queries (SMQs) or pre-specified Novo Nordisk-customized MedDRA searches (NNMQs). Furthermore, certain of these events including deaths, selected cardiovascular disorders, pancreatitis, neoplasms including thyroid disorders requiring thyroidectomy and microvascular complications (SUSTAIN 6 [CVOT] only) were subject to prospective, external, blinded adjudication by independent medical experts in all phase 3a trials, see Section 5.2. Please note that events included in the evaluation of cardiovascular endpoints (MACEs and expanded MACEs) and microvascular endpoints (nephropathy and retinopathy) were also included in the analyses of adverse events. Differences in incidence rates of particular events between the analyses are related to the use of adjudicated or non-adjudicated data and also to the different lengths of the follow-up period after treatment discontinuation/completion for the analyses. As is usually the case for safety evaluation of drugs during clinical development, the semaglutide development program was not designed to characterize very rare adverse events or events with an expected long latency, such as neoplasms.

Data integration strategy

Data from SUSTAIN 6 (CVOT) were presented separately from the other phase 3a trials, because of important differences in trial designs including size, duration and population. The primary evaluation of safety data from the seven phase 3a trials excl. the SUSTAIN 6 (CVOT) were performed on integrated data from these trials (phase 3a pool), see Figure 28. This was done to increase the level of evidence and was considered appropriate due to the overall consistency in trial design and safety results seen across the individual trials. To avoid confounding due to differences between trials (Simpson's paradox), adjusted proportions and rates from integrated summaries were calculated based on the method of Cochran-Mantel-Haenszel.[127] Using this method, large and balanced trials are receiving the greatest weight when integrating information from multiple trials. The pooling strategy was agreed to by the FDA.



Abbreviations: DPP-4: dipeptidyl peptidase-4; GLP-1 RA: glucagon-like peptide-1 receptor agonist; JP: Japan; met: metformin; N: number of randomized patients; OADs: oral antiglycemic drugs; OW: once-weekly.

Figure 28 Trials in phase 3a program: Data pooling strategy for evaluation of safety

Safety monitoring and overview

An external and independent data monitoring committee (DMC) was established for SUSTAIN 6 (CVOT) in order to protect patients enrolled in the trial from harm, see Section 5.2. The DMC did not identify any safety issues warranting changes in trial conduct. In addition, the DMC ensured adequate monitoring of cardiovascular safety across all phase 3a trials.

Selected events reported in the phase 3a trials were subject to external blinded assessment by independent medical experts including continuous monitoring of calcitonin concentrations, central reading of ECGs for detection of potential silent myocardial infarctions, and prospective event adjudication by the EAC (see Section 5.2).

9.2 Semaglutide adverse event profile

Adverse event profile including common adverse events

The semaglutide safety profile was consistent across the clinical development program. Semaglutide was well-tolerated when administered alone or in combination with other glucose lowering medicinal products for up to 2 years.

The proportion of patients reporting at least one adverse event was higher with semaglutide (0.5 mg and 1 mg) than comparators in the phase 3a pool (excluding CVOT) (Table 16).

Table 16 Phase 3a pool: Adverse events

	Semaglutide 0.5 mg			Semaglutide 1 mg			Comparators		
	N (Adj.%)	E	Adj.R	N (Adj.%)	E	Adj.R	N (Adj.%)	E	Adj.R
Number of patients	1,373			1,777			1,657		
Patient years of exposure	1,165			1,548			1,467		
Adverse events	1,015 (73.4)	4,292	370.7	1,301 (72.7)	5,724	370.0	1,136 (68.7)	4,220	284.4
Serious adverse events (SAEs)	92 (6.6)	138	12.0	118 (6.7)	152	10.0	95 (5.8)	117	7.9
Severity									
Severe	79 (5.8)	127	11.3	104 (6.0)	148	9.9	75 (4.4)	107	7.1
Moderate	349 (26.0)	746	67.2	479 (27.5)	1,154	76.7	445 (26.4)	1,022	67.6
Mild	916 (65.9)	3,419	292.2	1,150 (63.9)	4,422	283.4	999 (60.5)	3,091	209.7
Outcome									
Fatal	7 (0.5)	7	0.6	3 (0.2)	3	0.2	6 (0.4)	6	0.4
Not recovered	386 (27.4)	695	59.0	495 (27.3)	859	54.8	473 (28.6)	859	57.7
Recovered with sequelae	6 (0.5)	7	0.6	10 (0.6)	13	0.9	9 (0.5)	14	0.9
Recovering	92 (6.6)	121	10.3	97 (5.2)	119	7.4	83 (5.1)	103	7.0
Recovered	940 (67.8)	3,461	299.9	1,204 (67.3)	4,725	306.4	1,018 (61.6)	3,235	218.1
Unknown	1 (<0.1)	1	<0.1	5 (0.3)	5	0.3	3 (0.2)	3	0.2
AEs leading to premature treatment discontinuation	84 (6.1)	131	11.6	156 (8.7)	241	15.6	51 (3.0)	83	5.5

Notes: SAS on-treatment. % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate. Please note that the number of fatal events occurring in the on-treatment period is based on the investigator-reported adverse event onset date.
Comparators: exenatide ER; insulin glargine; oral anti-glycemic drugs; sitagliptin, placebo.
Abbreviations: AE: adverse event; Adj.: adjusted; E: number of events; N: number of patients with event; PYE: patient-years of exposure; R: events per 100 PYE; SAE: serious adverse event; SAS: safety analysis set; %: proportion of patients with event.

In SUSTAIN 6 (CVOT) the proportions of patients reporting events were similar with semaglutide (0.5 mg and 1 mg) and placebo; however the rates were higher with semaglutide than with placebo (Table 17). The higher proportions and rates of adverse events observed with semaglutide in the phase 3a pool were mainly accounted for by patients experiencing gastrointestinal disorders (semaglutide 0.5 mg: 41.7%, 116.8 events per 100 PYE; semaglutide 1 mg: 42.1%, 143.5 events per 100 PYE; comparators: 22.0%, 50.7 events per 100 PYE). The higher proportions and rates of adverse events leading to premature treatment discontinuation with semaglutide in the phase 3a pool and SUSTAIN 6 (CVOT), were also mainly due to gastrointestinal (GI) disorders (Table 22).

Table 17 SUSTAIN 6 (CVOT): Adverse events

	Semaglutide 0.5 mg			Semaglutide 1 mg			Placebo		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of patients	823			819			1,644		
Patient years of exposure	1,488.3			1,443.9			3,034.8		
Adverse events	732 (88.9)	4,981	334.7	722 (88.2)	5,056	350.2	1,453 (88.4)	9,506	313.2
SAEs	264 (32.1)	599	40.2	240 (29.3)	481	33.3	574 (34.9)	1,256	41.4
Severity									
Severe	185 (22.5)	359	24.1	185 (22.6)	332	23.0	366 (22.3)	729	24.0
Moderate	476 (57.8)	1,522	102.3	476 (58.1)	1,657	114.8	934 (56.8)	3,073	101.3
Mild	646 (78.5)	3,099	208.2	633 (77.3)	3,067	212.4	1,285 (78.2)	5,699	187.8
Outcome									
Fatal	24 (2.9)	38	2.6	23 (2.8)	34	2.4	44 (2.7)	74	2.4
Not recovered	406 (49.3)	1,008	67.7	401 (49.0)	994	68.8	814 (49.5)	2,135	70.3
Recovered with sequelae	26 (3.2)	30	2.0	24 (2.9)	25	1.7	65 (4.0)	80	2.6
Recovering	90 (10.9)	165	11.1	80 (9.8)	165	11.4	160 (9.7)	314	10.3
Recovered	683 (83.0)	3,728	250.5	671 (81.9)	3,832	265.4	347 (81.9)	6,895	227.2
Unknown	7 (0.9)	12	0.8	3 (0.4)	6	0.4	5 (0.3)	8	0.3
AEs leading to premature treatment discontinuation	95 (11.5)	151	10.1	119 (14.5)	196	13.6	110 (6.7)	136	4.5

Note: SAS on-treatment. Please note that the number of fatal events occurring in the on-treatment period is based on the investigator-reported adverse event onset date.
Abbreviations: AEs: adverse events; E: number of events; N: number of patients with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; SAE: serious adverse event; SAS: safety analysis set; %: proportion of patients with event.

Overall, semaglutide had a safety profile consistent with that of other GLP-1 RAs both in patients with T2D evaluated for glycemic control (phase 3a pool) and in the more vulnerable population of patients with T2D at high risk of cardiovascular events (SUSTAIN 6 [CVOT]). All safety issues identified among commonly reported adverse events (Table 18 and Table 19) and serious adverse events (Table 20 and Table 21) in the phase 3a pool and SUSTAIN 6 (CVOT) are known from the GLP-1 RA class.

The most commonly reported adverse events with semaglutide (0.5 mg and 1 mg) were gastrointestinal disorders (see Section 9.4), which are known common side effects of GLP-1 RAs, particularly at initiation of treatment. The proportion of patients with gastrointestinal adverse events as well as the rate of events increased with semaglutide dose (Table 18). This was reflected in more adverse events and adverse events leading to premature treatment discontinuation with semaglutide 1 mg than with semaglutide 0.5 mg.

In addition to gastrointestinal events, decreased appetite, decreased weight, fatigue (including asthenia), dizziness, dysgeusia (altered taste perception) and cholelithiasis occurred more frequently with semaglutide than with placebo and comparators, and these adverse events are evaluated by Novo Nordisk to be causally related to semaglutide. In general, these reactions were mild or moderate in severity. In line with the increase in lipase and amylase levels observed with

semaglutide, and other GLP-1 RAs, adverse events of lipase and amylase increased were also reported more frequently with semaglutide (0.5 mg and 1 mg) than with placebo and active comparators.

Table 18 Phase 3a pool: Common (≥5% of patients) adverse events by system organ class and preferred term

	Semaglutide 0.5 mg			Semaglutide 1 mg			Comparators		
	N (Adj.%)	E	Adj.R	N (Adj.%)	E	Adj.R	N (Adj.%)	E	Adj.R
Number of patients	1,373			1,777			1,657		
Patient years of exposure	1,165			1,548			1,467		
Adverse events	1,015 (73.4)	4,292	370.7	1,301 (72.7)	5,724	370.0	1,136 (68.7)	4,220	284.4
Gastrointestinal disorders	580 (41.7)	1,345	116.8	755 (42.1)	2,202	143.5	66 (22.0)	754	50.7
Nausea	231 (17.0)	326	28.9	354 (19.9)	577	37.7	08 (6.3)	143	9.4
Vomiting	87 (6.4)	119	10.5	147 (8.4)	331	22.0	56 (3.3)	78	5.2
Dyspepsia	56 (4.1)	78	7.0	92 (5.2)	122	8.0	36 (2.1)	42	2.8
Diarrhea	166 (12.2)	234	20.6	238 (13.3)	380	24.9	94 (5.7)	128	8.7
Constipation	102 (6.9)	112	9.0	116 (6.2)	129	8.1	44 (2.7)	51	3.5
Infections and infestations	477 (33.9)	780	65.8	555 (30.7)	847	54.1	564 (34.6)	927	63.8
Nasopharyngitis	210 (14.5)	295	23.8	202 (10.7)	258	15.8	216 (13.8)	280	20.1
Investigations	234 (17.1)	375	32.7	309 (17.1)	469	30.3	247 (14.7)	417	27.6
Lipase increased	120 (8.7)	142	12.4	155 (8.5)	177	11.3	108 (6.3)	130	8.6
Nervous system disorders	165 (12.1)	340	30.1	233 (13.1)	384	25.0	190 (11.2)	302	19.9
Headache	71 (5.3)	183	16.4	112 (6.4)	196	12.8	94 (5.5)	145	9.6
Metabolism and nutrition disorders	161 (11.8)	206	18.2	230 (12.9)	272	17.7	154 (9.1)	180	11.9
Decreased appetite	87 (6.3)	103	8.9	131 (7.2)	139	8.8	35 (2.0)	39	2.6

Notes: SAS on-treatment. Data for the system organ class include all preferred terms and not only those reported in ≥5.0% of patients. The % is the Cochran-Mantel-Haenszel-adjusted percentage. Sorted by frequency with sema 1 mg.
Comparators: exenatide ER; insulin glargine; oral anti-glycemic drugs; sitagliptin, placebo.
Abbreviations: Adj: adjusted; E: number of events; ER: extended release; N: number of patients; PYE: patient years of exposure; R: event rate per 100 PYE; SAS: safety analysis set; sema: semaglutide; %: proportion of patients with event.

The semaglutide safety profile in patients at high cardiovascular risk (SUSTAIN 6 [CVOT]) generally resembled that observed in the broader T2D population (phase 3a pool). However, as expected the overall incidences of adverse events were higher in SUSTAIN 6 (CVOT) reflecting a population at high risk of comorbidities including cardiovascular disorders and a longer duration of the trial (Table 19).

In SUSTAIN 6 (CVOT), investigator-reported diabetic retinopathy and cataract were common adverse events (i.e., reported in ≥ 5% of patients) both with semaglutide and placebo. Events of diabetic retinopathy complications were evaluated by the independent external EAC; see Sections 10.2 and 10.5.

Table 19 SUSTAIN 6 (CVOT): Common (≥5% of patients) adverse events by system organ class and preferred term

	Semaglutide 0.5 mg			Semaglutide 1 mg			Placebo		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of patients	823			819			1,644		
Patient years of exposure	1,488.3			1,443.9			3,034.8		
Adverse events	732 (88.9)	4,981	334.7	722 (88.2)	5,056	350.2	1,453 (88.4)	9,506	313.2
Gastrointestinal disorders	415 (50.4)	1,208	81.2	426 (52.0)	1,370	94.9	564 (34.3)	1,230	40.5
Nausea	142 (17.3)	227	15.3	178 (21.7)	277	19.2	127 (7.7)	171	5.6
Vomiting	84 (10.2)	122	8.2	119 (14.5)	169	11.7	77 (4.7)	95	3.1
Diarrhea	145 (17.6)	274	18.4	145 (17.7)	242	16.8	177 (10.8)	264	8.7
Constipation	46 (5.6)	52	3.5	78 (9.5)	96	6.6	69 (4.2)	76	2.5
Dyspepsia	51 (6.2)	67	4.5	6 (7.7)	87	6.0	38 (2.3)	41	1.4
Abdominal pain upper	33 (4.0)	35	2.4	42 (5.1)	52	3.6	38 (2.3)	54	1.8
Abdominal pain	45 (5.5)	53	3.6	34 (4.2)	40	2.8	64 (3.9)	73	2.4
Infections and infestations	360 (43.7)	738	49.6	341 (41.6)	684	47.4	749 (45.6)	1,583	52.2
Urinary tract infection	75 (9.1)	100	6.7	63 (7.7)	75	5.2	127 (7.7)	176	5.8
Nasopharyngitis	59 (7.2)	80	5.4	52 (6.3)	69	4.8	139 (8.5)	178	5.9
Upper respiratory tract infection	50 (6.1)	56	3.8	45 (5.5)	53	3.7	118 (7.2)	152	5.0
Influenza	48 (5.8)	57	3.8	43 (5.3)	52	3.6	93 (5.7)	118	3.9
Bronchitis	40 (4.9)	47	3.2	35 (4.3)	38	2.6	99 (6.0)	116	3.8
Musculoskeletal and connective tissue disorders	218 (26.5)	323	21.7	202 (24.7)	313	21.7	474 (28.8)	828	27.3
Back pain	46 (5.6)	46	3.1	48 (5.9)	57	3.9	92 (5.6)	104	3.4
Arthralgia	39 (4.7)	42	2.8	30 (3.7)	35	2.4	107 (6.5)	130	4.3
Investigations	187 (22.7)	343	23.0	178 (21.7)	347	24.0	342 (20.8)	613	20.2
Lipase increased	87 (10.6)	106	7.1	81 (9.9)	115	8.0	120 (7.3)	144	4.7
Amylase increased	27 (3.3)	32	2.2	44 (5.4)	54	3.7	47 (2.9)	55	1.8
Nervous system disorders	191 (23.2)	296	19.9	191 (23.3)	302	20.9	404 (24.6)	687	22.6
Headache	54 (6.6)	75	5.0	55 (6.7)	86	6.0	138 (8.4)	221	7.3
Dizziness	48 (5.8)	51	3.4	43 (5.3)	49	3.4	77 (4.7)	100	3.3
Metabolism and nutrition	216 (26.2)	306	20.6	175 (21.4)	235	16.3	365 (22.2)	524	17.3
Decreased appetite	84 (10.2)	94	6.3	76 (9.3)	89	6.2	28 (1.7)	31	1.0
Eye disorders	149 (18.1)	199	13.4	143 (17.5)	209	14.5	272 (16.5)	367	12.1
Diabetic retinopathy	42 (5.1)	44	3.0	48 (5.9)	56	3.9	75 (4.6)	79	2.6
Cataract	51 (6.2)	54	3.6	41 (5.0)	46	3.2	79 (4.8)	84	2.8

Notes: SAS on-treatment. Data for the system organ class include all preferred terms and not only those reported in ≥5.0% of patients. On-treatment: on-set on or after the day of first randomized dose and not after the follow-up visit scheduled 5 weeks after the end-of-treatment.

Abbreviations: E: number of events; N: number of patients; PYE: patient years of exposure; R: event rate per 100 PYE; SAS: safety analysis set; %: proportion of patients with event.

Serious adverse events

In the phase 3a pool the proportion of patients with serious adverse events (SAEs) was low, and higher with semaglutide (0.5 mg: 6.6%; 1 mg: 6.7%) than with comparator products (5.8%) (Table 20). No clustering of SAEs across system organ classes or preferred terms was apparent, with no SAEs occurring in ≥1% of patients. SAEs of pancreatitis were reported in semaglutide-treated patients only; see Section 9.7 for further evaluation of pancreatitis.

Table 20 Phase 3a pool: Serious adverse events reported by ≥0.2% of patients by system organ class and preferred term

	Semaglutide 0.5 mg			Semaglutide 1 mg			Comparators		
	N	(Adj.%) E	Adj.R	N	(Adj.%) E	Adj.R	N	(Adj.%) E	Adj.R
Number of patients	1,373			1,777			1,657		
Patient years of exposure	1,165			1,548			1,467		
Serious adverse events (SAEs)	92 (6.6)	138	12.0	118 (6.7)	152	10.0	95 (5.8)	117	7.9
Infections and infestations	18 (1.3)	23	2.0	19 (1.1)	20	1.3	20 (1.2)	22	1.5
Pneumonia	6 (0.4)	6	0.5	2 (0.1)	2	0.1	2 (0.1)	2	0.1
Sinusitis	2 (0.2)	2	0.2	0 (0.0)			0 (0.0)		
Surgical and medical procedures	8 (0.6)	9	0.7	14 (0.8)	14	0.9	4 (0.3)	4	0.3
Coronary artery bypass	0 (0.0)			3 (0.2)	3	0.2	1 (<0.1)	1	<0.1
Coronary arterial stent insertion	2 (0.2)	2	0.2	2 (0.1)	2	0.1	0 (0.0)		
Gastrointestinal disorders	18 (1.3)	24	2.1	13 (0.7)	15	1.0	9 (0.5)	12	0.8
Pancreatitis	2 (0.2)	2	0.2	3 (0.2)	3	0.2	0 (0.0)		
Pancreatitis acute	2 (0.2)	2	0.2	0 (0.0)			0 (0.0)		
Umbilical hernia	2 (0.2)	2	0.2	1 (<0.1)	1	<0.1	1 (<0.1)	1	<0.1
Gastritis	2 (0.2)	2	0.2	0 (0.0)			1 (<0.1)	1	<0.1
Hemorrhoids	2 (0.2)	2	0.2	0 (0.0)			0 (0.0)		
Cardiac disorders	11 (0.8)	13	1.1	12 (0.7)	16	1.1	15 (0.9)	15	1.0
Atrial fibrillation	3 (0.2)	3	0.3	1 (<0.1)	1	<0.1	4 (0.2)	4	0.3
Nervous system disorders	7 (0.5)	7	0.6	8 (0.5)	9	0.6	10 (0.6)	10	0.6
Ischemic stroke	2 (0.2)	2	0.2	2 (0.1)	2	0.1	3 (0.2)	3	0.2
Hepatobiliary disorders	3 (0.2)	3	0.3	7 (0.4)	8	0.5	3 (0.2)	3	0.2
Cholecystitis acute	0 (0.0)			4 (0.2)	4	0.3	0 (0.0)		
Cholelithiasis	2 (0.2)	2	0.2	2 (0.1)	2	0.1	2 (0.1)	2	0.1
Metabolism and nutrition disorders	5 (0.4)	5	0.5	4 (0.2)	4	0.3	3 (0.2)	3	0.2
Hyponatremia	2 (0.2)	2	0.2	0 (0.0)			0 (0.0)		
Investigations	4 (0.3)	4	0.4	3 (0.2)	3	0.2	0 (0.0)		
Weight decreased	2 (0.2)	2	0.2	0 (0.0)			0 (0.0)		
Eye disorders	2 (0.2)	2	0.2	0 (0.0)			1 (<0.1)	1	<0.1
Cataract	2 (0.2)	2	0.2	0 (0.0)			1 (<0.1)	1	<0.1

Notes: SAS on-treatment. Data for the system organ class include all preferred terms and not only those reported in ≥0.2% of patients. The % is the Cochran-Mantel-Haenszel-adjusted percentage. Sorted by frequency in the semaglutide 1 mg group.
Comparators: exenatide ER; insulin glargine; oral anti-glycemic drugs; sitagliptin, placebo.
Abbreviations: Adj: adjusted; E: number of events; ER: extended release; N: number of patients; PYE: patient years of exposure; R: event rate per 100 PYE; SAS: safety analysis set; %: proportion of patients with event.

In SUSTAIN 6 (CVOT), the proportion of patients with SAEs was lower with semaglutide (0.5 mg: 32.1%; 1 mg: 29.3%) than with placebo (34.9%) (Table 21). The proportion of patients with SAEs was lower with semaglutide 1 mg than with 0.5 mg. In line with the distribution of EAC-confirmed cardiovascular events described in Sections 7.4 and 7.6.2, events within the system organ class 'Cardiac disorders' and 'surgical and medical procedures' were less common with semaglutide than with placebo.

Table 21 SUSTAIN 6 (CVOT): Serious adverse events reported by ≥1.0% of patients by system organ class and preferred term

	Semaglutide 0.5 mg				Semaglutide 1 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of patients	823				819				1,644			
Patient years of exposure	1,488.3				1,443.9				3,034.8			
Serious adverse events	264	(32.1)	599	40.2	240	(29.3)	481	33.3	574	(34.9)	1,256	41.4
Cardiac disorders	97	(11.8)	137	9.2	72	(8.8)	121	8.4	205	(12.5)	296	9.8
Atrial fibrillation	11	(1.3)	12	0.8	12	(1.5)	15	1.0	35	(2.1)	38	1.3
Angina unstable	10	(1.2)	11	0.7	11	(1.3)	14	1.0	39	(2.4)	42	1.4
Cardiac failure congestive	14	(1.7)	17	1.1	10	(1.2)	13	0.9	29	(1.8)	35	1.2
Acute myocardial infarction	13	(1.6)	14	0.9	9	(1.1)	9	0.6	38	(2.3)	39	1.3
Coronary artery disease	11	(1.3)	11	0.7	9	(1.1)	9	0.6	5	(0.3)	6	0.2
Cardiac failure	10	(1.2)	11	0.7	8	(1.0)	8	0.6	7	(0.4)	7	0.2
Myocardial infarction	4	(0.5)	4	0.3	8	(1.0)	8	0.6	19	(1.2)	21	0.7
Angina pectoris	8	(1.0)	8	0.5	7	(0.9)	8	0.6	25	(1.5)	26	0.9
Infections and infestations	59	(7.2)	77	5.2	42	(5.1)	50	3.5	128	(7.8)	159	5.2
Pneumonia	15	(1.8)	15	1.0	11	(1.3)	11	0.8	30	(1.8)	33	1.1
Urinary tract infection	8	(1.0)	8	0.5	2	(0.2)	2	0.1	13	(0.8)	13	0.4
Surgical and medical procedures	41	(5.0)	48	3.2	31	(3.8)	33	2.3	15	(7.0)	129	4.3
Coronary arterial stent insertion	10	(1.2)	11	0.7	7	(0.9)	8	0.6	30	(1.8)	33	1.1
Coronary revascularization	11	(1.3)	12	0.8	7	(0.9)	7	0.5	24	(1.5)	27	0.9
Coronary artery bypass	8	(1.0)	8	0.5	4	(0.5)	4	0.3	21	(1.3)	21	0.7
Nervous system disorders	36	(4.4)	42	2.8	28	(3.4)	39	2.7	81	(4.9)	97	3.2
Ischemic stroke	8	(1.0)	8	0.5	6	(0.7)	7	0.5	18	(1.1)	18	0.6
Renal and urinary disorders	32	(3.9)	36	2.4	20	(2.4)	24	1.7	62	(3.8)	72	2.4
Acute kidney injury	12	(1.5)	14	0.9	5	(0.6)	6	0.4	29	(1.8)	30	1.0
Chronic kidney disease	6	(0.7)	6	0.4	4	(0.5)	4	0.3	17	(1.0)	19	0.6
Injury, poisoning and procedural complications	23	(2.8)	26	1.7	18	(2.2)	20	1.4	41	(2.5)	49	1.6
Fall	9	(1.1)	9	0.6	4	(0.5)	4	0.3	14	(0.9)	14	0.5
Musculoskeletal and connective tissue disorders	12	(1.5)	14	0.9	5	(1.8)	16	1.1	40	(2.4)	51	1.7
Osteoarthritis	5	(0.6)	6	0.4	6	(0.7)	6	0.4	18	(1.1)	18	0.6

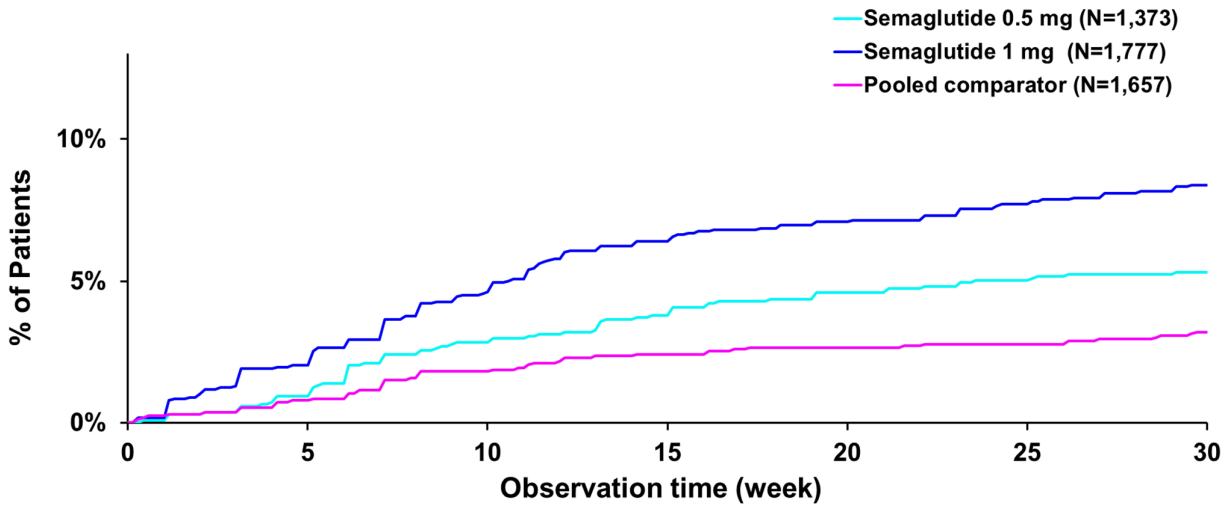
Notes: SAS on-treatment. Data for the system organ class include all preferred terms and not only those reported in ≥1.0% of patients. Table is sorted in descending order by class and/or term based on % with semaglutide 1 mg.
Abbreviations: E: Number of events; N: Number of patients experiencing at least one event; PYE: Patient years of exposure; R: Event rate per 100 PYE; SAS: Safety analysis set; %: proportion of patients with event.

Adverse events in subgroups

The adverse event profile, including serious adverse events and adverse events leading to premature treatment discontinuation, in subgroups of patients based on intrinsic factors (sex, baseline age, race, ethnicity, baseline BMI, baseline body weight, baseline hypertension, baseline cardiovascular comorbidities, baseline renal function, baseline hepatic function) and extrinsic factors (region, tobacco use and anti-glycemic background medication) was explored. The safety profile of semaglutide was consistent across all subpopulations of patients treated with semaglutide including the elderly, patients with renal impairment, and patients with established cardiovascular disease.

Adverse events leading to premature treatment discontinuation

More patients discontinued treatment prematurely due to adverse events with semaglutide (0.5 mg and 1 mg) than with placebo and active comparators across the phase 3a pool (semaglutide 0.5 mg: 6.1%; semaglutide 1 mg: 8.7%; comparators: 3.0%) (Figure 29) and SUSTAIN 6 (CVOT) (semaglutide 0.5 mg: 11.5%; semaglutide 1 mg: 14.5%; placebo: 6.7%). The majority of premature treatment discontinuations occurred in relation to treatment initiation and dose-escalation.



Note: SAS on-treatment.
Abbreviations: N: number of patients; SAS: safety analysis set.

Figure 29 Phase 3a pool: Adverse events leading to premature treatment discontinuation

The higher discontinuation rate with semaglutide was mainly attributable to the greater number of discontinuations related to gastrointestinal adverse events (e.g., nausea, vomiting, and diarrhea) (Table 22). Consistent with the dose-response observed for gastrointestinal adverse events, the proportion of patients who discontinued treatment prematurely was higher with semaglutide 1 mg than with semaglutide 0.5 mg.

Table 22 Phase 3a pool: Most frequent (≥0.2%) adverse events leading to premature treatment discontinuation by system organ class and preferred term

	Semaglutide 0.5 mg			Semaglutide 1 mg			Comparators		
	N (Adj.%)	E	Adj.R	N (Adj.%)	E	Adj.R	N (Adj.%)	E	Adj.R
Number of patients	1,373			1,777			1,657		
Patient years of exposure	1,165			1,548			1,467		
AEs leading to premature treatment discontinuation	84 (6.1)	131	11.6	156 (8.7)	241	15.6	51 (3.0)	83	5.5
Gastrointestinal disorders									
Nausea	21 (1.5)	21	1.9	45 (2.5)	48	3.1	9 (0.5)	9	0.6
Vomiting	7 (0.5)	7	0.6	28 (1.6)	28	1.9	2 (0.1)	2	0.1
Diarrhea	14 (1.1)	14	1.3	27 (1.5)	29	1.9	1 (<0.1)	1	<0.1
Dyspepsia	3 (0.2)	3	0.3	10 (0.5)	10	0.6	0 (0.0)		
Abdominal pain	4 (0.3)	4	0.4	8 (0.5)	8	0.5	3 (0.2)	3	0.2
Abdominal discomfort	4 (0.3)	4	0.3	6 (0.4)	7	0.5	0 (0.0)		
Abdominal distension	3 (0.2)	3	0.3	5 (0.3)	5	0.3	0 (0.0)		
Constipation	4 (0.3)	4	0.3	4 (0.2)	4	0.3	3 (0.2)	3	0.2
Abdominal pain upper	2 (0.2)	2	0.2	4 (0.2)	4	0.3	2 (0.1)	2	0.1
Pancreatitis	1 (<0.1)	1	<0.1	3 (0.2)	3	0.2	1 (<0.1)	1	<0.1
Gastrointestinal disorder	4 (0.3)	4	0.4	2 (0.1)	3	0.2	1 (<0.1)	1	<0.1
Eructation	3 (0.2)	3	0.3	2 (0.1)	2	0.1	0 (0.0)		
Pancreatitis acute	3 (0.2)	3	0.3	0 (0.0)			1 (<0.1)	1	<0.1
Investigations									
Lipase increased	5 (0.4)	5	0.5	5 (0.3)	5	0.3	4 (0.2)	4	0.3
Weight decreased	3 (0.2)	3	0.3	5 (0.2)	5	0.3	0 (0.0)		
Amylase increased	3 (0.2)	3	0.3	4 (0.2)	4	0.3	3 (0.2)	3	0.2
Metabolism and nutrition disorders									
Decreased appetite	8 (0.6)	8	0.7	15 (0.8)	15	0.9	0 (0.0)		
Nervous system disorders									
Dizziness	2 (0.2)	2	0.2	4 (0.2)	4	0.3	2 (0.1)	2	0.
Headache	1 (<0.1)	1	<0.1	3 (0.2)	3	0.2	2 (0.1)	2	0.
General disorders and administration site conditions									
Fatigue	2 (0.2)	2	0.2	3 (0.2)	3	0.2	0 (0.0)		
Injection site nodule	0 (0.0)			0 (0.0)			5 (0.3)	5	0.3
Skin and subcutaneous tissue disorders									
Rash	2 (0.2)	2	0.2	1 (<0.1)	1	<0.1	1 (<0.1)	1	<0.1
Urticaria	1 (<0.1)	1	<0.1	1 (<0.1)	1	<0.1	3 (0.2)	3	0.2
Infections and infestations									
Gastroenteritis	2 (0.2)	2	0.2	1 (<0.1)	1	<0.1	0 (0.0)		
Psychiatric disorders									
Insomnia	2 (0.2)	2	0.2	0 (0.0)			0 (0.0)		
Libido decreased	2 (0.2)	2	0.2	0 (0.0)			0 (0.0)		

Notes: SAS on treatment. % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.
Comparators: exenatide ER; insulin glargine; oral anti-glycemic drugs; sitagliptin, placebo.
Abbreviations: Adj.: adjusted; E: number of events; ER: extended release; N: number of patients with at least one event; PYE: patient-years of exposure; R: events per 100 PYE; SAS: safety analysis set; %: proportion of patients with event.

9.3 Deaths

Across the semaglutide development program, a total of 149 patients died. The majority of deaths (132 patients) occurred in the 2-year SUSTAIN 6 (CVOT) including 67 patients randomized to semaglutide and 65 patients randomized to placebo. In the other seven phase 3a trials, a total of 16 patients died; 10 (0.3%) randomized to semaglutide, and 6 patients (0.4%) randomized to comparator products. In addition, one patient included in a clinical pharmacology trial died during the follow-up period due to a traffic accident. Elleven of the deaths (one in phase 3a pool and ten in SUSTAIN 6 [CVOT])(5 with semaglutide and 5 with placebo) occurred in the period after the end-of-trial follow-up and until database lock in the trials.

The majority of deaths occurred during the trial i.e., prior to the scheduled follow-up, see Table 23.

Table 23 Phase 3a program - Deaths occurring during in-trial period

	Semaglutide 0.5 mg		Semaglutide 1 mg		Comparators	
	N	%	n	%	n	%
Phase 3a pool						
Number of patients	1,373		1,777		1,657	
Deaths	6	0.4	3	0.3	6	0.4
SUSTAIN 6 (CVOT)						
Number of patients	826		822		1,649	
Deaths	30	3.6	32	3.9	60	3.6

Note: SAS in-trial for phase 3a pool, FAS in-trial for SUSTAIN 6 (CVOT). % is the Cochran-Mantel-Haenszel-adjusted percentage. Please note that the number of fatal events occurring in the in-trial period is based on the onset date determined by the EAC.
Comparators: Phase 3a pool: exenatide ER; insulin glargine; oral anti-glycemic drugs; sitagliptin, placebo. SUSTAIN 6 (CVOT): placebo.
Abbreviations: CVOT: cardiovascular outcomes trial; EAC: event adjudication committee; ER: extended release; FAS: full analysis set; n: number of patients with event; SAS: safety analysis set; %: proportion of patients with event.

The reported deaths do not differ with respect to cause between treatments or from what would be expected for the patient population enrolled in the trials.

The low number of deaths in the phase 3a pool precludes a reliable evaluation of mortality. SUSTAIN 6 (CVOT) provides a more comprehensive and reliable assessment of mortality, and will therefore be the primary focus for the assessment. All-cause death and cardiovascular death were components of the composite MACE endpoints and extensive efforts were made to obtain vital status from all patients randomized in SUSTAIN 6 (CVOT). At the end of SUSTAIN 6 (CVOT), vital status was available for 99.6% of patients; 13 patients (6 with semaglutide and 7 with placebo) had unknown vital status.

Fatal events occurred throughout the entire treatment period of SUSTAIN 6 (CVOT), with no clustering of events in any time interval and with similar patterns seen with semaglutide and placebo. All deaths were evaluated by the EAC and the cause of death was categorized as cardiovascular deaths, non-cardiovascular deaths or undetermined cause of death. Deaths of

undetermined cause were presumed cardiovascular deaths in the analysis of MACEs. The majority of deaths were due to cardiovascular events. Among the cardiovascular deaths, sudden cardiac death, undetermined cause of death and death due to acute myocardial infarction were the most frequent causes, with no difference between treatments (see Table 4 in Appendix 2). For death classified by the EAC as 'undetermined cause of death', the investigator-reported term pertaining to the adverse events with fatal outcome indicated a cardiovascular cause in the majority of cases, see Appendix 2, Table 5 for further details. There were no significant differences between semaglutide (0.5 mg and 1 mg pooled) and placebo (pooled) for EAC-confirmed all-cause mortality or cardiovascular death. Please refer to Section 7.4 for analysis of fatal events as components of the MACE endpoint.

In conclusion, data from the semaglutide development program do not suggest that treatment with semaglutide (0.5 mg and 1 mg) is associated with an increased risk of death.

9.4 Gastrointestinal tolerability

Across the semaglutide development program, gastrointestinal adverse events were the most frequently reported adverse events during treatment with semaglutide. Events observed with semaglutide were as expected for a GLP-1 RA based therapy[24]. The most frequent gastrointestinal events were nausea, diarrhea, vomiting, constipation, dyspepsia and abdominal pain both in the phase 3a pool (data not shown) and SUSTAIN 6 (CVOT) (Table 24). Nausea was reported in up to 22% of patients across trials.

Less frequent gastrointestinal events associated with semaglutide included abdominal discomfort, gastro-esophageal reflux disease, abdominal distension, abdominal pain upper, gastritis, flatulence, and eructation.

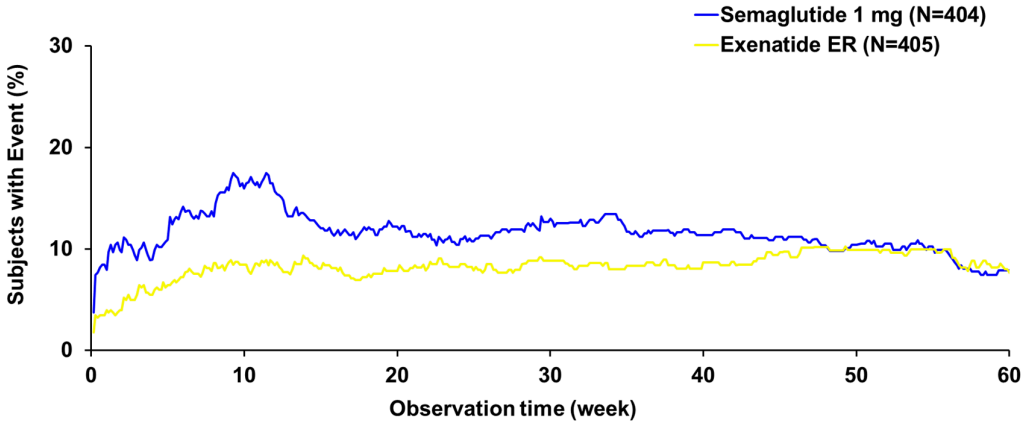
The proportion of patients with gastrointestinal events and the types of events observed with semaglutide (0.5 and 1 mg) (as shown in Table 24 for SUSTAIN 6 [CVOT]) were generally consistent for semaglutide across the phase 3a trials. Gastrointestinal adverse events were typically mild or moderate in severity with a median duration of nausea of 6 days, diarrhea of 3 days and vomiting of 1 day.

In general, gastrointestinal adverse events with semaglutide were consistent with those reported with other GLP-1-based therapies both with regard to events types, outcomes and seriousness.[24] The proportion of patients with gastrointestinal adverse events and the corresponding rates were higher with semaglutide (0.5 mg and 1 mg) than with comparators including placebo, non-GLP-1 RA comparator products and exenatide ER. The higher rate of gastrointestinal adverse events reported with semaglutide 1 mg than with exenatide ER 2 mg in SUSTAIN 3 was mainly observed during the dose escalation period (Figure 30).

Table 24 SUSTAIN 6 (CVOT): Most frequent (≥1%) gastrointestinal adverse events (MedDRA search) by preferred term

	Semaglutide 0.5 mg				Semaglutide 1 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of patients	823				819				1,644			
Patient years of exposure	1,488.3				1,443.9				3,034.8			
All GI adverse events (total)	415	(50.4)	1,208	81.2	426	(52.0)	1,370	94.9	564	(34.3)	1,230	40.5
Nausea	142	(17.3)	227	15.3	178	(21.7)	277	19.2	127	(7.7)	171	5.6
Diarrhea	145	(17.6)	274	18.4	145	(17.7)	242	16.8	177	(10.8)	264	8.7
Vomiting	84	(10.2)	122	8.2	119	(14.5)	169	11.7	77	(4.7)	95	3.1
Constipation	46	(5.6)	52	3.5	78	(9.5)	96	6.6	69	(4.2)	76	2.5
Dyspepsia	51	(6.2)	67	4.5	63	(7.7)	87	6.0	38	(2.3)	41	1.4
Abdominal pain upper	33	(4.0)	35	2.4	42	(5.1)	52	3.6	38	(2.3)	54	1.8
Abdominal discomfort	35	(4.3)	77	5.2	38	(4.6)	91	6.3	35	(2.1)	52	1.7
Gastro esophageal reflux disease	30	(3.6)	38	2.6	35	(4.3)	39	2.7	23	(1.4)	24	0.8
Abdominal pain	45	(5.5)	53	3.6	34	(4.2)	40	2.8	64	(3.9)	73	2.4
Flatulence	13	(1.6)	21	1.4	26	(3.2)	32	2.2	15	(0.9)	17	0.6
Abdominal distension	17	(2.1)	23	1.5	24	(2.9)	28	1.9	22	(1.3)	26	0.9
Gastritis	17	(2.1)	17	1.1	22	(2.7)	24	1.7	20	(1.2)	21	0.7
Eructation	10	(1.2)	13	0.9	19	(2.3)	21	1.5	0	(0.0)		
Large intestine polyp	8	(1.0)	8	0.5	11	(1.3)	13	0.9	17	(1.0)	19	0.6
Hemorrhoids	9	(1.1)	9	0.6	10	(1.2)	10	0.7	14	(0.9)	15	0.5
Gastrointestinal disorder	6	(0.7)	6	0.4	9	(1.1)	9	0.6	4	(0.2)	5	0.2
Toothache	12	(1.5)	14	0.9	8	(1.0)	10	0.7	25	(1.5)	33	1.1
Diverticulum	9	(1.1)	9	0.6	5	(0.6)	5	0.3	15	(0.9)	15	0.5
Irritable bowel syndrome	8	(1.0)	8	0.5	3	(0.4)	3	0.2	6	(0.4)	6	0.2

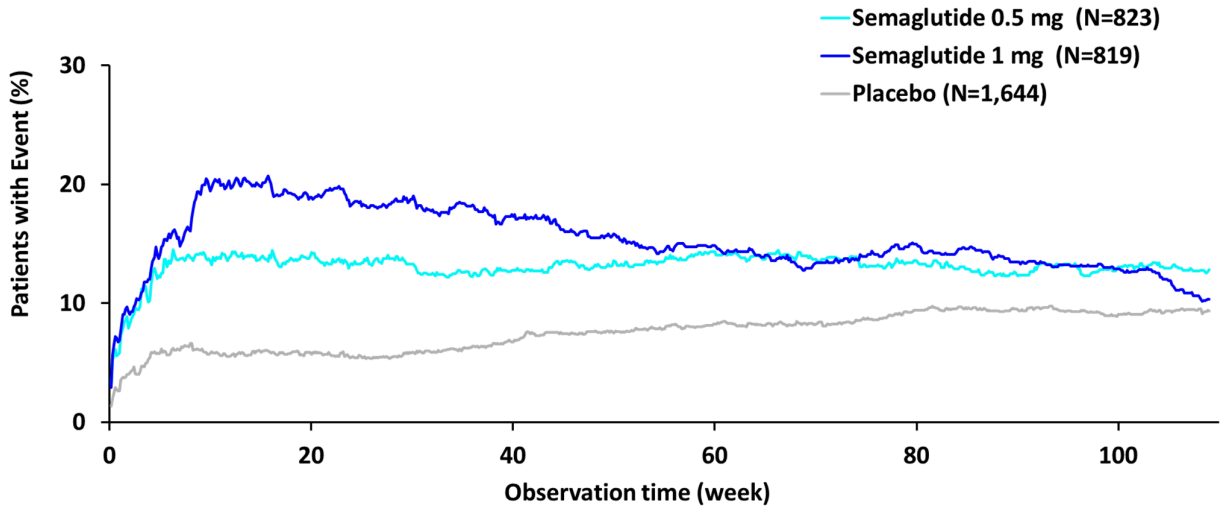
Notes: SAS on-treatment. Events are sorted by highest frequency in the semaglutide 1 mg group. On-treatment: onset on or after the day of first randomized dose and not after the follow-up visit scheduled 5 weeks after the end-of-treatment.
Abbreviations: E: Number of events; N: Number of patients experiencing at least one event; PYE: Patient years of exposure; R: Event rate per 100 PYE; SAS: Safety analysis set; %: proportion of patients with event.



Notes: SAS on-treatment.
Abbreviations: SAS: safety analysis set; sema: semaglutide.

Figure 30 SUSTAIN 3: Gastrointestinal adverse events by week

The gastrointestinal adverse events predominantly occurred during the dose-escalation period of treatment, i.e., within the initial 3 to 4 months of treatment depending on the dose given (see Figure 31 as an example). After 4 months, the rate of patients experiencing their first gastrointestinal event was similar for semaglutide and placebo and comparator products. The decrease in reporting rates of gastrointestinal adverse events over time is likely to be due to development of tolerance to the treatment as well as treatment discontinuation of patients most sensitive to gastrointestinal adverse events.



Notes: SAS on-treatment.
Abbreviations: SAS: safety analysis set; sema: semaglutide.

Figure 31 SUSTAIN 6 (CVOT): Proportion of patients with gastrointestinal adverse events (MedDRA Search) over time

Gastrointestinal adverse events led to premature treatment discontinuation in up to 5.9% of patients in the 30 and 56 week trials included in the phase 3a pool (0.5 mg: 3.9%; 1 mg: 5.9%; comparators: 0.9%) and up to 10% (0.5 mg: 5.8%; 1 mg: 10%; placebo: 1.4%) in the 104 week SUSTAIN 6 (CVOT). These events mainly occurred during the dose escalation period in the beginning of the trials.

Exposure-response analyses indicate that patients develop tolerance to nausea resulting in less nausea susceptibility over time despite similar exposure levels to semaglutide. Similar results were obtained when analyzing patients completing the trials, i.e., accounting for patients who discontinued treatment with trial product prematurely due to gastrointestinal adverse events. Development of tolerance to gastrointestinal events with semaglutide is consistent with the pattern seen with other GLP-1 RAs including exenatide once-weekly and liraglutide once-daily.[25, 26]

A dose-dependency was indicated in the proportion of patients reporting gastrointestinal events and gastrointestinal events leading to premature treatment discontinuation in SUSTAIN 6 (CVOT) and most of the phase 3a trials, suggesting that gastrointestinal events increase with semaglutide exposure. The dose-dependency was evident for events of nausea and vomiting but not for diarrhea and constipation.

Overall, gastrointestinal events seemed to have a relatively low clinical impact, based on the seriousness, severity and reversibility of the events. Moreover, based on a nausea questionnaire applied in SUSTAIN 1, between 87−93% of the patients with semaglutide reported that the experienced nausea affected work and social life to a minor degree or not at all.

9.5 Episodes of hypoglycemia

Episodes of hypoglycemia have a major impact on a patient's life in terms of physical, mental and social functioning. In patients with T2D, fear of hypoglycemia is one of the greatest barriers for achieving optimal glycemic control when treating diabetes.[128, 129]

Semaglutide lowers fasting and postprandial glycaemia in a glucose-dependent manner; it acts only when glucose levels are elevated. Hence, the risk of hypoglycemia with semaglutide is low when compared to many other glucose-lowering agents. The risk of episodes of hypoglycemia with semaglutide is however increased, like with other GLP-1RAs, when used in combination with other anti-glycemic agents such as SU and insulin which uncouple the glucose-dependent insulin secretion mode of semaglutide.[130] In general, the risk of hypoglycemia increases with insulin as the HbA_{1c} declines.[33] However, this is generally not seen with GLP-1 RAs in the absence of concomitant treatment with SUs or insulin.

The risk of hypoglycemia was evaluated across the phase 3a trials. Due to the impact of other glycemic therapy, the analysis was based on subgroups by baseline background glycemic medication each including patients from multiple trials. Episodes of hypoglycemia were categorized according to the American Diabetes Association (ADA) classification. Additionally, events were categorized using the Novo Nordisk definition of blood glucose confirmed symptomatic hypoglycemia defined as severe hypoglycemia according to the ADA classification (requiring the assistance of another person) or blood glucose confirmed by a plasma glucose measurement <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycemia.

Across phase 3a trials including SUSTAIN 6 (CVOT), episodes of hypoglycemia were infrequent when semaglutide was used as monotherapy or in combination with OADs excluding SUs.

In the phase 3a trials, no episodes of ADA severe hypoglycemia were observed when semaglutide s.c. was used as monotherapy (Table 25). Episodes of ADA severe hypoglycemia were infrequent when semaglutide was administered concomitantly with OADs excluding SUs and with no apparent differences between semaglutide and comparators including placebo. ADA severe hypoglycemia is a well-known risk with all insulin and SU medicinal products.[131]

No difference between semaglutide and non-insulin comparators in Novo Nordisk defined 'severe or blood glucose confirmed symptomatic episodes of hypoglycemia' was evident in patients on monotherapy or on a background of OADs excluding SUs (data not shown). The frequency of patients with episodes of hypoglycemia was lower with semaglutide than with insulin glargine and similar to exenatide ER. For patients treated with semaglutide as add-on to insulin, episodes were reported at higher frequencies than with placebo. The mean blood glucose concentrations achieved with semaglutide was substantially lower than achieved with placebo in these trials and likely explains the slightly higher rate of hypoglycemia reported with semaglutide.

In SUSTAIN 6 (CVOT) where semaglutide was administered in addition to standard-of-care, changes to background medication were allowed during the trial reflecting a real-life setting. Across all background medications, there were no significant differences between semaglutide and placebo with respect to number of episodes or patients experiencing episodes of ADA severe hypoglycemia or 'severe or blood glucose confirmed symptomatic hypoglycemia'. ADA severe episodes of hypoglycemia were infrequent with semaglutide and placebo (Table 25). Thus, in a real-life like setting in a vulnerable population where changes to anti-glycemic background medication were encouraged, treatment with semaglutide did not lead to an increased risk of hypoglycemia despite pronounced and significantly improved glycemic control compared to placebo. For patients treated with semaglutide as add-on to SUs or insulin, episodes of Novo Nordisk defined 'severe or blood glucose confirmed symptomatic episodes of hypoglycemia' were reported at higher frequencies than with placebo in addition to standard-of-care.

In conclusion, despite superior reductions in HbA_{1c} with semaglutide (down to appr. 6.5%-point) versus placebo and active comparators, semaglutide-treatment does not increase the risk of hypoglycemia unless combined with either SU or insulin. As expected for a therapy with a glucose-dependent mechanism of action, hypoglycemia incidence with semaglutide was lower than with insulin glargine and comparable to exenatide ER, consistent with previous findings both for once-daily[27] and once-weekly[28] GLP-1 RAs.

Table 25 Phase 3a trials incl. SUSTAIN 6 (CVOT): Episodes of ADA severe hypoglycemia by baseline background medication

	Semaglutide 0.5 mg	Semaglutide 1 mg	Comparators/Placebo
Monotherapy			
Phase 3a trials (a)			
N and PYE (year)	299 226	300 215	237 157
Severe episodes (N, (%), E, R)	0 (0.0) 0 0.0	0 (0.0) 0 0.0	0 (0.0) 0 0.0
Add-on to other OADs			
Phase 3a trials (b)			
N and PYE (year)	687 659	910 874	851 845
Severe episodes(N, (%), E, R)	0 (0.0) 0 0.0	1 (0.1) 1 0.1	3 (0.3) 3 0.3
SUSTAIN 6 (CVOT)			
N and PYE (year)	118 204.2	124 207	256 464.5
Severe episodes (N, (%), E, R)	1 (0.8) 1 0.5	0 (0.0) 0 0.0	1 (0.4) 1 0.2
Add-on to SU			
Phase 3a trials (c)			
N and PYE (year)	255 196	436 377	435 380
Severe episodes(N, (%), E, R)	2 (0.8) 4 2.3	5 (1.2) 11 3.0	4 (0.9) 4 1.0
SUSTAIN 6 (CVOT)			
N and PYE (year)	230 420.1	219 399.1	434 808.2
Severe episodes(N, (%), E, R)	3 (1.3) 3 0.7	3 (1.4) 3 0.8	2 (0.5) 4 0.5
Add-on to insulin			
Phase 3a trials (d)			
N and PYE (year)	132 84	131 82	133 84
Severe episodes(N, (%), E, R)	0 (0.0) 0 0.0	2 (1.5) 2 2.4	0 (0.0) 0 0.0
SUSTAIN 6 (CVOT)			
N and PYE (year)	358 653.3	345 599.6	678 1248.1
Severe episodes(N, (%), E, R)	8 (2.2) 8 1.2	3 (0.9) 7 1.2	14 (2.1) 23 1.8
Add on to SU + insulin			
SUSTAIN 6 (CVOT)			
N and PYE (year)	117 210.7	131 238.2	276 514.0
Severe episodes(N, (%), E, R)	2 (1.7) 3 1.4	3 (2.3) 3 1.3	9 (3.3) 12 2.3

a) Monotherapy subgroup comprises patients from SUSTAIN 1–3, SUSTAIN JP Mono and SUSTAIN JP OADs**.** **b**) 'Add-on to other OADs' subgroup comprises patients from SUSTAIN 1–4 and SUSTAIN JP OADs. **c**) 'Add-on to SU' subgroup comprises patients from SUSTAIN 2-4 and SUSTAIN JP OADs. **d**) 'Add-on to insulin' subgroup comprises patients from trials SUSTAIN 3 and SUSTAIN 5.

Notes: SAS on-treatment. Comparator in SUSTAIN 6 (CVOT) was placebo. The on-treatment summary of hypoglycemic episodes comprises treatment-emergent events from the hypo form reported with onset on or after the day of first randomized dose to date of last dose plus 42 days. The subgroups are based on the baseline medication. The patients included in each subgroup only consist of those patients from a trial, who fulfill the criteria. For phase 3a trials (excl. SUSTAIN 6 [CVOT]) the table only contains data from the on-treatment period without rescue medication and % and R are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.

Abbreviations: ADA: American Diabetes Association; CVOT: cardiovascular outcomes trial; E: Number of events, JP: Japan; N: Number of patients with events, OAD: Oral anti-glycemic drug, PYE: Patient years of exposure is calculated from the time of first drug date to the follow-up visit or first drug date of second treatment in crossover trials, R: Event rate per 100 PYE, SAS: safety analysis set; SU: Sulfonylurea, %: proportion of patients with event.

9.6 Neoplasms

GLP-1 RAs have not been associated with an increased risk of neoplasms in humans.[132] Neither semaglutide nor any of the other approved GLP-1 RAs are mutagenic or genotoxic based on nonclinical data.[133, 134] Besides thyroid C-cell neoplasia in rodents, no treatment-related neoplasms were observed in the nonclinical studies with semaglutide.

Although there was no prior indication of a causal relationship between neoplasms and treatment with GLP-1 RAs in general or semaglutide specifically, neoplasms were regarded as a safety area of special interest in the semaglutide development program. Thorough efforts were made to ensure that all potential neoplasm events were identified and evaluated, and a blinded adjudication process was employed.

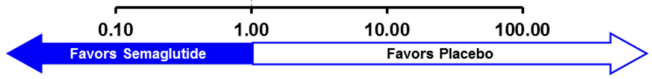
Analysis of data focused on comparison between pooled semaglutide doses versus pooled comparators, due to the low frequency nature of these events. Hazard ratios were estimated *post-hoc* in SUSTAIN 6 (CVOT) and the phase 3a pool. Due to the anticipated long lead-time for potential treatment related neoplasms, evaluation of the potential effects of semaglutide on the development of neoplasms was based primarily on data from the in-trial observation period.

The types of EAC-confirmed neoplasms occurring across the phase 3a trials reflected the neoplasms types expected in the target population. Number and proportion of patients with individual type of neoplasms, benign and malignant (Figure 32 and Figure 33) were low. When investigating the distribution of EAC-confirmed neoplasms across tissues, the estimated hazard ratios for semaglutide versus comparators/placebo were on either side of unity with no observed clustering within specific organ sites.

In SUSTAIN 6 (CVOT), there was a tendency towards higher frequencies for benign neoplasm with semaglutide than with placebo (HR: 1.35 $[0.99; 1.84]_{95\%CI}$). No apparent single types of benign neoplasms accounted for this difference. The difference between semaglutide and placebo was seen within the first 40 weeks in the trial indicating a short lead time. In the phase 3a pool, the proportion of patients with EAC-confirmed benign neoplasms was low and similar with semaglutide and comparator products (HR: 1.14 $[0.73; 1.78]_{95\%CI}$).

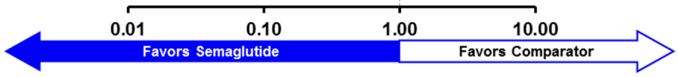
SUSTAIN 6 (CVOT)

Factor	HR (95% CI)	Patients with Events / Analyzed Semaglutide	Placebo
All benign neoplasms			
Overall result	1.35 (0.99; 1.84)	94 / 1,648	70 / 1,649
By organ of origin			
Bone	-	0 / 1,648	2 / 1,649
Brain / central nervous system	1.50 (0.25; 8.97)	3 / 1,648	2 / 1,649
Breast, female	-	2 / 635	0 / 660
Breast, male	-	1 / 1,013	0 / 989
Colorectal	1.09 (0.68; 1.76)	35 / 1,648	32 / 1,649
Female reproductive	1.46 (0.46; 4.59)	7 / 635	5 / 660
Gastric / intestinal	2.00 (0.50; 7.99)	6 / 1,648	3 / 1,649
Liver	2.00 (0.18; 22.04)	2 / 1,648	1 / 1,649
Male reproductive	6.84 (0.84; 55.61)	7 / 1,013	1 / 989
Naso-pharyngeal	-	0 / 1,648	1 / 1,649
Neuroendocrine	-	1 / 1,648	0 / 1,649
Oral	-	0 / 1,648	1 / 1,649
Skin	1.55 (0.72; 3.30)	17 / 1,648	11 / 1,649
Pancreatic	-	2 / 1,648	0 / 1,649
Renal / adrenal	4.99 (0.58; 42.68)	5 / 1,648	1 / 1,649
Thyroid	-	1 / 1,648	0 / 1,649
Other benign	0.66 (0.30; 1.48)	10 / 1,648	15 / 1,649



Phase 3a pool

Factor	HR (95% CI)	Patients with Events / Analyzed Semaglutide	Comparator
All benign neoplasms			
Overall result	1.14 (0.73; 1.78)	69 / 3,150	28 / 1,657
By organ of origin			
Brain / central nervous system	0.52 (0.03; 8.36)	1 / 3,150	1 / 1,657
Colorectal	2.40 (0.99; 5.81)	27 / 3,150	6 / 1,657
Esophageal	-	1 / 3,150	0 / 1,657
Female reproductive	0.54 (0.16; 1.86)	5 / 1,355	5 / 715
Gall bladder	-	1 / 3,150	0 / 1,657
Gastric / intestinal	1.58 (0.43; 5.85)	9 / 3,150	3 / 1,657
Liver	-	2 / 3,150	0 / 1,657
Male reproductive	-	1 / 1,795	0 / 942
Naso-pharyngeal	-	1 / 3,150	0 / 1,657
Oral	-	1 / 3,150	0 / 1,657
Pancreatic	-	0 / 3,150	1 / 1,657
Renal / adrenal	0.79 (0.13; 4.73)	3 / 3,150	2 / 1,657
Skin	0.53 (0.19; 1.50)	7 / 3,150	7 / 1,657
Thyroid	0.53 (0.03; 8.54)	1 / 3,150	1 / 1,657
Other benign ureter	-	1 / 3,150	0 / 1,657
Other benign	2.31 (0.66; 8.11)	13 / 3,150	3 / 1,657



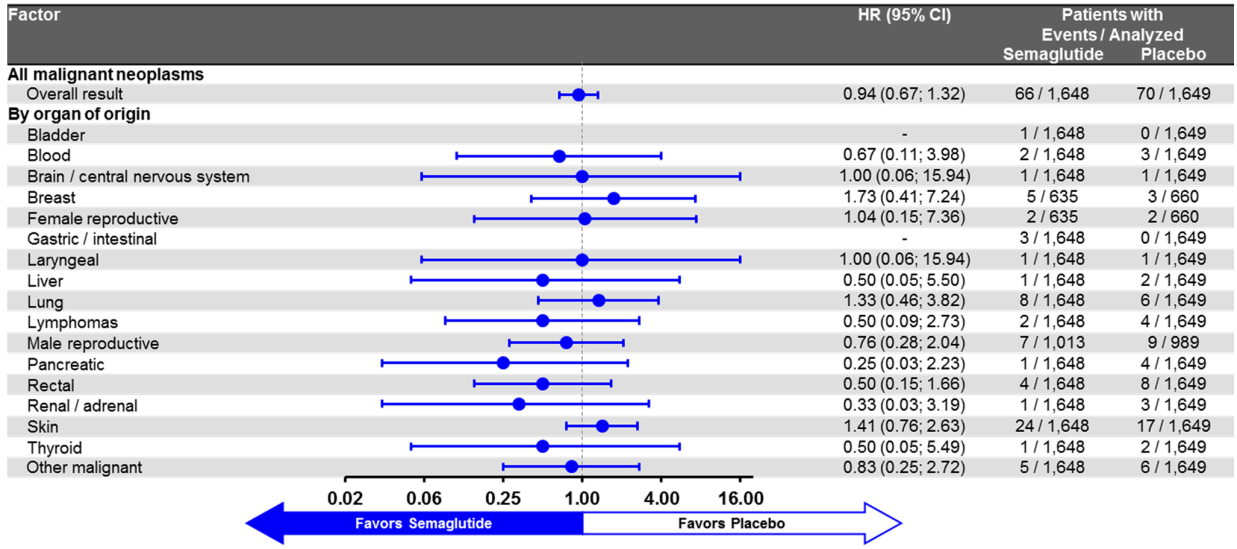
Notes: In-trial. Estimated HRs and associated CIs are from a Cox proportional hazard model with treatment as a fixed factor. All EAC-confirmed thyroid neoplasms were in subcategory 'other' (than C-cell related).
Comparators: exenatide ER; insulin glargine; oral anti-glycemic drugs; sitagliptin, placebo.
Abbreviations: CI: confidence interval; ER: extended release; HR: hazard ratio.

Figure 32 SUSTAIN 6 (CVOT) (top) and phase 3a pool (bottom): *Post-hoc* analyses of EAC-confirmed benign neoplasms by organ of origin

Malignant neoplasms were equally distributed with semaglutide and placebo (HR: 0.94 [0.67; 1.32]$_{95\%CI}$) in SUSTAIN 6 (CVOT) with no apparent differences for any types of malignant neoplasms (Figure 33). In the phase 3a pool there was more malignant neoplasms (HR: 1.61 [0.74;

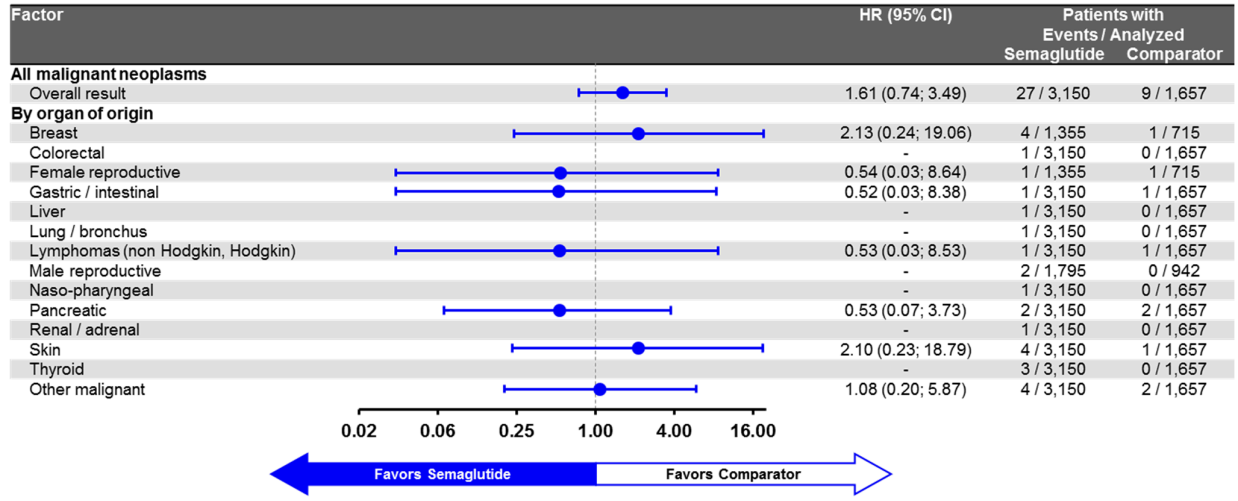
3.49]$_{95\%CI}$) with semaglutide than with comparators. Note that numbers of specific neoplasms were low. Also, there were no single types of malignant neoplasms accounting for this difference (see Figure 33).

SUSTAIN 6 (CVOT)



Factor	HR (95% CI)	Patients with Events / Analyzed Semaglutide	Placebo
All malignant neoplasms			
Overall result	0.94 (0.67; 1.32)	66 / 1,648	70 / 1,649
By organ of origin			
Bladder	-	1 / 1,648	0 / 1,649
Blood	0.67 (0.11; 3.98)	2 / 1,648	3 / 1,649
Brain / central nervous system	1.00 (0.06; 15.94)	1 / 1,648	1 / 1,649
Breast	1.73 (0.41; 7.24)	5 / 635	3 / 660
Female reproductive	1.04 (0.15; 7.36)	2 / 635	2 / 660
Gastric / intestinal	-	3 / 1,648	0 / 1,649
Laryngeal	1.00 (0.06; 15.94)	1 / 1,648	1 / 1,649
Liver	0.50 (0.05; 5.50)	1 / 1,648	2 / 1,649
Lung	1.33 (0.46; 3.82)	8 / 1,648	6 / 1,649
Lymphomas	0.50 (0.09; 2.73)	2 / 1,648	4 / 1,649
Male reproductive	0.76 (0.28; 2.04)	7 / 1,013	9 / 989
Pancreatic	0.25 (0.03; 2.23)	1 / 1,648	4 / 1,649
Rectal	0.50 (0.15; 1.66)	4 / 1,648	8 / 1,649
Renal / adrenal	0.33 (0.03; 3.19)	1 / 1,648	3 / 1,649
Skin	1.41 (0.76; 2.63)	24 / 1,648	17 / 1,649
Thyroid	0.50 (0.05; 5.49)	1 / 1,648	2 / 1,649
Other malignant	0.83 (0.25; 2.72)	5 / 1,648	6 / 1,649

Phase 3a pool



Factor	HR (95% CI)	Patients with Events / Analyzed Semaglutide	Comparator
All malignant neoplasms			
Overall result	1.61 (0.74; 3.49)	27 / 3,150	9 / 1,657
By organ of origin			
Breast	2.13 (0.24; 19.06)	4 / 1,355	1 / 715
Colorectal	-	1 / 3,150	0 / 1,657
Female reproductive	0.54 (0.03; 8.64)	1 / 1,355	1 / 715
Gastric / intestinal	0.52 (0.03; 8.38)	1 / 3,150	1 / 1,657
Liver	-	1 / 3,150	0 / 1,657
Lung / bronchus	-	1 / 3,150	0 / 1,657
Lymphomas (non Hodgkin, Hodgkin)	0.53 (0.03; 8.53)	1 / 3,150	1 / 1,657
Male reproductive	-	2 / 1,795	0 / 942
Naso-pharyngeal	-	1 / 3,150	0 / 1,657
Pancreatic	0.53 (0.07; 3.73)	2 / 3,150	2 / 1,657
Renal / adrenal	-	1 / 3,150	0 / 1,657
Skin	2.10 (0.23; 18.79)	4 / 3,150	1 / 1,657
Thyroid	-	3 / 3,150	0 / 1,657
Other malignant	1.08 (0.20; 5.87)	4 / 3,150	2 / 1,657

Notes: In-trial. Estimated HRs and associated CIs are from a Cox proportional hazard model with treatment as a fixed factor. All EAC-confirmed thyroid neoplasms were in subcategory 'other' (not C-cell related).
Comparators: exenatide ER; insulin glargine; oral anti-glycemic drugs; sitagliptin, placebo.
Abbreviations: CI: confidence interval; ER: extended release; HR: hazard ratio.

Figure 33 SUSTAIN 6 (CVOT) (top) and phase 3a pool (bottom): *Post-hoc* analyses of EAC-confirmed malignant neoplasms by organ of origin

A few specific types of neoplasms deserve further mentioning, either due to prior concerns in the GLP-1 RA class or due to findings in the semaglutide development program (Figure 32 and Figure 33 for data).

- Thyroid proliferative C-cell changes in rodents are a known class effect following GLP-1 receptor activation by GLP-1 RAs. Novo Nordisk implemented several measures to assess and minimize thyroid risk in the semaglutide development program. Patients with a personal or family history of MTC and patients with MEN 2 were not eligible for enrolment in the semaglutide development program. All suspected cases of thyroid disease requiring thyroidectomy and thyroid neoplasms were prospectively adjudicated and evaluated with regards to whether the event was a thyroid neoplasm, the malignancy status and whether the event was a MTC. No cases of MTC were identified during the semaglutide development program. Consistent with no identified MTCs, no effect of semaglutide treatment on calcitonin levels was observed and patients with increased calcitonin levels were few and levels >50 ng/L and >100 ng/L occurred at comparable frequencies with semaglutide and placebo/comparators.
- The incidence of pancreas neoplasms with semaglutide was low (5 cases: 3 malignant, 2 benign) and appeared not to be different from placebo and comparator products (7 cases; 6 malignant, 1 benign).
- Both benign and malignant skin neoplasms occurred in a higher proportion of patients and at a higher rate with semaglutide 1 mg than with semaglutide 0.5 mg or placebo in SUSTAIN 6 (CVOT). The difference was driven by malignant skin neoplasms arising from 2 different cell types (basal and squamous cell carcinoma) and 1 case of malignant melanoma (semaglutide 0.5 mg). The full treatment differences for both benign and malignant skin neoplasms appeared early in the SUSTAIN 6 (CVOT), making a drug-related effect unlikely. No differences were seen for either benign or malignant skin neoplasms in the phase 3a pool.
- The incidence of breast neoplasms with semaglutide was low and appeared not to be different from placebo or other comparators in the phase 3a trials and SUSTAIN 6 (CVOT).
- Benign colorectal neoplasms, primarily in the form of colon polyps, were observed in higher numbers in patients treated with semaglutide compared to comparators in the phase 3a pool. This was primarily driven by events in SUSTAIN JP OADs. In the 2-year placebo-controlled SUSTAIN 6 (CVOT), benign colorectal neoplasms were equally distributed between semaglutide and placebo. Malignant colorectal neoplasms occurred at a low rate, with an equal distribution between semaglutide and placebo/comparators in SUSTAIN 6 (CVOT) and the phase 3a pool.

In summary, the types of EAC-confirmed neoplasms occurring across the phase 3a program reflected the target population[135] with no unexpected types of neoplasms occurring with semaglutide. Differences between semaglutide and placebo/comparator products observed within the individual types of neoplasms are considered attributable to random variation due to the low

incidence of the individual cancer types. Where differences between semaglutide and placebo/comparators were seen, these in general appeared early in the trial indicating lead times that are inconsistent with a neoplastic/promotional effect. Taken together, the short lead time, low number of events, lack of biological plausibility and the absence of any signals from extensive clinical use of GLP-1 RAs supports that it is unlikely that semaglutide induces or accelerates neoplasm development.

9.7 Pancreatitis

Currently, a class labelling exists for all incretin-based therapies concerning the risk of pancreatitis. Consequently, Novo Nordisk implemented a comprehensive set of measures to assess and minimize the potential risk of pancreatitis in the semaglutide program. Patients with a history of chronic or idiopathic acute pancreatitis were excluded from the semaglutide development program and semaglutide was to be discontinued in case of suspicion of acute pancreatitis. Potential events of pancreatitis were evaluated by the external independent event adjudication committee (EAC). Across the phase 3a trials, an EAC-confirmed diagnosis of acute pancreatitis required that at least 2 of the following 3 criteria were met: a) characteristic abdominal pain, b) amylase and/or lipase above 3×upper limit of normal and/or c) characteristic findings on imaging of the pancreas.[136]

In SUSTAIN 6 (CVOT), the number of patients with EAC-confirmed acute pancreatitis was similar with semaglutide (8 patients) and placebo (10 patients) and all events were classified as 'mild acute pancreatitis' based on the revised Atlanta criteria.[29] In the phase 3a pool, few patients had EAC-confirmed events (semaglutide 0.5 mg: 5 patients, 0.4%; semaglutide 1 mg: 3 patients, 0.2%; exenatide ER: 3 patients, 0.2%; other comparators: 0 patients). In both SUSTAIN 6 (CVOT) and the phase 3a pool, EAC-confirmed pancreatitis events occurred throughout the course of the trial. No indications of semaglutide-induced acute pancreatitis were observed in any of the repeat dose toxicity studies in mice, rats and monkeys or the 2-year carcinogenicity studies in mice and rats. Taken together, a causal relationship between development of pancreatitis and treatment with semaglutide is not supported.

Regulatory authorities have requested pharmaceutical companies routinely monitor pancreatic enzyme activities (lipase and amylase) in clinical trials as potential biomarkers for pancreatitis. Serum lipase and amylase activities increased with semaglutide, similar to what has been described with other incretin-based therapies.[23, 26] After an initial increase in lipase and amylase, the activity levels showed no further change for up to 2 years, as assessed in SUSTAIN 6 (CVOT). Across the phase 3a program, very few patients with maximum lipase and/or amylase activities >3xULN at any post-baseline visit had EAC-confirmed pancreatitis. The evidence supports that, in the absence of other signs or symptoms of pancreatitis, elevation of lipase or amylase activities seen with semaglutide does not predict a later development of pancreatitis. This is consistent with data obtained for other GLP-1 RAs.[113, 137, 138] In conclusion, the frequent reporting of lipase and amylase activity elevations observed with semaglutide is not considered a safety concern.

9.8 Gallstones

Gallstones are common in the general population[139], however, the majority (up to 80%) of all individuals with gallstones do not experience biliary pain or complications such as acute cholecystitis, cholangitis or pancreatitis.[140] Patients with T2D are at higher risk of developing biliary diseases[141] which may be explained by frequent T2D-related comorbidities, including obesity, hyperinsulinemia and dyslipidemia.[141,142]

A link between incretin-based therapies and risk of gallbladder adverse events (i.e. cholelithiasis and cholecystitis) has been suggested.[143, 144] Proposed mechanisms for an increased risk of cholelithiasis include rapid weight loss, inhibition of gallbladder contraction and emptying, reduced production of bile acids and modulation of inflammation. The only nonclinical finding with semaglutide concerning the gallbladder was increased incidences of distension and abnormal content of the gallbladder in mice, which was considered to be secondary to low food consumption.

In the placebo-controlled 2-year SUSTAIN 6 (CVOT), the proportion of patients with gallbladder-related adverse events was similar with semaglutide and placebo, although cholelithiasis was reported more frequently with semaglutide than with placebo ((Table 26). In the phase 3a pool, gallbladder-related adverse events were reported more frequently with semaglutide than with comparator products; this difference was primarily accounted for by adverse events of cholelithiasis, especially with semaglutide 1 mg. Besides cholelithiasis, no other types of gallbladder-related adverse events were reported more frequent with semaglutide than with placebo or comparators.

Table 26 Phase 3a pool and SUSTAIN 6 (CVOT): Adverse events of gallbladder-related adverse events (MedDRA search) and cholelithiasis (preferred term)

		Semaglutide 0.5 mg				Semaglutide 1 mg				Comparators			
		N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Phase 3a pool (a)	**Gallbladder-related AEs (MedDRA search)**	**18**	**(1.3)**	**19**	**1.6**	**30**	**(1.7)**	**32**	**2.1**	**14**	**(0.8)**	**15**	**1.0**
	Cholelithiasis AEs	10	(0.7)	10	0.8	19	(1.1)	19	1.2	8	(0.5)	8	0.5
	Cholelithiasis SAEs	2	(0.2)	2	0.2	2	(0.1)	2	0.1	2	(0.1)	2	0.1
SUSTAIN 6 (CVOT)	**Gallbladder-related AEs (MedDRA search)**	**29**	**(3.5)**	**39**	**2.6**	**26**	**(3.2)**	**31**	**2.1**	**56**	**(3.4)**	**72**	**2.4**
	Cholelithiasis AEs	19	(2.3)	19	1.3	17	(2.1)	17	1.2	27	(1.6)	27	0.9
	Cholelithiasis SAEs	4	(0.5)	4	0.3	2	(0.2)	2	0.1	4	(0.2)	4	0.1

a) % and R are the Cochran-Mantel-Haenszel adjusted percentage and event rate.
Note: SAS on-treatment.
Comparators: phase 3a pool: exenatide ER; insulin glargine; oral anti-glycemic drugs; sitagliptin, placebo. SUSTAIN 6 (CVOT): placebo.
Abbreviations: AE: adverse event; ER: extended release; N: Number of patients experiencing at least one event, %: proportion of patients with event, E: Number of events, R: Events per 100 patient-years of observation; SAE: serious adverse event; SAS: safety analysis set.

A total of 16 serious adverse events (SAE) of cholelithiasis were reported across the phase 3a trials including SUSTAIN 6 (CVOT) with no apparent difference between semaglutide and comparators. All but one SAE of cholelithiasis led to cholecystectomy. There were 1−2 acute cholecystectomies with each of semaglutide and comparators, and the rest were elective operations. Of additional note, 15 of the SAEs were diagnosed based on symptomatic findings; 1 was diagnosed based on a routine examinations.

There was no apparent correlation between cholelithiasis and rapid weight loss with semaglutide. Importantly, the higher reporting of cholelithiasis with semaglutide was not associated with an increased risk of acute pancreatitis. The frequency of adverse events of cholecystitis, another potential complication of cholelithiasis, was similar between semaglutide and placebo/comparators in SUSTAIN 6 (CVOT) and the phase 3a pool. The increased risk of cholelithiasis with semaglutide is consistent with data on liraglutide when used for weight management[30, 145] and the liraglutide cardiovascular outcomes trial (LEADER[14]) whereas no increased risk was observed in phase 3a trials for liraglutide in T2D.[146, 147]

9.9 Immunogenicity

Semaglutide is a protein-based drug with the potential to cause immunogenic reactions. However, as semaglutide has a high homology (94%) to endogenous GLP-1, a low immunogenic potential is expected.

Injection site reactions were reported by a low (approximately 1%) proportion of patients with semaglutide and were not recurrent in those individuals despite continued treatment. Most injections site reactions were of mild or moderate severity, did not lead to premature treatment discontinuation and no differences between semaglutide and placebo and non-exenatide comparators were observed. In SUSTAIN 3, injection site reactions were reported in fewer patients with semaglutide 1 mg (1.2%) than with exenatide ER 2 mg (22.0%). Taken together a causal relationship between injection site reactions and semaglutide is likely although the risk is evaluated as low.

All patients exposed to semaglutide in the clinical development program were tested for presence of anti-semaglutide antibodies, including cross-reactivity to endogenous GLP-1 and *in vitro* neutralizing effect. No patients had anti-semaglutide neutralizing antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralizing effect. In the phase 3a trials including SUSTAIN 6 (CVOT), the proportion of patients that tested positive for anti-semaglutide antibodies at any time point post-baseline was low (1−2%). In patients that did test positive, the serum level of the anti-semaglutide antibodies was low and appeared to be transient as very few patients (less than 0.4%) had anti-semaglutide antibodies at the follow-up visit performed at least 5 weeks after last dose. In the few patients that tested positive for anti-semaglutide antibodies, approximately 60% had antibodies cross-reacting to endogenous GLP-1. In SUSTAIN 3, 3.2% (13 of 404) of patients were tested positive for anti-semaglutide antibodies. None of the antibodies were neutralizing to

semaglutide or endogenous GLP-1. In contrast, anti-exenatide antibodies were confirmed in the majority (87.7%, 355 of 405) of patients treated with exenatide ER 2 mg, in which 39 patients had an *in vitro* neutralizing effect on exenatide and none on endogenous GLP-1. There were no effects of anti-semaglutide-antibodies on semaglutide exposure, HbA_{1c} or semaglutide safety profile including no association with immunogenicity-related adverse events in patients with antibody formation. This is in contrast to some other GLP-1 RAs (exenatide ER [Bydureon], Byetta, Adlyxin/Lyxumia) where high anti-drug antibody titers have been associated with reduced efficacy as assessed by HbA_{1c} reduction.

Allergic reactions were reported by a low (4−6%) proportion of patients in the phase 3a trials with no difference between semaglutide and placebo/comparators. Most of the allergic reactions were non-serious, of mild or moderate severity, did not lead to premature treatment discontinuation and no differences between semaglutide and placebo/comparators were observed. One (1) event of anaphylactic shock was reported in a patient randomized to semaglutide; however the event was reported after more than one year of exposure to semaglutide 0.5 mg and as an adverse reaction to cefazolin. To mitigate the risk of severe allergic reaction, the use by patients with pre-existing hypersensitivity to the product or its excipients is included as a contraindication in the proposed product information.

9.10 Renal safety

In patients with T2D, adverse events of acute renal failure have been associated with some GLP-1 RAs, including liraglutide.[148] The majority of such events occurred in patients with pre-existing risk factors such as renal impairment, advanced age and concomitant use of diuretics. In some cases events of acute renal failure were reported in association with gastrointestinal symptoms such as nausea, vomiting and diarrhea leading to dehydration, as described in the GLP- 1 RA class label.

Safety in patients with renal impairment

To evaluate the impact of renal function on the pharmacokinetic profile of semaglutide a dedicated clinical pharmacology trial in subjects with various degrees of renal function was conducted. In addition, a population pharmacokinetic analysis was performed, including patients with renal function as covariate. Based on results from these evaluations, no dose adjustment of semaglutide is needed in patients with renal impairment. This is consistent with the fact that semaglutide is extensively metabolized in humans prior to elimination and excretion in the urine and feces with only 3% intact semaglutide excreted in urine. Thus, no accumulation was expected in patients with impaired renal function and this was confirmed by the population pharmacokinetic analysis.

In SUSTAIN 6 (CVOT), only patients requiring renal replacement therapy (chronic hemodialysis or chronic peritoneal dialysis) were excluded based on renal function, opposed to the other phase 3a trials where patients with severe and end-stage renal disease were excluded. In the phase 3a program including SUSTAIN 6 (CVOT) more than 900 patients with moderate renal impairment

(eGFR 30−<60 mL/ min/1.73 m^2), 95 patients with severe renal impairment (eGFR 15−<30 mL/min/ 1.73 m^2) and very few (12 patients) with end-stage renal disease (eGFR <15 mL/min/1.73 m^2) were enrolled. Based on subpopulation analyses, the safety profile of semaglutide (0.5 mg and 1 mg) was similar in patients with varying degrees of impaired renal function compared with patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2), and no precautions are warranted in those patients when exposed to semaglutide, besides prevention of dehydration.

Acute renal failure and renal function

In SUSTAIN 6 (CVOT), fewer adverse events related to acute renal failure were reported with semaglutide 1 mg (19 patients, 2.3%) than with semaglutide 0.5 mg (33 patients, 4.0%) or placebo (58 patients, 3.5%). All cases were associated with pre-existing morbidity, e.g., chronic renal impairment, and some were temporally associated with gastrointestinal adverse events that may have led to dehydration and, in turn, pre-renal decrease in glomerular filtration rate (GFR). In the phase 3a pool, adverse events related to acute renal failure were infrequent and with no apparent difference between semaglutide (0.5 mg: 3 patients, 0.2%; 1 mg: 9 patients, 0.5%) and comparator products (5 patients, 0.3%).

Semaglutide was consistently associated with an initial decrease in the estimated GFR (eGFR). In SUSTAIN 6 (CVOT), where patients with a range of degrees of renal function were included, the decrease in eGFR was primarily seen in patients with normal renal function or mild renal impairment at baseline, whereas the decline was less pronounced in patients with moderate or severe renal impairment at baseline.

In active-controlled phase 3a trials, the eGFR decrease seen with semaglutide was seen to a similar degree with sitagliptin, exenatide, insulin glargine and OADs. In SUSTAIN 6 (CVOT), the initial decrease in eGFR was greater with semaglutide than with placebo. However, at end-of-treatment, the mean eGFR did not differ significantly between semaglutide and placebo (ETR 1.00 $[0.97;1.02]_{95\%CI}$ for semaglutide 0.5 mg and ETR 1.02 $[1.00; 1.05]_{95\%CI}$ for semaglutide 1 mg), suggesting that the eGFR decreased during the trial period at a more constant and faster rate with placebo than with semaglutide. The effect seen with placebo likely reflects the expected decline of renal function over time in T2D population, and the fact that this was less pronounced with semaglutide, may suggest a kidney-sparring effect of semaglutide. This is supported by a semaglutide-associated decrease in urinary albumin-to-creatinine ratio (UACR). UACR values were below baseline values with semaglutide at end-of-treatment, while increasing over the entire trial period with placebo (ETR 0.78 $[0.68;0.89]_{95\%CI}$ for semaglutide 0.5 mg and ETR 0.71 $[0.62;0.81]_{95\%CI}$ for semaglutide 1 mg).

9.11 Pregnancy

Semaglutide has not been systematically studied in pregnant or lactating women, and no information on the excretion of semaglutide in human milk or effects on the nursing infant is

available. Studies in animals have shown reproductive toxicity of unknown relevance to humans, see Section 2.2.3.

Within the semaglutide clinical development program, women of childbearing potential were required to use contraception; pregnancy or the intention of becoming pregnant was an exclusion criterion and women who became pregnant were to discontinue trial product immediately. Nonetheless, some pregnancies occurred and their outcomes are reviewed below. As of the cut-off date for the NDA (April 18, 2016), a total of 8 pregnancies (4 with semaglutide and 4 with placebo/ comparators), had been reported. All 4 semaglutide-treated women had healthy children; with comparators 2 had healthy children and 2 had elective abortions. No miscarriages or congenital abnormalities were reported. Based on maternal exposure to semaglutide, fetal exposure may have occurred for 9 weeks or less, including the 5 weeks of exposure from last dosing due to the long half-life of semaglutide. As per December 06, 2016, four additional pregnancies were reported in ongoing semaglutide s.c. once-daily trials; 1 miscarriage with semaglutide once-daily, 1 ongoing pregnancy with comparator product (liraglutide 1.2 mg), and 1 healthy child and 1 ongoing pregnancy where treatment is blinded.

In line with the pregnancy labeling of currently marketed GLP-1 RAs, semaglutide is not recommended for use during pregnancy.

9.12 Hepatic safety

Safety in patients with hepatic impairment

The result from a dedicated single-dose pharmacokinetic phase 1 trial in subjects with various degrees of hepatic function, show no need for dose adjustment of semaglutide in patients with hepatic impairment.

The phase 3a program had no exclusion criteria related to hepatic function except in SUSTAIN 6 (CVOT), where patients with end-stage liver disease were excluded. The safety profile of semaglutide (0.5 mg and 1 mg) appeared similar in patients with normal hepatic function at baseline (defined as <75% AST/ALT percentiles) and patients with elevated AST/ALT baseline levels (≥75% AST/ALT percentiles), and no precautions are warranted in patients with elevated hepatic enzymes when exposed to semaglutide.

Hepatic disorders

Overall, the proportion of patients with ALT/AST >3x ULN and >5x ULN were similar with semaglutide (0.5 mg and 1 mg) and placebo/active comparator products; there was no pattern or clustering in the timing or duration of the ALT/AST peaks. Serious or severe adverse events of hepatic disorders were infrequent and the proportions of patients with events were similar with semaglutide and comparators. None of the serious adverse events or liver test results was indicative of semaglutide-induced liver toxicity, as evaluated based on individual case narratives. Thorough screening for Hy's law was performed and no cases were confirmed.

9.13 Additional adverse event categories

Based on pre-defined MedDRA searches among adverse events reported in the clinical trials, no clinically relevant differences between semaglutide and comparators were noted for medication errors, suspected transmission of infectious disease via trial product, or rare events.

9.14 Post-marketing experience

Semaglutide has not been marketed in any country; therefore no post-marketing data are available.

9.15 Discussion and conclusions on clinical safety

The safety of semaglutide was studied in the large semaglutide development program (5,710 semaglutide-treated patients) including patients across the T2D disease spectrum and most commonly associated comorbidities.

The semaglutide phase 3a program is comprehensive in terms of the number of patients with long-term exposure data. The program provides semaglutide safety data from a long-term (104-weeks) controlled cardiovascular outcomes trial, from 7 phase 3a trials, one phase 2 dose-finding trial and 16 phase 1 clinical pharmacology trials. Full adverse event reporting was performed throughout SUSTAIN 6 (CVOT). All patients were followed for the entire duration of the trials regardless of treatment adherence and the amount of missing data was low. The semaglutide safety profile was consistent across the clinical development program.

The safety profile of semaglutide was overall consistent with the GLP-1 RA class, with gastro-intestinal adverse events, reduced appetite and weight decrease and hypoglycemia (when semaglutide was combined with insulin or SU) as adverse drug reactions. As for other GLP-1 RAs, MTC and acute pancreatitis were potential risks with semaglutide. No MTC cases or imbalances in calcitonin abnormalities occurred. No imbalances in events of pancreatitis were evident. Cardiovascular safety of semaglutide was established in the cardiovascular outcomes trial SUSTAIN 6 (CVOT) with a hazard ratio of 0.74 $[0.58; 0.95]_{95\%CI}$, see Section 7.4.

The safety profile was consistent across subgroups of sex, age, race, ethnicity, body weight, BMI, hypertension, cardiovascular history, renal function, hepatic function, region, anti -glycemic background medication and tobacco use, thus supporting the safe use of semaglutide across these subpopulations. Except for diabetic retinopathy complications in SUSTAIN 6 (CVOT) (see Section 10), no relevant differences were found between the semaglutide safety profile in the less comorbid population in the phase 3a trials (excl. CVOT) compared to the comorbid population in SUSTAIN 6 (CVOT). Only gastrointestinal events showed evidence of a dose-response relationship. More patients discontinued treatment prematurely due to adverse events with semaglutide than with placebo and active comparators, mainly attributable to the greater number of discontinuations related to gastrointestinal events. Gastrointestinal events tended to have onset early in the trials, were generally not associated with sequelae, and seemed to have a relatively low clinical impact, based on the seriousness, severity and reversibility of the events.

10 Diabetic retinopathy

Summary

- The proportion of patients with investigator-reported adverse events of diabetic retinopathy (MedDRA search) was low in the phase 3a pool (excluding the CVOT), events were overall evenly-balanced with semaglutide (0.5 mg: 2.1%; 1 mg: 1.5 %) and comparator products (2%).
- In SUSTAIN 6 (CVOT), a significant increased risk of EAC-confirmed events of microvascular diabetic retinopathy complications was observed with semaglutide (50 [3.0%] patients) as compared with placebo (29 [1.8%] patients) (HR: 1.76 $[1.11; 2.78]_{95\%CI}$).
- Analyses support that the effect of semaglutide could be explained in large part by the HbA_{1c} reduction during the first 3-4 months, indicating that a pronounced initial decline in blood glucose was likely causing the well-recognized effect of early worsening of pre-existing diabetic retinopathy that follow pronounced improvements in glycemic control.
- Risk minimization activities proposed by Novo Nordisk include labelling.
- Methodological limitations of SUSTAIN 6 (CVOT) preclude definitive conclusions regarding the effect of semaglutide on development and progression of diabetic retinopathy.

10.1 Background

Glycemic control is known to prevent or delay microvascular complications, and dedicated evaluations of microvascular complications including diabetic retinopathy were included as a secondary endpoint in SUSTAIN 6 (CVOT), see Section 8. However, an increased risk of diabetic retinopathy complications in patients with pre-existing diabetic retinopathy was seen in SUSTAIN 6 (CVOT). Novo Nordisk has performed a thorough evaluation of these events and consulted with external ophthalmology experts to better understand the potential implications of the finding and to identify those patients most at risk. The increase in diabetic retinopathy complications with semaglutide observed in SUSTAIN 6 (CVOT) is consistent with early worsening in diabetic retinopathy after improvements in glycemic control as seen with other highly efficacious blood glucose lowering therapies, most notably insulin. Besides the magnitude of HbA_{1c} reductions, the clinical characteristics and potential predictors of T2D patients at risk for diabetic retinopathy complications include pre-existing diabetic retinopathy, poor control and long duration of diabetes, and co-use of insulin.

In order to achieve a broader understanding of the diabetic retinopathy finding in SUSTAIN 6 (CVOT), the established knowledge about diabetic retinopathy and published data on diabetic

retinopathy associated with other anti-diabetic products, including other GLP-1 RAs are summarized shortly below.

Diabetic retinopathy

Diabetic retinopathy is the most prevalent of the microvascular complications and is a progressive and potentially sight-threatening disease of the retina that follows sustained hyperglycemia.

Diabetic retinopathy affects the vascular component of the retina, the back portion of the eye.[31] Diabetic retinopathy represents a spectrum of changes in the retina that progress in severity; and the pathophysiology of diabetic retinopathy is similar in patients with T1D and T2D. Retinal microangiopathy is the most prominent clinical feature but other conditions linked to diabetes mellitus such as inflammation and neurodegeneration also occur.[149, 150] Diabetic retinopathy is classified into 2 stages: non-proliferative and proliferative, according to the absence or presence of abnormal new vessels. The non-proliferative stage is further sub-classified as mild, moderate or severe, based on morphological findings in the retina. These changes include micro-aneurysms, retinal hemorrhages, cotton wool exudates, venous bleeding and intra-retinal micro-vascular abnormalities. The non-proliferative disease stage is typically asymptomatic and can be reversed. As the disease progresses to the proliferative stage, ischemia in the retina worsens, promoting the growth of new fragile blood vessels. The new abnormal blood vessels are prone to rupture, causing vitreous hemorrhage, and the growth of vessels also promotes fibrosis and retinal distortion or detachment. These are the causes of vision loss. Even at this late stage of severe complications however, it is possible to reverse visual loss with specific surgical and therapeutic interventions. Diabetic maculopathy is another component of diabetic retinopathy which is classified separately.[151] It can occur at both the proliferative and non-proliferative stages and is characterized by increased vascular permeability leading to macular edema and deposition of hard exudates in the macula (central retina, responsible for vision). Diabetic maculopathy is the main cause of blindness in patients with diabetes.

The prevalence of diabetic retinopathy correlates with both the duration of diabetes and level of glycemic control. Around 20% of newly diagnosed patients with T2D have evidence of diabetic retinopathy and after 10–20 years more than 50% of the patients will have developed diabetic retinopathy. Some patients (4–8%) will develop sight threatening diabetic retinopathy, and it is the most frequent cause of blindness among adults in developed countries. In addition to diabetic retinopathy, glaucoma, cataracts, and other disorders of the eye also occur earlier and more frequently in people with diabetes.[31]

The risk factors for development and progression of diabetic retinopathy include increasing age, long duration of diabetes, poor glycemic control, poorly treated hypertension and dyslipidaemia.[8, 11, 152-156] Treatment strategies reducing these risk factors are therefore essential in preventing development of diabetic retinopathy or its progression.

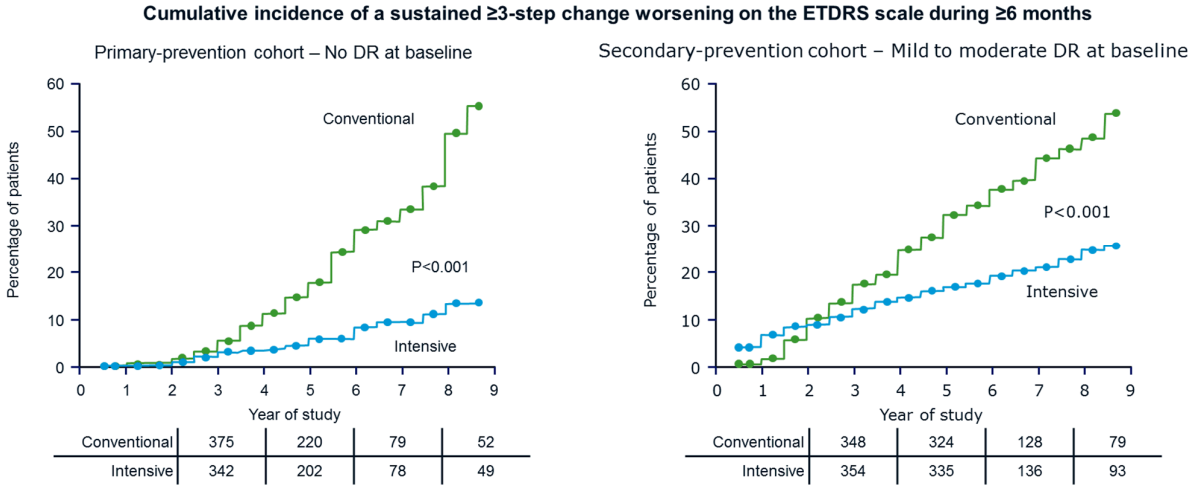
As diabetic retinopathy is largely asymptomatic, regular eye examinations (at a frequency depending on the patient's level of diabetic retinopathy) are mandated by good medical practice guidelines.[31] These guidelines are in place so that ophthalmologists can identify signs of worsening diabetic retinopathy and initiate treatment as needed. Several effective treatment options exist, such as laser photocoagulation, intra-vitreal injections of corticosteroids or anti–vascular endothelial growth factor (VEGF) agents.[31] If appropriate treatment is initiated in a timely manner, more than 95% of severe visual loss from diabetic retinopathy can be prevented.

Prevention or delay in onset of diabetic retinopathy

The risk of diabetic retinopathy is highly associated with the degree of glycemic control and reduction of hyperglycemia. Maintaining glycemic control as close to that of individuals without diabetes (HbA_{1c} <7%), can delay both the onset and the progression of diabetic retinopathy.[157] This paradigm is true for both proliferative diabetic retinopathy and diabetic macular edema, and T1D and T2D. In addition to good glycemic control, optimized blood pressure and serum lipid control may prevent or delay the progression of diabetic retinopathy.[11, 43]

The impact of long-term stringent glycemic control on prevention or delay in onset or progression of diabetic retinopathy is well-established based on numerous large, rigorous, multicenter clinical trials.[11, 32, 34, 35, 38-43, 158] A recent meta-analysis of four large, long-term trials: ACCORD, ADVANCE, UKPDS, and VADT including 27,049 patients with T2D and a median follow-up of 5.0 years, showed that more intensive glucose control reduced the risk of eye events (including development and progression of retinopathy) by 13% compared with less intensive control.[159]

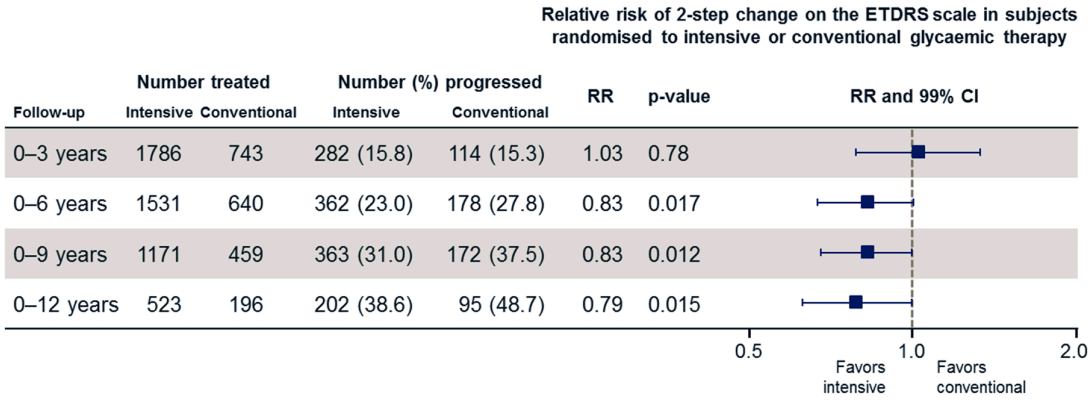
Data conclusively demonstrating this benefit is exemplified by the results of the Diabetes Control and Complications Trial, referred to as the DCCT.[38] The DCCT evaluated over 1,400 patients with T1D who were randomly assigned to receive conventional diabetes therapy, or intensive therapy that was aimed at normalizing HbA_{1c}. Development of diabetic retinopathy was evaluated in a primary prevention cohort without retinopathy at baseline, and progression of diabetic retinopathy was evaluated in a secondary intervention cohort with mild to moderate retinopathy at baseline. Intensive treatment was associated with a 76% reduction (after 9 years) in the risk of retinopathy onset in the primary prevention cohort as compared with the conventional therapy group (Figure 34, left panel). Similar major reductions in retinopathy associated risks were observed in the secondary intervention cohort (Figure 34, right panel), including benefits for retinopathy progression, development of severe retinopathy, and need for laser treatment or ocular surgery.



Note: Redrawn from The Diabetes Control and Complications Trial Research Group.[38]
Abbreviations: DR: diabetic retinopathy; ETDRS: Early Treatment Diabetic Retinopathy Study.

Figure 34 Diabetes Control and Complications Trial (DCCT) in patients with T1D: Progression of diabetic retinopathy with intensive versus conventional glycemic therapy

The benefits of intensive glycemic control also applies to patients with T2D as demonstrated by the United Kingdom Prospective Diabetes Study, referred to as the UKPDS.[43] This study evaluated the effects of intensive glycemic control on microvascular and other complications in over 3800 newly diagnosed patients with T2D. Intensive glycemic treatment significantly reduced the risk of diabetic retinopathy progression by 17% after 6 years and 21% through 12 years (Figure 35).



Note: Redrawn from UK Prospective Diabetes Study (UKPDS) Group.[43]
Abbreviations: CI: confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study; RR: relative risk.

Figure 35 UK Prospective Diabetes Study (UKPDS) in patients with T2D: Progression of diabetic retinopathy with intensive versus conventional glycemic therapy

In the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) the beneficial effect was not evident until after at least 3 years of treatment (Figure 34 and Figure 35).[34, 35, 38-42] The beneficial effect of long-term tight control on diabetic retinopathy is also supported by the recently published follow-up study of ACCORD.[11]

Impact of early improvement in glycemic control on diabetic retinopathy

Although the long-term benefits of intensive treatment and improved glycemic control on development and progression of diabetic retinopathy is well-established, an apparent paradoxical worsening of diabetic retinopathy has been reported with improved glycemic control in multiple small studies and confirmed by the DCCT.[32-35, 160] This phenomenon, termed early worsening, is well-known for insulin therapy (and is reflected in the product information for insulin products). Increased risk of worsening of diabetic retinopathy has also been reported in circumstances leading to pronounced improvements in glycemic control, such as after bariatric surgery or pancreas transplants and in diabetic pregnancies.[45, 161-167]

The risk of early worsening has especially been seen in patients with long-standing diabetes, poor glycemic control, large reduction in HbA_{1c} and pre-existing diabetic retinopathy.[32-35] In patients with advanced retinopathy at baseline, a progression is more likely to result in clinically detected retinal complications. In line with this, an early worsening of diabetic retinopathy was observed in patients with T1D in the DCCT after intensive treatment in the secondary intervention cohort, i.e., in patients with pre-existing diabetic retinopathy (Figure 34, right panel). The increased risk was seen during the first 2 years of treatment; however, from two years on, the intensive therapy group was increasingly and substantially protected from retinopathy progression as compared to the conventional therapy group. Hence, the benefit of intensive therapy far exceeds the degree of detriment observed early in the study, and the relative magnitude of the benefit continues to increase over time. Although early worsening at either the 6 or 12 month visit was higher in the intensive treatment group, more than half of these patients had completely recovered from their early worsening by 18 months. Thus, early worsening is often reversible within a relatively short period. The early worsening seems to be counter-balanced by the long-term reduction in retinal complications with improved glycaemia, based on the results of the large, long-term trials.[11, 32, 34, 35, 38-42, 158] No evidence was found in the DCCT to suggest that a more gradual reduction of glycemia might be associated with less risk of early worsening.[34]

An initial increase in risk of diabetic retinopathy progression following treatment intensification has also been observed in patients with T2D. In a case-control study evaluating progression of retinopathy in patients with T2D switching from oral anti-hyperglycemic agents to insulin, patients with the greatest reduction in HbA_{1c} encountered the most severe progression of retinopathy.[168] Furthermore, in the UKPDS in patients with T2D, the results for the first 3 years also showed a slightly higher risk of diabetic retinopathy progression in the intensive treatment group compared to conventional treatment (Figure 35). A lower risk of diabetic retinopathy progression with intensive treatment was first observed over a longer treatment period (6 years and beyond).

The mechanism(s) behind the potential initial worsening of diabetic retinopathy following pronounced reduction in blood glucose levels are not fully understood. Retinal ischemia, volume and osmotic changes, and increase in growth factors have been proposed.[169]

Retinopathy with other antiglycemic agents

Pronounced improvement in glycemic control following initiation of intensified antiglycemic therapy has been associated with a transient worsening of diabetic retinopathy[32-35], and this risk is well-known for insulin products and reflected in their product information.

Diabetic retinopathy is not considered a general concern for the GLP-1 RA or incretin drug class. Published data on pre-approval studies for other GLP-1 RA contain little information about evaluation of diabetic retinopathy and reflect that the risk of diabetic retinopathy was assessed by standard adverse event reporting in a low risk patient population. Hence, available data mainly relate to serious adverse events with a consequently low number of events due to the mostly non-serious nature of the disease. However, transient worsening in diabetic retinopathy has been reported in case reports for exenatide.[45, 161, 162] In the cardiovascular outcome trial with sitagliptin (TECOS[170, 171]), a higher risk of diabetic retinopathy was observed for sitagliptin compared to placebo (2.8% vs. 2.2%; relative risk: 1.30 $[1.06; 1.59]_{95\% CI}$, p=0.012). Furthermore, in the albiglutide phase 3a program, 3.6% of patients reported diabetic retinopathy with albiglutide compared to 1.7% with placebo. In the ongoing dulaglutide cardiovascular outcomes trial (REWIND), evaluation of diabetic retinopathy is included as part of a secondary composite microvascular endpoint. In the completed liraglutide cardiovascular outcomes trial (LEADER)[14], using a similar composite endpoint for diabetic retinopathy complications and high risk population as SUSTAIN 6 (CVOT), the proportion of patients with diabetic retinopathy complication was 2.3% with liraglutide and 2.0% with placebo with a hazard ratio of 1.15 $[0.87; 1.52]_{95\%CI)}$).

Nonclinical data related to diabetic retinopathy

No treatment-related effects of semaglutide on the retina were observed in nonclinical studies. In the toxicology studies conducted in mice, rats and cynomolgus monkeys, no treatment-related changes, including retinopathy, were observed in the eyes of the more than 800 animals evaluated by ophthalmoscopy or histopathology. Furthermore, analyses have shown limited expression of the GLP-1 receptor (GLP-1 R) in the human eye, confined to single neuronal cells in the ganglion cell layer, and with no expression in the vasculature or epithelium (Novo Nordisk data on file). In human eyes from patients with advanced diabetic retinopathy, no GLP-1R expression was found in any structures, including epiretinal membranes (Novo Nordisk data on file).

10.2 Methods for evaluation of diabetic retinopathy in the phase 3a program

This section summarizes how diabetic retinopathy was assessed across the phase 3a program and how assessments differed in the phase 3a pool and SUSTAIN 6 (CVOT). Whilst the methods used for the collection of eye data seemed appropriate at the time of trial design, the lack of fundus

photographs, standardized pupil dilation and grading of fundal images places important limitations on the ability to evaluate the effect of treatment intervention on ophthalmological endpoints used in SUSTAIN 6 (CVOT).

Please also note that the EAC-confirmed diabetic retinopathy complications endpoint used in SUSTAIN 6 (CVOT) is not a complete representation of progression of diabetic retinopathy. In studies such as DCCT, UKPDS and ACCORD where the progression of diabetic retinopathy was assessed, retinal imaging was used systematically and grading of the retinal photographs using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale enabled assessment of the progression of diabetic retinopathy.

Baseline assessments of diabetic retinopathy status in phase 3a trials

The presence of pre-existing diabetic retinopathy was recorded at baseline as part of the medical history and concomitant illness based on patient feedback, reviews of patient's medical history and baseline assessments including baseline fundoscopy/fundus photography (Table 27). In SUSTAIN 6 (CVOT) more detailed information was recorded on a dedicated Diabetes History/Diabetes Complications form including type of retinopathy (proliferative, non-proliferative), presence of macular edema, previous laser therapy/treatment with intravitreal agents, or previous surgical treatment (e.g., vitrectomy). Evaluation of visual acuity (VA) was not part of the baseline assessment and no other types of eye examinations were required per trial protocol.

Assessments of diabetic retinopathy during the phase 3a program

Diabetic retinopathy was evaluated during the trials based on multiple sources of information (Table 27).

Table 27 Trials in phase 3a program: Assessment of diabetic retinopathy

	Phase 3a pool	SUSTAIN 6 (CVOT)
At baseline		
Medical history and concomitant illness	X	X
Dedicated retinopathy history form		X
Fundoscopy or fundus photography	X	X
During the trials		
Scheduled fundoscopy or fundus photography		
Year 1, year 2		X
Premature treatment discontinuation	X	X
End-of-treatment	X (SUSTAIN JP Mono and OAD)	X
Adverse event reporting	X	X
Adjudication of diabetic retinopathy complications		X

Abbreviations: CVOT: cardiovascular outcomes trial; JP: Japan; Mono: monotherapy.

Evaluations were based on a) scheduled eye examinations (fundoscopy or fundus photography) performed at baseline in all phase 3a trials, at end-of –treatment in the Japanese phase 3a trials, and after 1 year and after 2 years/at end-of-trial in SUSTAIN 6 (CVOT); b) investigator –reported adverse event as part of standard safety evaluation; and c) events confirmed by an external event adjudication committee (EAC) to meet the pre-defined criteria for the microvascular endpoint 'diabetic retinopathy complications' (SUSTAIN 6 [CVOT] only).

Funduscopy or Fundus photography

In SUSTAIN 6 (CVOT) changes in the retina were captured by fundoscopic examinations, but no central evaluation was performed and the detailed ETDRS scale was not used. Hence, the data must be viewed with caution due to limitations in the way the assessments were performed. Fundoscopic examinations were scheduled at baseline (randomization visit or within 90 days prior to this visit, if there was no deterioration in visual function since the last assessment), after 1 year of treatment, at premature treatment discontinuation visits and at end-of-treatment visits. The examination could be either direct fundoscopy or digital / fundus photography; it was not recorded which method was used. Fundoscopic examinations were to be performed by the investigator, a local ophthalmologist or an optometrist according to local practice; it was not recorded who performed the examination. Pupillary dilation was not required but could have been employed; it was not recorded which examinations were done with a dilated pupil. The result of the examination was interpreted locally by the investigator and categorized as: 'normal', 'abnormal, not clinically significant' or 'abnormal, clinically significant'. No central reading of fundus photographs was performed. If available, fundus photographs were provided to the EAC adjudicators.

Adverse event reporting

In all phase 3a trials including SUSTAIN 6 (CVOT), diabetic retinopathy was evaluated as part of the general safety evaluation based on investigator reported adverse events.

An adverse event was defined as any untoward medical occurrence in a patient administered a product, including an event which does not necessarily have a causal relationship with the treatment. Any clinically significant worsening of a concomitant illness was also to be reported as adverse events, whereas pre-existing conditions were not to be reported as adverse events. Hence, abnormal findings from the eye examinations reflecting pre-existing conditions were not to be reported as adverse events, unless they represented a worsening of baseline conditions. During each contact with the trial site staff, the patients were asked about adverse events, for example by asking: "Have you experienced any problems since the last contact?" The severity of the adverse events were graded by the investigators as mild (no or transient symptoms, no interference with the patient's daily activities), moderate (marked symptoms, moderate interference with the patient's daily activities) or severe (considerable interference with the patient's daily activities; unacceptable).

All adverse events observed by the investigator based on scheduled or unscheduled assessments as well as events reported by the patients were to be recorded as adverse events by the investigator. If available, the diagnosis should be recorded; if no diagnosis was available, the investigator was to record each sign and symptom as individual adverse events.

Adverse events terms potentially related to diabetic retinopathy were summarized using a predefined medical dictionary (MedDRA) search among all investigator-reported adverse events.

Adverse events potentially fulfilling the criteria of diabetic retinopathy complications were pre-defined as medical events of special interest (MESIs). These events were identified by the investigators and additional information was collected on dedicated forms. In SUSTAIN 6 (CVOT) all potential events of diabetic retinopathy complications identified by the investigators were forwarded to the EAC together with relevant source data. In addition, a pre-defined search was performed among all adverse events to identify further events potentially fulfilling the criteria of diabetic retinopathy complications and thus qualifying for adjudication.

Adjudication of diabetic retinopathy complications in SUSTAIN 6 (CVOT)

Potential events of diabetic retinopathy complications were identified based on 1) adverse events referred by the investigator, 2) events identified by EAC during review of source documents, and 3) by a broad search among all adverse events reported. All potential events were adjudicated by the external event adjudication committee (EAC) including 2 medical specialists within ophthalmology, see details in Appendix 2, Section 4.

Analyses were based on a composite endpoint based on fulfilment of one or more of the 4 criteria (Table 15), two criteria reflected the need for treatment (photocoagulation or intravitreal agents) and 2 criteria related to diagnoses (vitreous hemorrhage and diabetes-related blindness). Diabetes-related blindness was defined as an episode of visual loss at time of evaluation (Snellen visual acuity of 20/200 [6/60] or less, or visual field of less than 20 degrees, in the better eye with best correction possible). Note that the definition of 'diabetes-related blindness' used in the trial, does not mean it was a permanent loss of vision and could include a temporary reduction in visual acuity). By definition therefore, the patient's vision could have improved later in the trial. A single EAC-confirmed event could concomitantly fulfill more than one of the criteria. Thus, a single event could count in more than one of the analyses of the individual components of the composite endpoint.

10.3 Diabetic retinopathy at baseline including risk factors

As in phase 3 programs for other GLP-1 RAs, trials included in the phase 3a pool had the standard exclusion criterion: "Known proliferative retinopathy or maculopathy requiring acute treatment according to the opinion of the investigator". In SUSTAIN 6 (CVOT), there was no specific exclusion criteria related to diabetic retinopathy, i.e., patients with all stages of retinopathy were eligible; also there was no upper limit for baseline HbA_{1c}.

The patient population enrolled in SUSTAIN 6 (CVOT) had advanced diabetes with high cardiovascular risk, and was at high risk of having diabetic retinopathy complications. Patients had a mean age of 64.6 years, a long diabetes duration of 13.9 years, a mean baseline HbA_{1c} of 8.7%, 58.0% of patients used insulin, and 29.4% of patients had pre-existing diabetic retinopathy (non-proliferative in the majority [77.4%] of cases) at baseline (Table 28).

Table 28 Trials in phase 3a program: Baseline characteristics related to risk of diabetic retinopathy

	SUSTAIN							
	1 N=387	**2** N=1,225	**3** N=809	**4** N=1,082	**5** N=396	**JP Mono** N=308	**JP OAD** N=600	**6** N=3,297
Age, years	53.7	55.1	56.6	56.6	58.8	58.3	58.5	64.6
HbA_{1c}, %	8.1	8.1	8.3	8.2	8.4	8.2	8.1	8.7
T2D duration, years	4.2	6.6	9.2	8.6	13.3	8.0	8.9	13.9
SBP, mm Hg	128.8	132.6	133.5	132.1	134.8	129.1	129.2	135.6
Insulin use, n (%)	0	0	1 (0.1)	0	396 (100)	0	0	1,913 (58)
Diabetic retinopathy, n (%)	15 (3.9%)	94 (7.7%)	30 (3.7%)	50 (4.6%)	55 (13.9%)	42 (13.6%)	87 (14.5%)	969 (29.4%)

Note: FAS on-treatment.
Abbreviations: JP: Japan; mono: mono-therapy; N: number of patients; n: number of patients with events; OAD: anti-glycemic drugs; SBP: systolic blood pressure; T2D: type 2 diabetes mellitus; %: proportion of patients with events.

10.4 Adverse events related to diabetic retinopathy

In order to obtain an overview of all adverse events potentially related to diabetic retinopathy, a pre-defined MedDRA search was performed within the system organ class (SOC) of eye disorders to capture all events and group them together. The MedDRA search identifying 'adverse events of diabetic retinopathy' covered several preferred terms (including also event types like 'retinal exudates', 'macular edema', and 'visual acuity reduced').

A low proportion of patients in the phase 3a pool (excluding the CVOT) had adverse events of diabetic retinopathy (as identified by the pre-defined MedDRA search); events were overall evenly-balanced with semaglutide and comparator products (Table 29). There was no difference in the types of events, and the preferred term 'diabetic retinopathy' accounted for more than half of all event identified by the MedDRA search. The proportion of patients with adverse events with semaglutide in the phase 3a pool appeared lower than the frequency reported with other products in the class including albiglutide (3.6%, see Section 10.1).

The proportion of patients with events varied from below 1% in SUSTAIN 1 in treatment naïve patients to around 6-8% in the Japanese OAD trial. The two Japanese trials accounted for more than half of the events, and the majority of these events were reported in connection with the end-of-treatment fundoscopy both with semaglutide and comparators. The higher number of events reported in the two Japanese trials is likely due to the fact that fundoscopy was performed at both baseline and end of treatment rather than just at baseline as in SUSTAIN 1–5. In addition, the

widespread use of the Fukuda criteria for classifying and grading the severity of diabetic retinopathy in Japan[172] may have increased the likelihood of identifying and reporting of worsening of diabetic retinopathy by the Japanese investigators, as these criteria allow a more detailed and specific grading of the stage/severity of retinopathy.

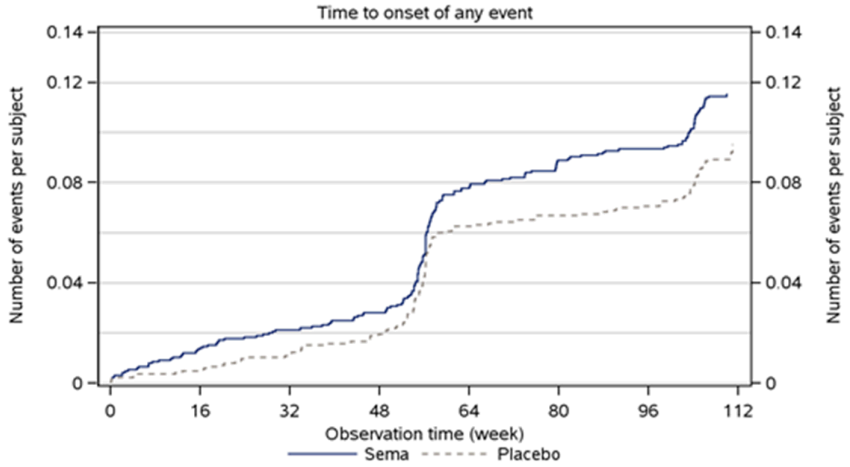
Table 29 Trials in phase 3a program: Investigator-reported adverse events of diabetic retinopathy (MedDRA search)

	Semaglutide 0.5 mg				Semaglutide 1 mg				Comparators			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Phase 3a pool (a)	32	(2.1)	35	2.6	30	(1.5)	36	1.9	31	(2.0)	31	2.1
SUSTAIN 1 sema vs. Placebo (Mono)	0	(0.0)			0	(0.0)			1	(0.8)	1	1.2
SUSTAIN 2 sema vs Sita (OADs)	5	(1.2)	5	1.1	1	(0.2)	2	0.4	10	(2.5)	10	2.1
SUSTAIN 3 sema vs. Exe ER (OADs)	Not applicable				4	(1.0)	8	1.7	4	(1.0)	4	0.9
SUSTAIN 4 sema vs. IGlar (OADs)	3	(0.8)	3	1.3	0	(0.0)			5	(1.4)	5	2.1
SUSTAIN 5 sema vs. Placebo (Insulin)	4	(3.0)	5	5.7	1	(0.8)	1	1.1	0	(0.0)		
SUSTAIN JP Mono sema vs. Sita	4	(3.9)	4	5.7	4	(3.9)	4	5.9	4	(3.9)	4	5.7
SUSTAIN JP OAD sema vs. OAD	16	(6.7)	18	6.5	20	(8.3)	21	7.6	7	(5.8)	7	5.0
SUSTAIN 6 (CVOT) sema vs Placebo (SoC)	74	(9.0)	86	5.0	82	(10.0)	99	5.8	125	(7.6)	145	4.3

a) % and R for the phase 3a pool are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.
Note: In-trial.
Comparators: Phase 3a pool: Exe ER; IGlar; OAD; sita, placebo. SUSTAIN 6 (CVOT): placebo.
Abbreviations: CVOT: cardiovascular outcomes trial; E: number of events; Exe ER: exenatide extended release; IGlar: insulin glargine; Mono: montherapy; N: number of patients with at least one event; OAD: oral antiglycemic drugs; PYO: patient-years of observation; %: proportion of patients with event; R: events per 100 PYO; sema: semaglutide; sita: sitagliptin; SoC: standard-of-care.

In SUSTAIN 6 (CVOT), the proportion of patients with adverse events of diabetic retinopathy (as identified by the MedDRA search), was higher than in the trials included in the phase 3a pool (Table 29). This is consistent with patients being at higher risk of development or progression of diabetic retinopathy than the patients enrolled in the other trials. Furthermore, the trial was of longer duration (2 years vs. 30 or 56 weeks). The proportion of patients with adverse events of diabetic retinopathy was higher for semaglutide (9.5%) than placebo (7.6%).

The time of onset of many investigator-reported adverse events coincided with the preplanned 1- and 2-year eye examination in the trial (Figure 36) consistent with the largely asymptomatic nature of diabetic retinopathy.



Notes: FAS, in-trial. Mean cumulative function estimates for diabetic retinopathy adverse events (MedDRA search). Patients are censored at their planned end-of-trial visit, death, or last direct contact, whichever came first.

Figure 36 SUSTAIN 6 (CVOT): Time to adverse event of diabetic retinopathy (MedDRA search)

Adverse events related to diabetic retinopathy were reported as non-serious adverse events, none were severe, and none led to premature treatment discontinuation. There were no treatment differences regarding severity or type of events; most events were non-serious adverse events, and of mild or moderate severity (Table 30).

Table 30 Phase 3a pool and SUSTAIN 6 (CVOT): Investigator-reported adverse events of diabetic retinopathy (MedDRA search) by seriousness and severity

	Semaglutide 0.5 mg				Semaglutide 1 mg				Comparators			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Phase 3a pool (a)												
All adverse events	32	(2.1)	35	2.6	30	(1.5)	36	1.9	31	(2.0)	31	2.1
Serious adverse events (SAEs)	0	(0.0)			0	(0.0)			0	(0.0)		
Severe adverse events	0	(0.0)			0	(0.0)			0	(0.0)		
Moderate adverse events	3	(0.2)	4	0.3	3	(0.2)	5	0.3	6	(0.4)	6	0.4
Mild adverse events	29	(1.9)	31	2.3	27	(1.3)	31	1.6	25	(1.6)	25	1.7
SUSTAIN 6 (CVOT)												
All adverse events	74	(9.0)	86	5.0	82	(10.0)	99	5.8	125	(7.6)	145	4.3
Serious adverse events (SAEs)	6	(0.7)	7	0.4	5	(0.6)	6	0.4	8	(0.5)	8	0.2
Severe adverse events	5	(0.6)	6	0.4	5	(0.6)	5	0.3	7	(0.4)	7	0.2
Moderate adverse events	27	(3.3)	33	1.9	22	(2.7)	25	1.5	35	(2.1)	37	1.1
Mild adverse events	44	(5.3)	47	2.8	57	(6.9)	69	4.1	86	(5.2)	101	3.0

a) % and R for the phase 3a pool are the Cochran-Mantel-Haenszel-adjusted percentage and event rate.
Note: FAS in-trial.
Comparators: Phase 3a pool: exenatide ER; insulin glargine; oral anti-glycemic drugs; sitagliptin, placebo. SUSTAIN 6 (CVOT): placebo.
Abbreviations: E: number of events; FAS: full analysis set. N: number of patients with at least one event; PYO: patient-years of observation; %: proportion of patients with event; R: events per 100 PYO.

10.5 EAC evaluation of diabetic retinopathy complications in SUSTAIN 6 (CVOT)

A total of 98 events in 79 patients were confirmed by the EAC as diabetic retinopathy complications (Figure 37). As shown in Figure 37, the majority of confirmed events were reported by the investigators as per protocol (see details in Appendix 2, Section 4).

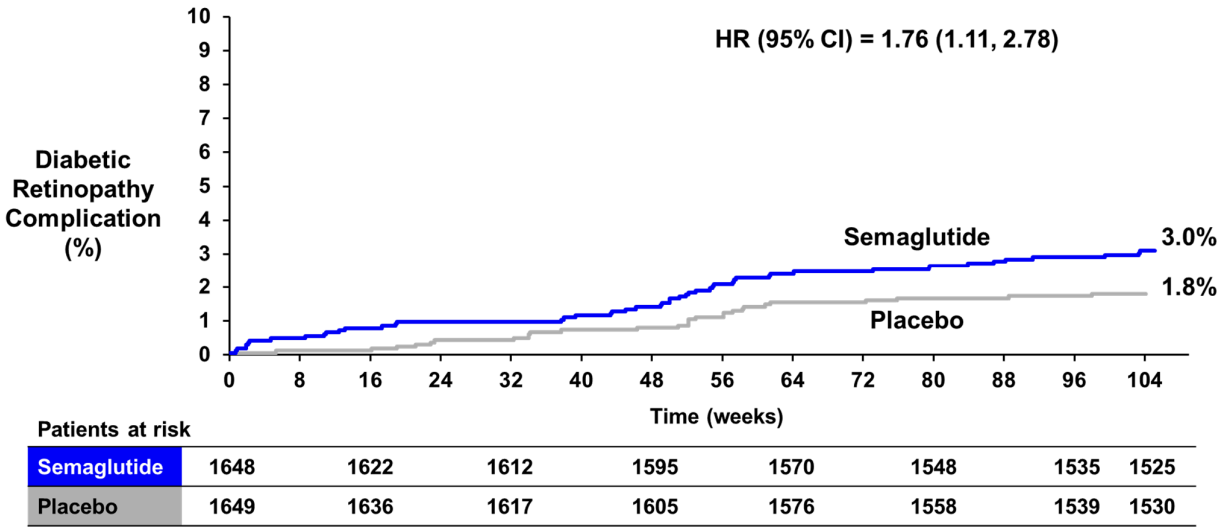
	EAC-confirmed events
Diabetic retinopathy complications, fulfilling at least one of the following criteria: Need for retinal photocoagulation Need for intravitreal agents Diagnosis of vitreous hemorrhage Onset of diabetes-related blindness	**98**
- Investigators were asked to report diabetic retinopathy complications	85
- Event adjudication committee was asked to look for additional events when doing the adjudication	3
- All adverse events in the database were screened to ensure that no diabetic retinopathy complications were missed	10

Figure 37 SUSTAIN 6 (CVOT): Identification of EAC-confirmed diabetic retinopathy complications

Time to EAC-confirmed first diabetic retinopathy complication

A significantly increased risk of EAC-confirmed events of diabetic retinopathy complications was observed with semaglutide (50 [3.0%] patients) as compared with placebo (29 [1.8%] patients) (Figure 25 and Figure 38). The treatment difference appeared early and persisted throughout the trial. The majority of EAC-confirmed events of diabetic retinopathy complications (both with semaglutide [74%] and placebo [86%]) were based on routine eye examinations, either the scheduled fundoscopy in the trial or the scheduled eye examination at the patients' own eye clinics.

Differences between semaglutide and placebo were observed for all four components of the endpoint and were similar with semaglutide 0.5 mg and 1 mg (i.e., dose-independent) (Table 31). As previously stated, each EAC-confirmed event of diabetic retinopathy complications could fulfill more than one criterion. Diagnoses of vitreous hemorrhage and diabetes-related blindness were often associated with other criteria, including need for treatment.



Notes: FAS in-trial. Kaplan-Meier estimates.
Abbreviations: CI: confidence interval; EAC: event adjudication committee; HR: hazard ratio.

Figure 38 SUSTAIN 6 (CVOT): Time to first EAC-confirmed events of diabetic retinopathy complication

Table 31 SUSTAIN 6 (CVOT): EAC-confirmed diabetic retinopathy complications

	Sema 0.5 mg			Sema 1 mg			Total sema			Total placebo		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Number of patients	826			822			1,648			1,649		
Patient years of observation	1,708.4			1,699.8			3,408.2			3,401.1		
Diabetic retinopathy complications	25	(3.0)	28	25	(3.0)	34	50	(3.0)	62	29	(1.8)	36
Need for retinal photocoagulation	21	(2.5)	21	17	(2.1)	22	38	(2.3)	43	20	(1.2)	24
Need for intravitreal agents	6	(0.7)	6	10	(1.2)	12	16	(1.0)	18	13	(0.8)	14
Onset of vitreous hemorrhage	7	(0.8)	7	9	(1.1)	12	16	(1.0)	19	7	(0.4)	8
Onset of diabetes-related blindness	4	(0.5)	4	1	(0.1)	1	5	(0.3)	5	1	(0.1)	1

Note: FAS in-trial.
Abbreviations: E: number of events; EAC: event adjudication committee; N: number of patients; %: proportion of patients with event; sema: semaglutide.

EAC-confirmed events of diabetic retinopathy complications could be clinically heterogeneous depending on the criteria met (see Methods of evaluation, Section 10.2). In order to further understand the nature of the EAC-confirmed events of diabetic retinopathy complications, patients with confirmed events were divided into four mutually exclusive groups depending on the criteria met for each patient. Among the patients with EAC-confirmed events of diabetic retinopathy complications, 2/3 (53 of 79 patients) of patients had a need for treatments (photocoagulation or vitreous agents) without a diagnosis of vitreous hemorrhage or diabetes-related blindness; 32 patients with semaglutide and 21 patients with placebo (Table 32). A total of 20 patients had vitreous hemorrhage (not related to diabetes-related blindness) during the trial, 16 of these also had a need for treatment.

Six patients had events confirmed by the EAC as meeting the criterion: 'Onset of diabetes-related blindness' defined as an episode of visual loss at time of evaluation (Snellen visual acuity of 20/200 [6/60] or less, or visual field of less than 20 degrees, in the better eye with best correction possible). (Table 32). Details on these events are presented in Table 33. The 5 semaglutide-treated patients with an EAC-confirmed event of onset of diabetes-related blindness, all had a history of severe proliferative diabetic retinopathy at baseline and had received laser therapy or treatment with intravitreal agents prior to trial entry. These patients had diabetes duration of 13.2 to 43.3 years, the age ranged from 57 to 71 years and all patients were receiving concomitant insulin therapy at the time of onset of event.

Table 32 SUSTAIN 6 (CVOT): Components fulfilled in patients with EAC-confirmed diabetic retinopathy complications

	Sema 0.5 mg			Sema 1 mg			Total sema			Total placebo		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Number of patients	826			822			1,648			1,649		
Patient years of observation	1,708.4			1,699.8			3,408.2			3,401.1		
Diabetic retinopathy complications	25	(3.0)	28	25	(3.0)	34	50	(3.0)	62	29	(1.8)	36
Treatment only												
Need for retinal photocoagulation (a)	13	(1.6)		8	(1.0)		21	(1.3)		13	(0.8)	
Need for intravitireal agents (b)	3	(0.4)		8	(1.0)		11	(0.7)		8	(0.5)	
Diagnoses												
Onset of vitreous hemorrhage (c)	5	(0.6)		8	(1.0)		13	(0.8)		7	(0.4)	
Onset of diabetes-related blindness (d)	4	(0.5)		1	(0.1)		5	(0.3)		1	(0.1)	

a) Without onset of diabetes-related blindness, vitreous hemorrhage or need for intravitreal agents.
b) Without onset of diabetes-related blindness or vitreous hemorrhage± Need for retinal photocoagulation. With semaglutide, 5 out of these 11 patients had treatments with intravitreal agents and photocoagulation, with placebo 1 out of these 8 patients had treatments with intravitreal agents and photocoagulation
c) Without onset of diabetes-related blindness± Need for intravitreal agents, need for retinal photocoagulation. With semaglutide 3 out of 13 patients had vitreous hemorrhage only; with placebo 1 patient had vitreous hemorrhage only.
d) ± Onset of vitreous hemorrhage, need for intravitreal agents, need for retinal photocoagulation.
Notes: FAS in-trial. Table is based on all EAC-confirmed diabetic retinopathy complications during the trial period. The categories are mutually exclusive, i.e. each patient is only counted once.
Abbreviations: E: number of events; EAC: event adjudication committee; N: number of patients; %: proportion of patients with event; sema: semaglutide.

Further details regarding the 6 patients with EAC-confirmed onset of diabetes-related blindness, including vision status, were collected after completion of the trial. Based upon latest data on vision available for each patient, 3 semaglutide-treated patients had clinically significant improvements in visual acuity and were no longer considered blind, as evaluated using the EAC criteria of diabetes–related blindness. No further data are available regarding eye status of the 2 other semaglutide-treated patients. Thus, there were no cases of irreversible blindness or long-term loss of visual acuity with semaglutide in patients for whom follow-up was available. The placebo-treated patient with an EAC-confirmed 'onset of diabetes-related blindness' had no pre-existing diabetic retinopathy. The patient had not recovered 16 days after onset of the event and no follow-up data are available.

Table 33 SUSTAIN 6 (CVOT): Overview of events confirmed by the EAC as diabetes-related blindness

	Semaglutide					Placebo
Patient	1	2	3	4	5	6
Baseline eye status	Proliferative diabetic retinopathy Laser treatment or intravitreal agents Cataract Macular edema	Proliferative diabetic retinopathy Laser treatment or intravitreal agents Cataract	Proliferative diabetic retinopathy Laser treatment or intravitreal agents Cataract	Proliferative diabetic retinopathy Laser treatment or intravitreal agents Cataract surgery (during trial)	Proliferative diabetic retinopathy Laser treatment or intravitreal agents Cataract surgery (2008)	No diabetic retinopathy
Diabetes duration (years) at baseline	13.5	13.2	20.5	20.5	43.3	25.2
Baseline HbA_{1c} (%)	8.8	8.7	8.9	8.9	7.5	9.7
Baseline history of hypertension (yes/no)	Yes	Yes	Yes	Yes	Yes	Yes
ΔHbA_{1c} (%) at week 16	-2.3	-1.0 at week 8	-2.7	-1.6	-0.5	-0.5
Insulin therapy at onset of event (yes/no)	Yes	Yes	Yes	Yes	Yes	Yes
Onset day of event (a)	15	60	121	304	323	239
Latest status on vision	Not blind, 18 months after event	Not blind, 18 months after event	Not blind, 21 days after event	Unavailable	Unavailable, patient died	Blind, 16 days after event

a): day 1 equals day of initial dose. **Note**: Diabetes-related blindness was defined as an episode of visual loss at time of evaluation (Snellen visual acuity of 20/200 [6/60] or less, or visual field of less than 20 degrees, in the better eye with best correction possible).

Characterization of patients with EAC-confirmed events

In order to identify what characterized the patients at risk of diabetic retinopathy complications, the 79 patients with EAC-confirmed events of diabetic retinopathy complications during the trial were compared to the overall population.

Compared to the total SUSTAIN 6 (CVOT) trial population, the 79 patients who had EAC-confirmed events of diabetic retinopathy complications were characterized by pre-existing retinopathy at baseline, a longer duration of diabetes, a higher baseline HbA_{1c}, and were more likely to be treated with insulin at baseline (Table 34). In addition, the pre-existing diabetic retinopathy were often at a more advanced stage as reflected by a higher proportion of patients with proliferative retinopathy, maculopathy, and/or a history of treatment with laser therapy or intravitreal agents prior to entry into the trial. These characteristics are in accordance with the known risk factors for the development or progression of diabetic retinopathy, as presented in the Background Section 10.1.

Table 34 SUSTAIN 6 (CVOT): Baseline characteristics of patients with EAC-confirmed diabetic retinopathy complications versus overall population

Baseline characteristics	Patients with EAC-confirmed events			All patients
	Semaglutide (N =50)	Placebo (N=29)	Total (N=79)	Total (N=3,297)
Age (years), Mean (SD)	63.0 (5.6)	61.8 (7.0)	62.6 (6.1)	64.6 (7.4)
Sex. Male, n (%)	34 (68.0)	17 (58.6)	51 (64.6)	2,002 (60.7)
Diabetes duration (years), Mean (SD)	17.08 (9.15)	18.29 (6.89)	17.53 (8.37)	13.89 (8.11)
HbA_{1c} (%), Mean (SD)	9.18 (1.95)	9.71 (1.83)	9.37 (1.91)	8.70 (1.46)
Insulin treatment, n (%)	38 (76.0)	22 (75.9)	60 (75.9)	1,913 (58.0)
Baseline diabetic retinopathy, n (%)	42 (84.0)	24 (82.8)	66 (83.5)	969 (29.4)
Proliferative	14 (28.0)	9 (31.0)	23 (29.1)	202 (6.1)
Macular edema	3 (6.0)	1 (3.4)	4 (5.1)	31 (0.9)
Laser therapy/intravitreal agents	10 (20.0)	4 (13.8)	14 (17.7)	112 (3.4)
Surgery	2 (4.0)	2 (6.9)	3 (3.8)	24 (0.7)
Non-proliferative	26 (52.0)	13 (44.8)	39 (49.4)	750 (22.7)
Macular edema	7 (14.0)	4 (13.8)	11 (13.9)	64 (1.9)
Laser therapy/intravitreal agents	10 (20.0)	5 (17.2)	15 (19.0)	100 (3.0)
Surgery	0 (0.0)	0 (0.0)	0 (0.0)	10 (0.3)

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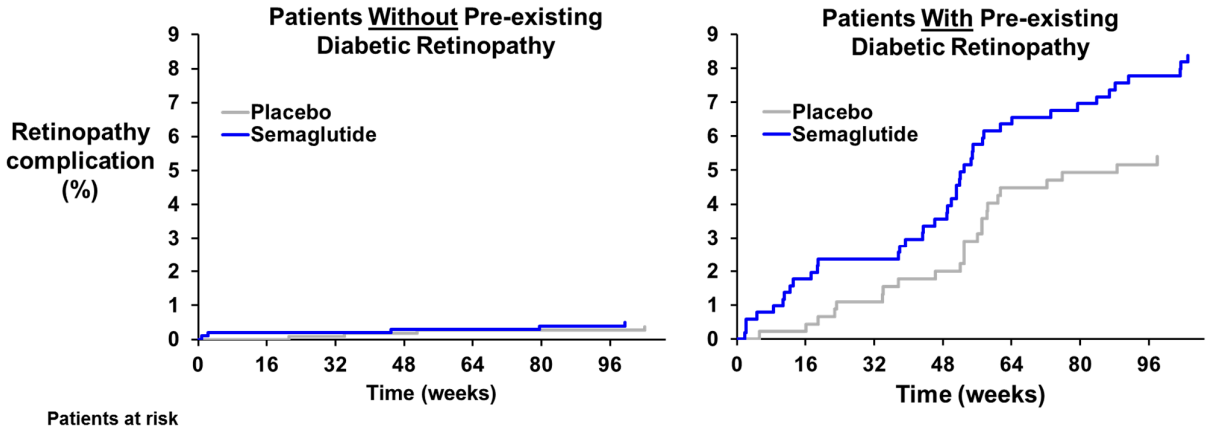
Baseline characteristics	Patients with EAC-confirmed events			All patients
	Semaglutide (N =50)	Placebo (N=29)	Total (N=79)	Total (N=3,297)
Unknown retinopathy status	2 (4.0)	2 (6.9)	4 (5.1)	17 (0.5)
Macular edema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Laser therapy/intravitreal agents	1 (2.0)	0 (0.0)	1 (1.3)	4 (0.1)
Hypertension (a)	48 (96.0)	25 (86.2)	73 (92.4)	3,042 (92.3)

a) Includes both hypertension and essential hypertension.
Abbreviations: EAC: event adjudication committee; FAS: full analysis set; N: number of patients; n: number of patients with events; %: proportion of patient; SD: standard deviation.

Risk of diabetic retinopathy complications by baseline retinopathy status

Among patients without pre-existing diabetic retinopathy, few had EAC-confirmed diabetic retinopathy complications (5 semaglutide-treated vs. 4 placebo-treated patients), with no evidence of a difference in time to first event with semaglutide versus placebo (Figure 39). Hence, EAC-confirmed events of diabetic retinopathy complications occurred mainly in patients with pre-existing diabetic retinopathy and hence, is consistent with what was seen in the DCCT trial as presented in the background section (Section 10.1).



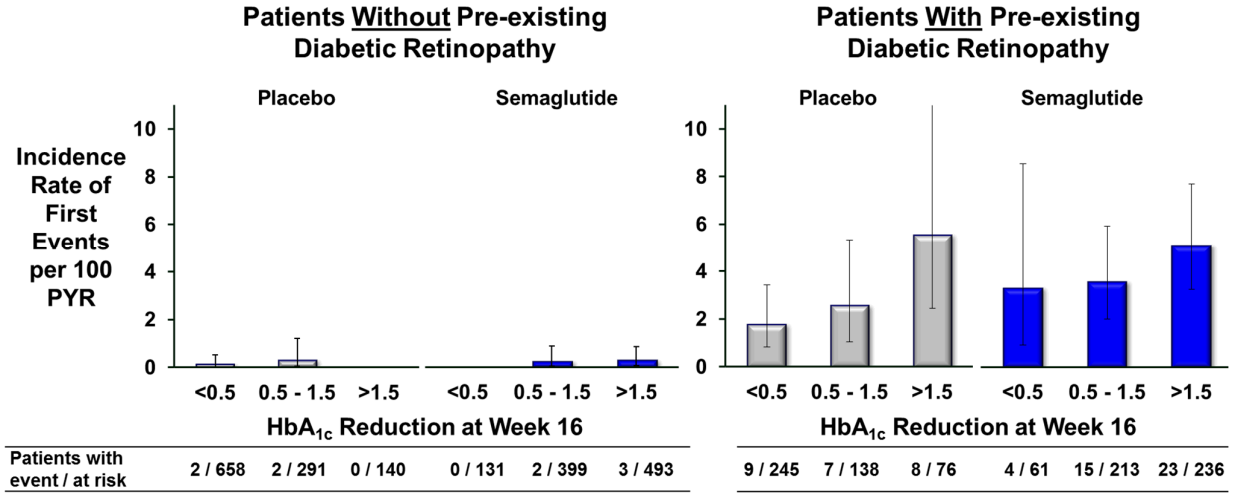
Notes: FAS in-trial. Kaplan-Meier estimates: Analysis of time from randomization to first EAC-confirmed event of diabetic retinopathy complications. Patients are censored at their planned end-of-trial visit, last direct patient-site contact or all-cause death of the patient, whichever came first.

Figure 39 SUSTAIN 6 (CVOT): Time to first EAC-confirmed events of diabetic retinopathy complication by baseline retinopathy status

Impact of early improvement in glycemic control on diabetic retinopathy

As stated in Section 10.1, long-term glycemic control can prevent or delay the progression or onset of diabetic retinopathy but initial improvements in glycemic control can be associated with a transient worsening of diabetic retinopathy. Since semaglutide treatment also results in significant improvements in glycemic control (Figure 10); this potential effect was explored further in SUSTAIN 6 (CVOT). HbA_{1c} change at week 16 was considered the best and most robust measure for the initial change in blood glucose as the full treatment effect on HbA_{1c} was attained at this time point and HbA_{1c} at week 16 is less impacted by any premature treatment discontinuation (higher with semaglutide than with placebo) than measurements at later time points. The patients were divided into 3 categories based on magnitude of the HbA_{1c} reduction at week 16 (<0.5, 0.5-1.5 and >1.5 %-points); please note that this does not fully account for the generally larger HbA_{1c} reductions with semaglutide compared to placebo. Furthermore, some of the subgroups have few patients at risk and thus very few patients with events, as reflected in the wide confidence intervals.

Despite these limitations, the analysis illustrates that in patients without diabetic retinopathy at baseline, there was a low incidence of EAC-confirmed events of diabetic retinopathy complications, regardless of the magnitude of HbA_{1c} reduction (Figure 40).



Notes: FAS in-trial. Observed incidence rates per 100 PYR are calculated as 100 times the number of patients with events divided by the total risk time. A patient's risk time is the time from randomization until the patient's first EAC confirmed event or censoring. Error bars represent 95% confidence intervals.
Abbreviations: EAC: event adjudication committee; FAS: full analysis set; PYR: patient years of risk time.

Figure 40 SUSTAIN 6 (CVOT): EAC-confirmed diabetic retinopathy complications by baseline retinopathy status and early HbA_{1c} reduction

Among patients with pre-existing diabetic retinopathy, pronounced glucose reductions appear to be associated with higher risk of worsening of diabetic retinopathy, and patients that had a reduction of >1.5% had the highest incidence rates of events both with semaglutide and placebo. This is

consistent with the hypothesis that an early and pronounced glycemic improvement can be associated with worsening of diabetic retinopathy in patients with pre-existing diabetic retinopathy seen with insulin products.

To further evaluate the potential impact of the initial decline in blood glucose levels on risk of diabetic retinopathy complications, a *post-hoc* mediation analysis was performed (Table 35). In order not to confound the analysis, parameters predictive for a reduction in HbA_{1c} and risk factors for diabetic retinopathy were included in the model.[173] Hence, the model included: treatment (semaglutide, placebo), change in HbA_{1c} (%-points) at week 16, HbA_{1c} at baseline, retinopathy at baseline (Yes, No, Unknown/missing) and baseline duration of diabetes.

When adjusting for the HbA_{1c} reduction at week 16, the effect of semaglutide versus placebo on diabetic retinopathy complications was reduced from a hazard ratio of 1.76 $[1.11; 2.78]_{95\%CI}$ to a hazard ratio of 1.22 $[0.71; 2.09]_{95\%CI}$ (Table 35). The estimated effect of change in HbA_{1c} (%-points) at week 16 was 1.26 in both treatment groups. This correspond to a significant increase in risk of 26% with each HbA_{1c} decrease of 1%-point; consistent with the observation in Figure 40. This result suggests that the overall effect of semaglutide can be explained by the initial decline in blood glucose associated with semaglutide treatment. These data are consistent with a worsening of diabetic retinopathy being associated with large initial improvement in glycemic control.

Table 35 SUSTAIN 6 (CVOT): Time to first EAC-confirmed event of diabetic retinopathy complications – *post-hoc* mediation analysis of change in HbA_{1c} at week 16

Analysis	Estimate [95% CI]	p-value	Patients with EAC-confirmed events of diabetic retinopathy complications vs. all patients	
			Semaglutide	Placebo
Pre-specified analysis				
Total effect of treatment (a)	1.76 [1.11;2.78]	0.0159	50/1,648	29/1,649
***Post-hoc* mediation analysis**				
Effect of treatment adjusted for change in HbA_{1c} (%-points) at week 16 (a)	1.22 [0.71;2.09]	0.4793	50/1,648	29/1,649
Effect of change in HbA_{1c} (%-points) at week 16 (b)	1.26 [1.03;1.57]	0.0290	-	-
Proportion eliminated	0.72	-	-	-

a) HR for semaglutide vs. placebo. **b**) HR ratio for one unit larger reduction.
Notes: Unstratified Cox proportional hazards model with treatment as a fixed factor and change in HbA_{1c} at week 16, HbA_{1c} at baseline, pre-existing retinopathy at baseline and baseline duration of diabetes. Missing values of HbA_{1c} were imputed as predicted values from a MMRM. 'Proportion eliminated' is calculated as the absolute risk reduction from the mediation analysis divided by the total excess risk.
Abbreviations: ANCOVA: Analysis of covariance; CI: Confidence interval; EAC: event adjudication committee; HR: hazard ratio mixed model for repeated measures.

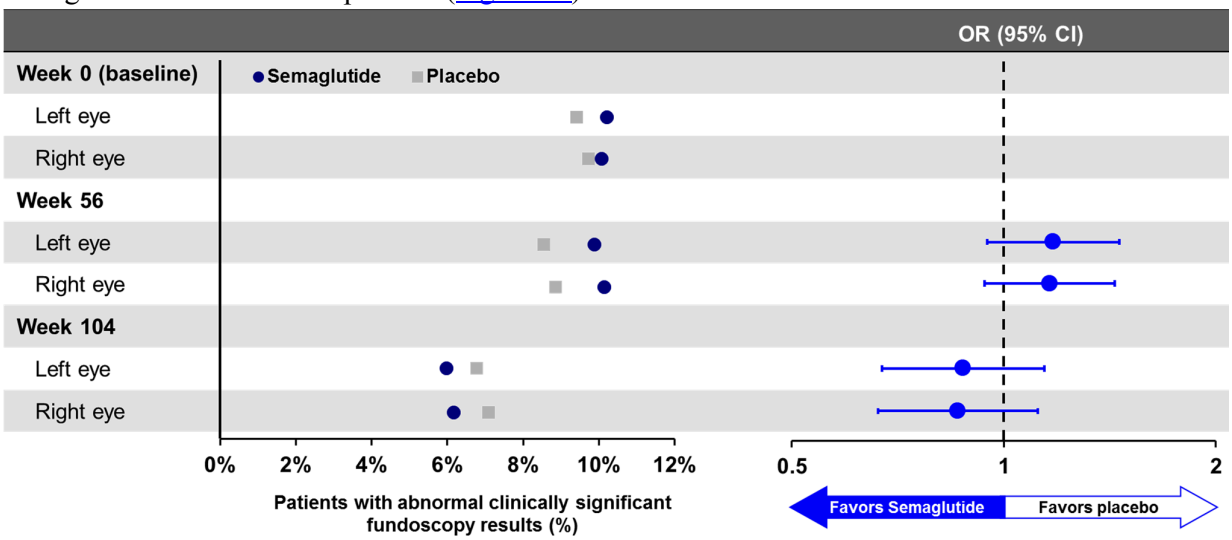
10.6 Fundoscopy or fundus photography findings

Evaluation of the results of fundoscopy (including fundus photography) must be viewed with caution due to limitations in the way the examinations were performed and the outcome evaluated, see Section 10.2. Despite these limitations of a diabetes trial versus a dedicated eye study, the data provide the best available evidence of the changes in the retina during the 2-year period of SUSTAIN 6 (CVOT) and thereby the late complications of diabetic retinopathy.

Approximately half of the patients had normal fundoscopy results at baseline. A small percentage of these patients (appr. 20%) developed abnormalities with either semaglutide or placebo. This probably represents the natural course of the diabetic retinopathy in these lower risk patients.

At baseline, 47-48% of fundoscopy results were abnormal in semaglutide-treated patients and 45% to 47% of fundoscopies in placebo-treated patients. Results from the 1- and 2-year fundoscopies in patients with abnormal baseline findings, did not indicate a detrimental effect of semaglutide compared with placebo.

A *post-hoc* logistic regression analysis was made comparing the proportion of patients with abnormal clinically significant fundoscopy findings with semaglutide versus placebo at baseline and at year 1 and year 2. In the analysis, missing data were assumed to be missing at random. Clinically significant abnormalities were present at baseline in approximately 10% of patients. At week 56, the proportion of patients with clinical significant abnormal fundoscopy findings was unchanged with semaglutide and lower with placebo (Figure 41).



Notes: FAS and in-trial. Data are analyzed based on a logistic model from which semaglutide and placebo at different time points are compared in terms of ORs. The probability of an abnormal clinical significant finding is modelled.
Abbreviations: CI: confidence interval; OR: Odds ratio.

Figure 41 SUSTAIN 6 (CVOT): *Post-hoc* analyses of change from baseline in proportion of patients with abnormal clinical significant fundoscopy findings

At week 104, the proportion of patients with abnormal clinical significant findings had decreased from baseline and was lower with semaglutide than with placebo. None of the treatment differences were statistically significant. However, the findings at week 56 could be considered consistent with an early worsening of diabetic retinopathy with semaglutide, and data from week 104 indicate long-term effects of semaglutide treatment on diabetic retinopathy similar to the effect of stringent glycemic control on diabetic retinopathy seen in the DCCT, UKPDS and ACCORD.[11, 34, 35, 38-42]

10.7 Benefit and risk evaluation in patients with pre-existing diabetic retinopathy

In order to assess if the cardiovascular safety of semaglutide was preserved for patients at risk for diabetic retinopathy complications, a *post-hoc* subgroup analysis of MACEs by pre-existing diabetic retinopathy (yes/no) was made, demonstrating cardiovascular safety both in patients with pre-existing diabetic retinopathy (HR: 0.52 [0.34; 0.80]$_{95\%CI}$) and in those without (HR: 0.77 [0.55; 1.08]$_{95\%CI}$).

Furthermore, the number of patients needed to treat (NNT) versus numbers needed to harm (NNH) showed a positive benefit-risk ratio for semaglutide also in patients with pre-existing diabetic retinopathy at baseline, with 19 patients needed to treat for 104 weeks to prevent 1 patient having a MACE, versus an increased risk of 1 additional event of EAC-confirmed diabetic retinopathy complications for every 36 patients treated for 104 weeks (Table 36). In addition, other benefits of semaglutide include efficient glycemic control, a once-weekly treatment regimen, reductions in blood pressure and weight loss, as well as a long-term reduced risk of microvascular complications, which are also important benefits in this group of patients.

Table 36 SUSTAIN 6 (CVOT): Numbers need to treat during 104 weeks of treatment

	NNT for 3-component MACE (primary endpoint)	NNH for EAC-confirmed diabetic retinopathy complication
Total population	45	77
Pre-existing retinopathy at baseline	19	36
No retinopathy at baseline	61	456

Note: 216 patients had unknown/missing status at baseline.
Abbreviations: EAC: event adjudication committee; NNH: numbers needed to harm; NNT: numbers needed to harm; MACE: major adverse cardiovascular event.

10.8 Discussion and conclusions on diabetic retinopathy

The trials in the phase 3a program were not designed for a systematic evaluation of diabetic retinopathy progression; the risk of diabetic retinopathy with semaglutide was evaluated using multiple sources of data. New or worsening diabetic retinopathy with semaglutide was recorded as adverse events across all phase 3a trials. In addition, diabetic retinopathy complications were evaluated in SUSTAIN 6 (CVOT) based on EAC-confirmed events. Importantly, this endpoint does not specifically address progression in diabetic retinopathy, and therefore may not be applicable as a safety measure unlike endpoints such as ETDRS (Early Treatment Diabetic Retinopathy Study) assessing both severity and changes over time.

There were no differences in diabetic retinopathy adverse events between semaglutide (0.5 mg: 2.1%; 1 mg: 1.5%) and comparator products (2.0 %) in the 3a pool. However, there was a difference observed in SUSTAIN 6 (CVOT) with more events reported with semaglutide (0.5 mg: 9.0%; 1 mg: 10.0%) than with placebo (7.6%). An increased risk of EAC-confirmed diabetic retinopathy complications with semaglutide versus placebo (50 vs. 29 patients with events) was also identified in SUSTAIN 6 (CVOT). In SUSTAIN 6 (CVOT), EAC-confirmed events of diabetic retinopathy complications appeared early and continued throughout the trial. Results from a *post-hoc* mediation analysis of data from SUSTAIN 6 (CVOT) are consistent with a worsening of diabetic retinopathy being associated with pronounced improvement in glycemic control and, therefore, consistent with what also has been observed with insulin products. In addition, pre-existing diabetic retinopathy, long duration of diabetes, high baseline HbA_{1c} and insulin co-use was identified as potential predictors of T2D patients at high risk for diabetic retinopathy complications.

Despite a potential risk of an initial deterioration of diabetic retinopathy following intensified glycemic control, several long-term studies have established that tight glycemic control in the longer term provides substantial reduction in the risk of development and/or progression of diabetic retinopathy.[11, 38, 43-45] These studies have also shown that it can take more than 3 years before the potential benefit is evident. The risk of development or worsening of diabetic retinopathy can be mitigated by standard-of-care eye examinations in patients with established diabetic retinopathy, followed by treatment when appropriate in accordance with existing good clinical practice.[49] Current guidelines for high risk patients, stress the importance of regular eye examinations and ophthalmology input in such patients where intensification of diabetes treatment is needed.[31] These guidelines are in place so that ophthalmologists can identify signs of 'early worsening' of the diabetic retinopathy and initiate treatment. As a result, it is recommended not to delay intensification of diabetes treatment as the long-term benefits outweigh the short-term risk. Thus, the imbalances in early worsening of diabetic retinopathy with semaglutide represents effective intensification of diabetes treatment, and patients initiating semaglutide treatment can and should be managed similar to all other patients undergoing treatment intensification, and according to local guidelines.*Post-hoc* analyses showed that the cardiovascular safety of semaglutide is preserved for patients with pre-existing diabetic retinopathy (HR: 0.52 $[0.34; 0.80]_{95\%CI}$). Furthermore, a beneficial ratio of 19 patients needed to treat with semaglutide to prevent one patient from having a MACE versus 36 patients needed to treat to observe diabetic retinopathy complications in one patient, was shown for these patients. In addition, other benefits of semaglutide include superior glycemic control, a once-weekly treatment regimen, as well as reductions in blood pressure and weight loss which are also important benefits in this group of patients.

Appropriate wording addressing the risk of diabetic retinopathy complications in high risk patients is proposed for the 'warning and precautions' section of the semaglutide product information, see Section 11. Specially, the product information will recommend caution when initiating semaglutide if the patient has diabetic retinopathy.

11 Post-marketing activities

Summary

- The post-marketing risk management program for semaglutide 0.5 mg and 1 mg will build on post-marketing programs for marketed GLP-1 RAs, and will emphasize appropriate patient selection, patient and physician education on the potential risks and further investigations on the uncertainties identified.
- Risk minimization activities proposed by Novo Nordisk include labelling.
- Semaglutide 0.5 mg and 1 mg will be incorporated into the national MTC registry that is already ongoing for all approved long-acting GLP-1 RAs in the US.

11.1 Labelling

The packaging for semaglutide 0.5 mg and 1 mg will include a physician insert along with a Medication Guide that is targeted to patients. As with other GLP-1 RAs, based on nonclinical rodent findings, semaglutide 0.5 mg and 1 mg will include a boxed warning regarding the potential risk of medullary thyroid cancer (MTC). The labeling will also include information on pancreatitis and gallbladder disorders. In keeping with other glucose lowering therapies, including insulin, the proposed label for semaglutide will include a warning on diabetic retinopathy. In addition, the labeling will include a section on 'Females of Reproductive Potential' in 'USE IN SPECIFIC POPULATIONS' which will recommend that women do not become pregnant while using semaglutide 0.5 mg and 1 mg.

11.2 Medullary Thyroid Carcinoma (MTC) registry

Semaglutide 0.5 mg and 1 mg will be incorporated into the national MTC registry that is already ongoing for all approved long-acting GLP-1 RAs in the US. The ongoing MTC registry systematically monitors the annual incidence of MTC in the US through the North American Association of Central Cancer Registries (NAACCR) to identify any possible increase related to the introduction of long-acting GLP-1 RAs into the US market.

12 Benefits and risks

Summary

- The semaglutide clinical development program was designed according to FDA guidance for T2D products and included more than 9,000 patients.
- Data from the semaglutide clinical development program demonstrate unprecedented, superior and sustained glycemic control and clinically relevant, sustained weight loss both when semaglutide was used as monotherapy in drug-naïve patients and in combination with other anti-glycemic agents in patients with T2D[1-4], including those at high cardiovascular risk.
  - Mean HbA_{1c} levels at end-of-treatment of 6.60−6.96% with semaglutide 0.5 mg and 6.46−6.81% with semaglutide 1 mg.
  - Mean reductions in HbA_{1c} of up to 1.45 %-points with semaglutide 0.5 mg and 1.85 %-points with semaglutide 1 mg.
  - An HbA_{1c} <7% was achieved for up to 74% of patients with semaglutide 0.5 mg and 79% of patients with semaglutide 1 mg.
  - Mean reductions in body weight of up to 4.28 kg (4.9%) with semaglutide 0.5 mg and 6.42 kg (7.3%) with semaglutide 1 mg.
- Cardiovascular safety of semaglutide was established in a dedicated CVOT with a hazard ratio of 0.74 $[0.58; 0.95]_{95\%CI}$).
- The overall safety profile of semaglutide was consistent with the well-established GLP-1 RA safety profile.
- In SUSTAIN 6 (CVOT), more patients experienced microvascular events of diabetic retinopathy complications with semaglutide (3.0%) than with placebo (1.8%). In keeping with other glucose lowering therapies, including insulin, the proposed label for semaglutide will include a warning on diabetic retinopathy.
- Semaglutide was efficacious and safe across subpopulations evaluated, including those with renal impairment and other T2D comorbidities. Hence, no dose adjustments are necessary.
- Evaluation of current knowledge on the benefits and potential risks of semaglutide yield a favorable benefit-risk balance for semaglutide. Thus, semaglutide would offer an additional valuable choice in the armamentarium for patients and physicians for the treatment of patients with T2D including those at high risk of cardiovascular events.

Semaglutide 0.5 mg and 1 mg as monotherapy or in combination with other anti-glycemic agents is a new treatment option for patients with T2D, including those at high risk of cardiovascular events.

Semaglutide provides superior long-term glycemic control with a low risk of hypoglycemia as compared to currently available and commonly used non-insulin antiglycemic products.[1-4] The mean HbA_{1c} levels achieved at end-of-treatment (SUSTAIN 1–5), of 6.46−6.81% with semaglutide 1 mg and 6.60−6.96% with semaglutide 0.5 mg, are clinically unprecedented in a large clinical trial program.[1-4] The reductions in HbA_{1c} achieved with semaglutide were clinically relevant with mean reductions in HbA_{1c} of 1.54−1.85 %-points with semaglutide 1 mg and 1.21−1.45 %-points with semaglutide 0.5 mg. ADA-defined treatment target of HbA_{1c} <7% was achieved for up to 74% of patients with semaglutide 0.5 mg and 79% of patients with semaglutide 1 mg.

Semaglutide also provided clinically meaningful and sustained weight loss. The magnitude of the weight loss (up to 4.28 kg [4.9%] with semaglutide 0.5 mg and 6.42 kg [7.3%] with semaglutide 1 mg) is greater than what has been previously reported with GLP-1 RAs for treatment of T2D.[1-4]

Some semaglutide-associated health benefits are immediate, such as the effects on glycemic control, weight loss and blood pressure and may encourage patients to remain on treatment and undertake enduring lifestyle changes. The benefits on glycemic control and weight loss are known to be associated with improvements in perceived physical and mental health and quality-of-life.[47, 48] In addition, semaglutide treatment has the potential to increase adherence to therapy with a simple and flexible once-weekly regimen and easy to use, pre-filled, multi-use pens. Other benefits may manifest with longer-term semaglutide treatment as direct effects or as results of improved glycemic control and weight loss. These include improvements in β-cell function, reduced insulin resistance, reduced risk of micro- and macrovascular complications, and reduced need for additional glycemic agents and agents needed to control diabetes–related comorbidities.

The semaglutide safety profile is well-documented based on data from the large nonclinical and clinical development programs. The semaglutide clinical development program was designed according to FDA guidance for T2D products and included more than 9,000 patients. The safety profile with semaglutide 0.5 mg and 1 mg was consistent with the well-known profile of GLP-1 RAs. As expected, semaglutide was associated with a higher frequency of gastrointestinal adverse events compared with placebo and active comparators. In addition, reduced appetite and weight decrease, fatigue, dizziness, dysgeusia (altered taste perception), cholelithiasis, increased serum lipase and amylase activity levels and hypoglycemia (when combined with insulin or SU) are adverse drug reactions related to semaglutide treatment. There was no indication of a dose- or exposure-response relationship for safety parameters, except for gastrointestinal side effects, which generally occurred early during dose-escalation, were of mild or moderate severity and resolved without sequelae. Adverse effects were mostly predictable based on the known effects of GLP-1 RAs, infrequent in the case of serious adverse drug reactions, easily diagnosed and monitored, and reversible upon treatment discontinuation. The cardiovascular safety of semaglutide was established in the cardiovascular outcomes trial with a hazard ratio of 0.74 $[0.58; 0.95]_{95\%CI}$).

One safety finding emerged from SUSTAIN 6 (CVOT); semaglutide treatment was associated with an increased risk of diabetic retinopathy complications in patients with pre-existing diabetic retinopathy. The available data are consistent with a worsening of diabetic retinopathy being associated with pronounced improvement in glycemic control. As seen with other glucose-lowering therapies, such as insulin therapy, a risk of worsening of diabetic retinopathy can be mitigated by routine eye examinations in patients with pre-existing diabetic retinopathy, followed by treatment when appropriate in accordance with good clinical practice and standards of care.[49] Appropriate wording addressing the risk of diabetic retinopathy complications is proposed for the 'warning and precautions' section of the product information. Importantly, the absolute risk of diabetic retinopathy was low. *Post-hoc* analyses showed that the cardiovascular safety of semaglutide is preserved for patients with pre-existing diabetic retinopathy (HR: 0.52 $[0.34; 0.80]_{95\%CI}$). Furthermore, a beneficial ratio of 19 patients needed to treat with semaglutide to prevent one patient from having a MACE versus 36 patients needed to treat to observe diabetic retinopathy complications in one patient, was shown for patients with pre-existing diabetic retinopathy. In addition, other benefits of semaglutide include superior glycemic control, a once-weekly treatment regimen, as well as reductions in blood pressure and weight loss which are also important benefits in this group of patients.

The efficacy and safety of semaglutide was established across a broad range of patients in terms of age, race, regions, duration of diabetes, level of HbA_{1c} control at baseline, and comorbidities including some of the most vulnerable patient populations such as elderly patients (≥75 years of age), patients with established cardiovascular disease, and patients with severe renal impairment. Across all subgroups and populations investigated, semaglutide provided improved glycemic control and clinically relevant weight loss with established cardiovascular safety and no differences in the safety profile thus supporting the use of semaglutide in these subpopulations without a need for dose adjustment. Specifically in patients with renal impairment across all stages, the efficacy and safety profile of semaglutide were comparable to patients with normal renal function. Many anti-diabetic medications have restrictions in their label, often precluding treatment in patients at later stages of renal dysfunction, and hence, this T2D subpopulation currently has more limited treatment options. The results from the SUSTAIN program support the use of semaglutide in patients across all stages of renal impairment without a need for dose adjustment.

Data from the clinical development program demonstrate that semaglutide is a significantly improved treatment option for patients with T2D, including those at high risk of cardiovascular events. Semaglutide allows patients to manage their disease by providing superior glycemic control and weight loss, with the potential to favorably impact their diabetes-related complications. Hence, semaglutide offers an additional valuable choice in the armamentarium for patients and physicians in treatment of patients with T2D. Based on these benefits taken together with the potential and identified risks, Novo Nordisk evaluates the benefit-risk balance for semaglutide as positive.

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Semaglutide s.c. OW

Treatment to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus

NDA 209637

Briefing Document
Appendix 1
Major design features of phase 3a trials

Endocrinologic and Metabolic Drug Advisory Committee

October 18, 2017

Advisory Committee Briefing Materials: Available for Public Release

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1 Major design features of the phase 3a trials

1.1 Tabular summary of phase 3a trials

Trial ID	Primary objective and primary endpoint	[1)] Trial population [2)] Anti-glycemic background medication	[1)] Trial product (maintenance dose(s), N) [2)] Comparator (maintenance dose(s), N) [3)] Randomization ratio and blinding	Duration of treatment[a]
SUSTAIN 1 **vs Placebo (Mono)** **(3623)**	**Primary objective**: To demonstrate superiority of OW dosing of two dose levels of semaglutide vs placebo on glycemic control after 30 weeks of treatment in drug-naïve patients with T2D **Primary endpoint**: Change from baseline to week 30 in HbA_{1c}	1) Multinational (incl. US); T2D; HbA_{1c} of 7.0−10.0%; no treatment with glucose lowering agents in 90 days prior to screening; eGFR ≥30 mL/min/1.73 m^2	1) Semaglutide (0.5 mg, 128; 1 mg, 130) 2) Placebo[b] (0.5 mg and 1 mg, 129) 3) 2:2:1:1[b], double-blind	30 weeks
SUSTAIN 2 **vs Sita (OADs)** **(3626)**	**Primary objective**: To compare the effect of OW dosing of two dose-levels of semaglutide vs sitagliptin 100 mg once-daily on glycemic control after 56 weeks of treatment **Primary endpoint**: Change from baseline to week 56 in HbA_{1c}	1) Multinational; T2D; HbA_{1c} of 7.0−10.5%; eGFR ≥60 mL/min/ 1.73 m^2 2) Stable treatment with Met, TZD or Met/TZD	1) Semaglutide (0.5 mg, 409; 1 mg, 409) 2) Sitagliptin[b] (100 mg and semaglutide placebo 0.5 mg, 203); sitagliptin (100 mg and semaglutide placebo 1 mg, 204) 3) 2:2:1:1, double-blind, double-dummy	56 weeks
SUSTAIN 3 **vs Exe ER (OADs)** **(3624)**	**Primary objective**: To compare the effect of semaglutide 1 mg OW vs exenatide ER 2 mg OW on glycemic control after 56 weeks of treatment **Primary endpoint**: Change from baseline to week 56 in HbA_{1c}	1) Multinational (incl. US); T2D; HbA_{1c} of 7.0−10.5%; eGFR ≥60 mL/min/1.73 m^2 2) Stable treatment with 1–2 OADs (Met, TZD, SU)	1) Semaglutide (1 mg, 404) 2) Exenatide ER (2 mg, 405) 3) 1:1, open-label	56 weeks
SUSTAIN 4 **vs IGlar (OADs)** **(3625)**	**Primary objective**: To compare the effect of OW dosing of two dose levels of semaglutide vs insulin glargine once-daily on glycemic control after 30 weeks of treatment in insulin-naïve patients with T2D **Primary endpoint**: Change from baseline to week 30 in HbA_{1c}	1) Multinational (incl. US); T2D; HbA_{1c} of 7.0−10.0 %; eGFR ≥30 mL/min/1.73 m^2 2) Stable treatment with Met or Met/SU, insulin naïve	1) Semaglutide (0.5 mg, 362; 1 mg, 360) 2) Insulin glargine (starting dose 10 units, 360) 3) 1:1:1, open-label	30 weeks
SUSTAIN 5 **vs Placebo (Insulin)** **(3627)**	**Primary objective**: To demonstrate superiority of OW dosing of two dose levels (0.5 mg and 1 mg) of semaglutide vs placebo on glycemic control in patients with T2D on basal insulin. **Primary endpoint**: Change from baseline to week 30 in HbA_{1c}	1) Multinational (incl. US); T2D; HbA_{1c} of 7.0−10.0%; eGFR ≥30 mL/min/1.73 m^2 2) Stable treatment with basal insulin alone or in combination with Met	1) Semaglutide (0.5 mg, 132; 1 mg, 131) 2) Placebo[b] (0.5 mg and 1 mg, 133) 3) 2:2:1:1, double-blind	30 weeks

Trial ID	Primary objective and primary endpoint	[1] Trial population [2] Anti-glycemic background medication	[1] Trial product (maintenance dose(s), N) [2] Comparator (maintenance dose(s), N) [3] Randomization ratio and blinding	Duration of treatment[a]
SUSTAIN 6 (CVOT) **vs Placebo** **(3744)**	**Primary objective**: To confirm that treatment with semaglutide does not result in an unacceptable increase in cardiovascular risk as compared to placebo in adults with T2D. This is done by demonstrating that the upper limit of the two-sided 95% confidence interval of the hazard ratio for semaglutide vs placebo is less than 1.8 when comparing time to first occurrence of a major adverse cardiovascular event (MACE). **Primary endpoint**: Time from randomization to first occurrence of a MACE, defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke	1) Multinational (incl. US); T2D; HbA_{1c} ≥7.0%; ≥50 years and clinical evidence of CVD or ≥60 years and subclinical evidence of CVD 2) Standard-of-care, e.g. non-investigational glucose lowering medications adjusted to maintain target glycemic control (avoiding other GLP-1 RAs, DPP-4 inhibitors or pramlintide)	1) Semaglutide (0.5 mg, 826; 1 mg, 822) 2) Placebo (0.5 mg, 824; 1 mg, 825) 3) 1:1:1:1, double-blind	104 weeks
SUSTAIN JP Mono **vs Sita (Mono), JP** **(4092)**	**Primary objective**: To compare the safety of OW dosing of semaglutide (0.5 and 1 mg) vs sitagliptin (100 mg) once daily, both as monotherapy during 30 weeks of treatment in Japanese patients with T2D **Primary endpoint**: Number of treatment emergent adverse events during 30 weeks of treatment	1) Japan; T2D; HbA_{1c} of 6.5−9.5% or 7.0−10.5%; eGFR ≥60 mL/min/1.73 m^2 2) On stable OAD monotherapy at a half-maximum dose or below and HbA_{1c} 6.5−9.5%, or on diet and exercise therapy and HbA_{1c} 7.0−10.5%	1) Semaglutide (0.5 mg, 103; 1 mg, 102) 2) Sitagliptin (100 mg, 103) 3) 1:1:1, open-label	30 weeks
SUSTAIN JP OADs **vs OAD (OAD), JP** **(4091)**	**Primary objective**: To compare the safety of OW dosing of semaglutide (0.5 and 1 mg) in monotherapy or in combination with one OAD (either of SU, glinide, α-GI or TZD) vs OAD therapy during 56 weeks of treatment in Japanese patients with T2D who are insufficiently controlled on diet/exercise therapy or OAD monotherapy (either of SU, glinide, α-GI or TZD) **Primary endpoint**: Number of treatment emergent adverse events during 56 weeks of treatment	1) Japan; T2D; HbA_{1c} 7.0−10.5%; eGFR ≥30 mL/min/1.73 m^2 2) Stable treatment with diet and exercise or in combination with OAD monotherapy (either of SU, glinide, α-GI or TZD) within approved Japanese labelling	1) Semaglutide (0.5 mg, 239; 1 mg, 241) 2) Additional OAD (120) 3) 2:2:1, open-label	56 weeks

Note: FAS. Placebo controlled trials: volumes equivalent to the applied semaglutide doses were used for the placebo treatment groups. [a] Due to escalation of semaglutide, the maintenance dose was reached after 4 weeks for 0.5 mg, and after 8 weeks for 1 mg. Escalation treatment and maintenance dose treatment are both included in the duration of treatment; [b] Comparator pooled in analyses to support an equal distribution across treatment groups;

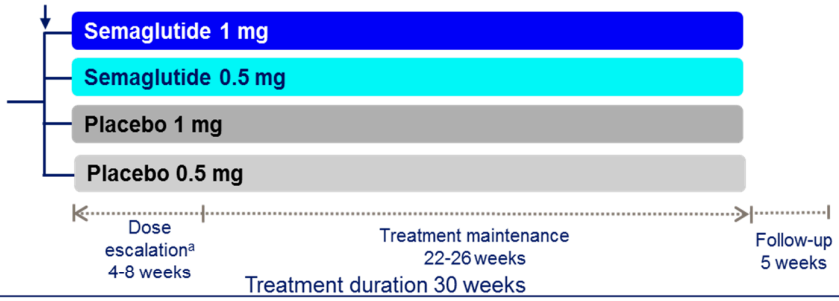
Abbreviations: α-GI: α-glucosidase inhibitor; CVD: cardiovascular disease; CVOT: cardiovascular outcomes trial; DPP-4: dipeptidyl peptidase-4; eGFR: estimated glomerular filtration rate; ER: extended release; Exe: exenatide; IGlar: Insulin glargine; JP: Japan; MACE: major adverse cardiovascular event; Met: metformin; N: number of patients randomized; OAD: oral anti-glycemic drug; OD: once-daily; OW: once-weekly; s.c.: subcutaneous; Sita_ sitagliptin; SU, sulfonylurea; T2D: type 2 diabetes; TZD: thiazolidinedione; US: United States.

1.2 Schematic overview of phase 3a trials

1.2.1 SUSTAIN 1: Trial design

388 patients with T2D

- Age ≥18 years
- HbA_{1c} 7.0–10.0 %
- No treatment with glucose lowering agents in 90 days prior to screening
- eGFR >30 mL/min/1.73 m^2



Trial information

- Double-blinded, placebo-controlled parallel-group, multi-center, multi-national, four-armed trial
- Patients from the two placebo groups are pooled in the analysis
- Conducted in Canada, Italy, Japan, Mexico, Russia, South Africa, UK, USA

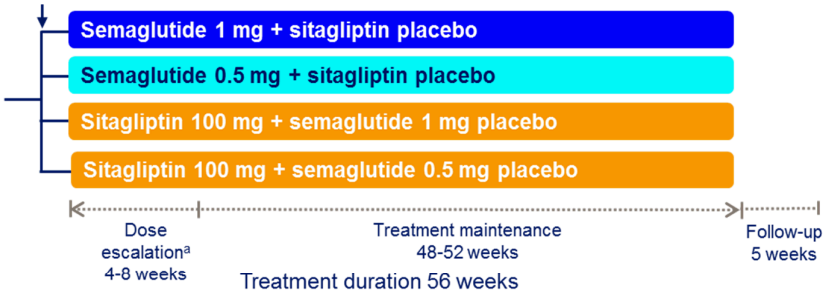
a: Dose escalation from starting dose of 0.25 mg, dose doubled each step until trial dose achieved.

www.ClinicalTrials.gov (NCT02054897). Novo Nordisk, Data on file

1.2.2 SUSTAIN 2: Trial design

1231 patients with T2D

- Age ≥18 years
- HbA_{1c} 7.0–10.5 %
- Stable treatment with metformin, TZD or metformin/TZD 90 days prior to screening



Trial information

- Double-blinded, double-dummy, active-controlled, parallel-group, multi-center, multi-national, four-armed trial
- Patients from the two active sitagliptin arms are pooled in the analysis
- Conducted in 10 countries in Europe, Argentina, Hong Kong, India, Japan, Mexico, Russia, South Africa and Thailand

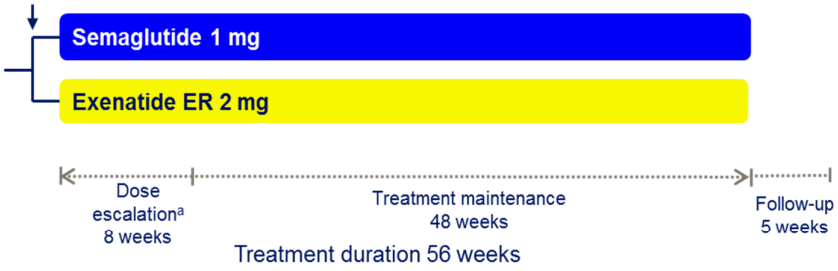
a: Dose escalation from starting dose of 0.25 mg, dose doubled each step until trial dose achieved.

www.ClinicalTrials.gov (NCT01930188). Novo Nordisk, Data on file

1.2.3 SUSTAIN 3: Trial design

813 patients with T2D

- Age ≥18 years
- Stable treatment with 1–2 OADs (Met, TZD, SU)
- HbA_{1c} 7.0–10.5 %
- eGFR > 60 ml/min/1.73 m^2



Trial information

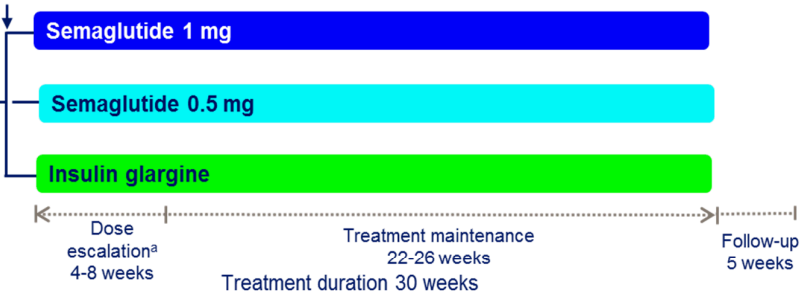
- Open-label, active-controlled parallel-group, multi-center, multi-national, two-armed trial
- Conducted at 141 sites in 12 countries in Europe, USA and South America

a: Semaglutide dose escalation from starting dose of 0.25 mg, dose doubled each step until trial dose achieved.
www.ClinicalTrials.gov (NCT01885208). Novo Nordisk, Data on file

1.2.4 SUSTAIN 4: Trial design

1089 patients with T2D

- Age ≥18 years
- HbA_{1c} 7.0–10.0 %
- Insulin-naïve patients on stable diabetes treatment with metformin or metformin and SU for at least 90 days prior to screening
- eGFR >30 ml/min/1.73 m^2



Trial information

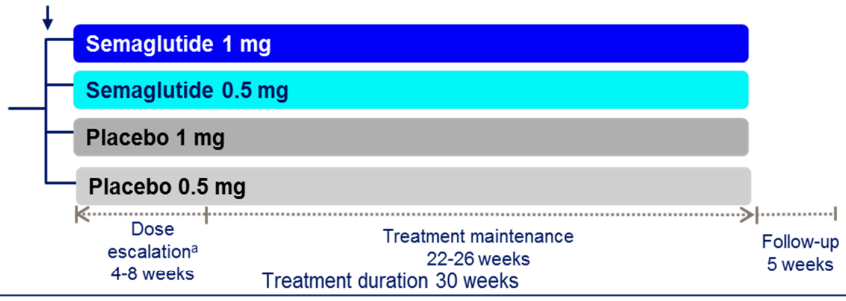
- Open-label, active-controlled parallel-group, multicentre, multi-national, three-armed trial
- Conducted in Argentina, Croatia, France, Germany, India, Macedonia, Mexico, Netherlands, Romania, Slovakia, Slovenia, South Africa, UK, USA
- Patients were stratified based on their pre-trial oral diabetes treatment (metformin or metformin and SU)

a: Semaglutide: Dose escalation from starting dose of 0.25 mg, dose doubled each step until trial dose achieved.
www.ClinicalTrials.gov (NCT02128932). Novo Nordisk, Data on file.

1.2.5 SUSTAIN 5: Trial design

397 patients with T2D

- Age ≥18 years
- HbA_{1c} 7.0–10.0 %
- Stable treatment with basal insulin alone or in combination with metformin
- eGFR >30 mL/min/1.73 m^2



Trial information

- Double-blinded, placebo-controlled parallel-group, multi-center, multi-national, four-armed trial
- Randomization was stratified according to HbA_{1c} level at screening (≤8.0% or >8.0%) and use of metformin (yes or no)
- Patients with HbA_{1c} ≤ 8.0% at screening should have the insulin dose reduced by 20% at initiation of trial product
- Conducted in Germany, Japan, Serbia, Slovakia, USA

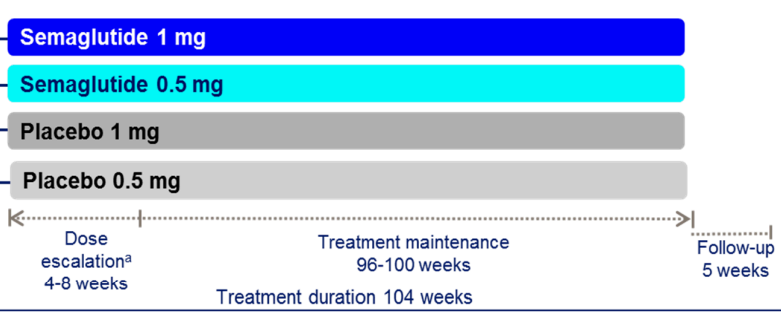
a: Dose escalation from starting dose of 0.25 mg, dose doubled each step until trial dose achieved.

www.ClinicalTrials.gov (NCT02054897). Novo Nordisk, Data on file

1.2.6 SUSTAIN 6 (CVOT): Trial design

3,297 patients with T2D

- Age ≥50 years with established CV disease or ≥60 years with evidence of CV risk factors
- Previously on 0–2 OADs, basal or pre-mix insulin ± 0–2 OADs
- HbA_{1c} ≥7.0



Trial information

- Randomisation was stratified by evidence of cardiovascular disease, insulin treatment and renal impairment
- 109 weeks of observation time and at least 122 Major Adverse Cardiovascular Events (MACE)
- No change in dose of trial product was permitted during the treatment period
- Additional glucose-lowering medication was added to achieve glycaemic control at the discretion of investigator
- Conducted in 8 countries in Europe, 5 in Asia, 3 in North America, 2 in South America, 1 in Africa and 1 in Australasia

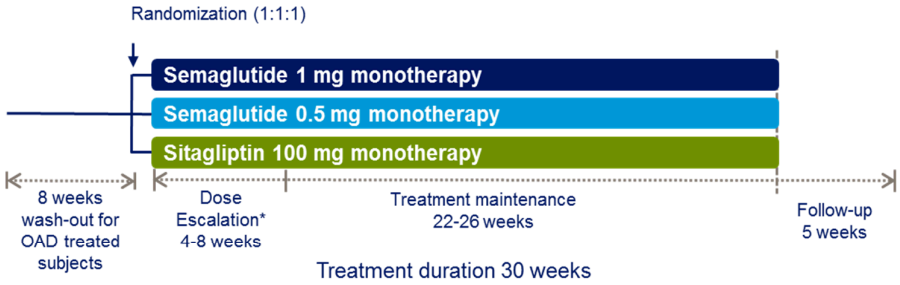
a: Dose escalation from a starting dose of 0.25 mg, dose doubled each step until trial dose achieved.

www.ClinicalTrials.gov (NCT01720446). Novo Nordisk, Data on file

1.2.7 SUSTAIN JP MONO: Trial design

308 Japanese patients with T2DM
- Age ≥ 20 years

a. On stable OAD monotherapy at a half-maximum dose or below and HbA_{1c} 6.5-9.5%
or
b. On diet and exercise therapy and HbA_{1c} 7.0-10.5%



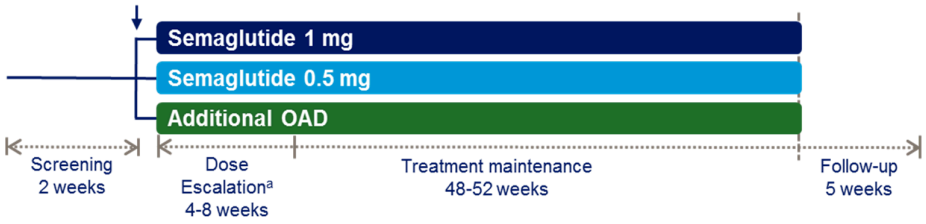
Trial information
- Open-label, active-controlled, parallel-group, multicenter, single country trial
- Patients were stratified based on their pre-trial treatment at screening (diet and exercise therapy or OAD monotherapy)

a: Dose escalation from starting dose of 0.25 mg, dose doubled each step until trial dose achieved.
www.ClinicalTrials.gov (NCT02254291). Novo Nordisk, Data on file

1.2.8 SUSTAIN JP OAD: Trial design

601 Japanese patients with T2DM
- Age ≥ 20 years
- HbA_{1c} 7.0-10.5%
- Stable treatment with

a. diet and exercise therapy
b. OAD monotherapy (either of SU, glinide, α-GI or TZD)



Trial information
- Open-label, active-controlled, parallel-group, multi-centre, single country trial
- Patients were stratified based on their pre-trial treatment (diet and exercise therapy, SU, glinide, α-GI or TZD)
- Randomised treatment was administered as add-on to the pre-trial treatment
- The type and dosage of the additional OAD (comparator arm) was selected by the Investigator

a: Dose escalation from starting dose of 0.25 mg, dose doubled each step until trial dose achieved.
www.ClinicalTrials.gov (NCT02207374). Novo Nordisk, Data on file

2 Selection criteria

2.1 Inclusion criteria in phase 3a trials

Table 1 Inclusion criteria in the phase 3a trials

		SUSTAIN						
Inclusion criteria (abbreviated form)	**1**	**2**	**3**	**4**	**5**	**6 CVOT**	**JP Mono**	**JP OAD**
HbA_{1c} in the interval 7.0−10.0 % (both inclusive)	x			x	x			
HbA_{1c} in the interval 7.0−10.5 % (both inclusive)		x	x				x[a]	x
HbA_{1c} ≥7.0%						x		
Patients with T2D; treated with diet and exercise for at least 30 days prior to screening	x							
Patients with T2D; stable treatment with Met, TZD or Met/TZD for at least 90 days prior to screening		x						
Patients with T2D; treated stable treatment with 1–2 OADs (Met, TZD and/or SU) for at least 90 days prior to screening			x					
Insulin-naïve patients with T2D; stable treatment with Met or Met/SU for at least 90 days prior to screening				x				
Patients with T2D; stable treatment with basal insulin alone or in combination with Met for at least 90 days prior to screening					x			
Anti-diabetic drug naïve, or treated with 1 or 2 OAD(s), or treated with human NPH insulin or long-acting insulin analogue or pre-mixed insulin, alone or in combination with 1 or 2 OAD(s).						x		
Japanese patients with T2D; treated with stable diet and exercise alone or in combination with OAD monotherapy for at least 30 days prior to screening							x	
Japanese patients with T2D; stable treatment with diet and exercise therapy for at least 30 days prior to screening or stable treatment with diet and exercise in combination with OAD monotherapy (either of SU, glinide, α-GI or TZD) for at least 60 days prior to screening								x
Age ≥50 years at screening and **clinical evidence of CV disease** or or Age ≥60 years at screening and **subclinical evidence of CV disease**						x		
Informed consent obtained before any trial-related activities.	x	x	x	x	x	x	x	x
Male or female; age ≥ 18 years at the time of signing informed consent. *For Japan only: Age ≥ 20 years*	x	x	x	x	x		x	x
Male or female with T2D						x		

Note: [a]HbA_{1c} in the interval 7.0−10.5% (both inclusive) for patients treated only with diet and exercise therapy at screening; HbA1c in the interval 6.5−9.5% (both inclusive) for patients treated with OAD monotherapy in combination with diet and exercise at screening..

2.2 Cardiovascular inclusion criteria in SUSTAIN 6 (CVOT)

Age ≥50 years at screening and **established cardiovascular disease** (clinical evidence of CV disease) *defined as meeting at least 1 of the below criteria (a - h).*

a) prior MI.
b) prior stroke or TIA.
c) prior coronary, carotid or peripheral arterial revascularisation.
d) >50% stenosis on angiography or imaging of coronary, carotid or lower extremity arteries.
e) history of symptomatic coronary heart disease documented by e.g. positive exercise stress test or any cardiac imaging or unstable angina with ECG changes.
f) asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or stress echo or any cardiac imaging.
g) chronic heart failure NYHA class II-III.
h) chronic renal impairment, documented (prior to screening) by eGFR <60 mL/ min/1.73 m^2 per MDRD.

or:

Age ≥60 years at screening and **presence of cardiovascular risk factors** (subclinical evidence of CV disease) *defined as meeting at least 1 of the below criteria (i - l).*

i) persistent microalbuminuria (30-299 mg/g) or proteinuria.
j) hypertension and left ventricular hypertrophy by ECG or imaging.
k) left ventricular systolic or diastolic dysfunction by imaging.
l) ankle/brachial index <0.9.

2.3 Exclusion criteria in the phase 3a trials

Table 2 Exclusion criteria in the phase 3a trials

	SUSTAIN							
Exclusion criteria (abbreviated form)	**1**	**2**	**3**	**4**	**5**	**6 CVOT**	**JP Mono**	**JP OAD**
T1D						x		
Known or suspected hypersensitivity to trial product(s)	x	x	x	x	x	x	x	x
Previous participation in this trial	x	x	x	x	x	x	x	x
Simultaneous participation in any other clinical trial of an investigational agent. Participation in a clinical trial with investigational stent(s) is allowed.						x		
Female who is pregnant, is breast-feeding, intends to become pregnant or is of child-bearing potential and not using adequate contraceptive method	x	x	x	x	x	x	x	x
Receipt of any investigational medicinal product within 90 days before screening	x	x	x	x	x		x	x
Receipt of any IMP within 30 days prior to screening (visit 1) or according to local requirements, if longer.						x		
Any chronic disorder or severe disease which may jeopardize patient's safety or compliance with the protocol	x	x	x	x	x	x	x	x
Treatment with once-weekly glucagon-like peptide-1 (GLP-1) receptor agonists within 90 days prior to screening							x	x
Use of GLP-1 RA (exenatide (twice daily or OW), liraglutide, or other) or pramlintide within 90 days prior to screening.						x		
Use of any DPP-4 inhibitor within 30 days prior to screening.						x		
Treatment with any glucose lowering agent(s), other than stated in the inclusion criteria, in a period of 90 days prior to screening	x	x	x	x	x		x	x
Treatment with insulin other than basal and pre-mixed insulin, within 90 days prior to screening - except for short-term use in connection with intercurrent illness.						x		

	SUSTAIN							
Exclusion criteria (abbreviated form)	**1**	**2**	**3**	**4**	**5**	**6 CVOT**	**JP Mono**	**JP OAD**
Experienced more than 3 episodes of severe hypoglycemia within 6 months prior to screening, and/or hypoglycemia unawareness				x	x			
Acute decompensation of glycemic control requiring immediate intensification of treatment to prevent acute complications of diabetes within 90 days prior to screening.						x		
Known use of non-prescribed narcotics or illicit drugs.						x		
History of chronic or idiopathic acute pancreatitis	x	x	x	x	x	x	x	x
Screening calcitonin value ≥ 50 ng/L (pg/mL)	x	x	x	x	x	x	x	x
Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2	x	x	x	x	x	x	x	x
Personal history of non-familial medullary thyroid carcinoma						x		
Impaired renal function	x[a]	x[b]	x[b]	x[a]	x[a]		x[b]	x[a]
End stage liver disease						x		
A prior solid organ transplant or awaiting solid organ transplant.						x		
Acute coronary or cerebrovascular event within 90 days before randomization	x	x	x	x	x	x	x	x
Currently planned coronary, carotid or peripheral artery revascularization.						x		
Heart failure, New York Heart Association class IV	x	x	x	x	x	x	x	x
Known proliferative retinopathy or maculopathy requiring acute treatment	x	x	x	x	x		x	x
Chronic hemodialysis or chronic peritoneal dialysis						x		
Diagnosis of malignant neoplasm in the previous 5 years	x	x	x	x	x	x[c]	x	x
Mental inability, unwillingness or language barrier precluding adequate understanding of or compliance with study procedures	x	x	x	x	x	x	x	x

Note: [a]eGFR <30 mL/min/1.73 m^2. [b]eGFR <60 mL/min/1.73 m^2.[c] except basal cell skin cancer or squamous cell skin cancer.

Semaglutide s.c. OW

Treatment to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus

NDA 209637

Briefing Document
Appendix 2
Definitions and classifications of events sent for EAC evaluation

Endocrinologic and Metabolic Drug Advisory Committee

October 18, 2017

Advisory Committee Briefing Materials: Available for Public Release

Table of contents

Page

1 Adjudication process

1.1 Purpose

An external independent event adjudication committee (EAC) was established to perform ongoing blinded validation of selected adverse events according to pre-defined diagnostic criteria. The same committee was used in all semaglutide phase 3a trials. The adjudication made by the EAC, given its independence and in-depth analysis of each event with use of uniform diagnostic criteria across countries, was ascribed a greater importance than the assessment made by the investigator and in areas where adjudication was performed it was used as the main source of information for analyses and presentations of safety data. Results from the adjudication process were supplemented by the results of the MedDRA search(es) among investigator reported events.

The adjudication process was managed by an external, independent vendor (Quintiles Limited) who managed and compiled information including source documents from the clinical trial sites for relevant events and forwarded this to the EAC in a blinded manner.

1.2 EAC committee

The EAC worked in accordance with written guidelines in an EAC charter, which outlined the criteria and definitions to be used for adjudication (see Section 2). The charter described the composition, tasks, responsibilities and work processes of the committee. The charter was finalized prior to adjudication of the first event. The various definitions in the charter are based on consensus guidelines and FDA guidance. The role of the EAC was solely to adjudicate events in a blinded manner. The EAC did not have any authorization to impact the trial conduct, trial protocol or protocol amendments. The results of the adjudication were entered into the clinical trial database and are presented in this summary.

The EAC comprised of 18 primary adjudicators covering relevant medical specialties, overseen by the EAC chairman. The EAC members had to disclose any potential conflicts of interest and were independent of Novo Nordisk:

- Cardiology (4 members including the EAC chairman)
- Endocrinology (1 member)
- Gastroenterology (2 members)
- Nephrology (3 members)
- Neurology (3 members)
- Oncology (3 members)
- Ophthalmology (2 members)

The type of adverse events that were adjudicated in the phase 3a trials and the specialty of the assigned adjudicators from the EAC are summarized in Table 1.

1.3 Adjudication process

Event adjudication by the EAC was completed based on a review of source information collected from the sites. The source data were blinded to treatment assignment and anonymized of personal identifiers. The EAC reviewed translated copies in English of medical documentation received in the adjudication packages (e.g., imaging reports, discharge summaries, pathology reports and death certificates). The investigator was to provide these documents as soon as possible upon receiving a request from Novo Nordisk or Quintiles Limited. The types of adverse events that were adjudicated in the phase 3a trials are summarized in Table 1.

Table 1 Phase 3a trials: Adjudicated adverse events

Adjudicated events	Specialty of assigned adjudicator
Fatal events • Cardiovascular death • Non-cardiovascular death • Undetermined cause of death	Cardiologist/neurologist[a]
Acute coronary syndrome • Myocardial infarction (MI), i.e., spontaneous MI, percutaneous coronary intervention related MI, coronary artery bypass graft surgery related MI and silent MI. • Unstable angina pectoris (UAP) requiring hospitalization	Cardiologist[b]
Cerebrovascular event • Stroke • Transient ischemic attack (TIA)	Neurologist
Coronary revascularization procedure	Cardiologist
Heart failure requiring hospital admission	Cardiologist
New or worsening of nephropathy (SUSTAIN 6 [CVOT])	Nephrologists
Diabetic retinopathy complications (SUSTAIN 6 [CVOT])	Ophthalmologists
Neoplasm (excluding thyroid neoplasm) • Malignant neoplasm • *In situ* neoplasm • Benign neoplasm • Neoplasms of uncertain or unknown behavior	Oncologist
Thyroid neoplasm or events resulting in thyroidectomy	Endocrinologist and oncologist[c]
Pancreatitis or clinical symptoms leading to suspicion of pancreatitis • Acute pancreatitis • Chronic pancreatitis	Gastroenterologist

Notes: a: Fatal events were submitted to 2 neurologist if likely related to a neurological event and to 2 cardiologists for all other events.
b: Silent myocardial infarctions (not reported by sites but identified via ECG screening) were submitted directly to full committee and reviewed by 3 cardiologists including the chair to achieve consensus adjudication.
c: Thyroid neoplasm/disease events were submitted to one endocrinologist and one oncologist.

Events to be adjudicated could be identified via one or more of the five following paths:

1. Investigator: The investigator identified the event as relevant for adjudication based on pre-defined criteria (Table 1). The event was sent to Quintiles Limited, who forwarded the event together with relevant source documentation (all anonymized and blinded) to the EAC, whose members performed an independent blinded adjudication and classification of the events based on the collected information.
2. Adverse event search: Pre-defined MedDRA searches, referred to as 'AE' searches, (based on relevant terms from standardized MedDRA queries [SMQs], high level group terms [HLGTs], high level terms [HLTs] and relevant PTs) on all reported adverse events to identify potential events for adjudication. If identified events had not already been sent for adjudication, the event was sent to the EAC chair or delegate, who pre-evaluated the identified events in an objective and independent manner and provided a rationale for why a particular event should/should not proceed for adjudication. If the event was deemed relevant for adjudication, the investigator was asked to submit relevant source documentation for the reported event. The event was forwarded to the EAC for adjudication (together with source documentation).
3. Events identified by the EAC during review of source data for another event sent for adjudication. The Novo Nordisk Event Adjudication Group notified the investigator of the finding and he/she decided whether or not to report the identified event as a new event. If the investigator decided not to report the event as an adverse event, the event was forwarded to the EAC.
4. Silent myocardial infarction (MI): all scheduled ECGs were evaluated by a group of external Central ECG readers (Quintiles Cardiac Safety Services) for evidence of new silent MI as compared to the previous ECG. If the central ECG reader identified signs of new MI (presence of a new-q-wave which met electrocardiographic criteria of prior MI),[43] these cases were identified in the web portal by Quintiles Limited and forwarded to the EAC for adjudication together with relevant source documentation. Silent MI events (not reported by sites) were submitted directly to full committee and reviewed by 3 cardiologists including the EAC chair to achieve consensus adjudication.
5. Laboratory nephropathy events: Out-of-range laboratory values from the central laboratory (alerts based on pre-defined algorithms for serum creatinine and creatinine clearance per MDRD or urinary albumin/creatinine ratio) (SUSTAIN 6 [CVOT] only). These were sent to the EAC for confirmation of nephropathy without collection of additional source documentation.

EAC procedures for evaluation of events sent for adjudication

Each event was initially sent to two adjudicators of the appropriate specialty(s). These two adjudicators performed an independent review using the pre-specified definitions and guidelines provided in the EAC charter (see Section 2). If the two reviewers were in agreement, the event was submitted to the EAC chair for signature. In case adjudicators disagreed on pre-specified important outcomes, the two primary adjudicators were allowed to discuss the case based on a review of each other's evaluation documents with the possibility to update their own evaluation. If an agreement

(consensus) could not be reached, the event was sent for second consensus meeting including a minimum of two reviewers of the appropriate medical specialty and the chair, or his designee in case he acts as a primary reviewer.

2 EAC evaluation definitions and classifications of events

During the EAC evaluation, the assigned adjudicators performed the adjudication based on the definitions and classifications predefined in an appendix to the adjudication charter. Events were to be adjudicated on the basis of strict application of the event definition in Table 2 based on the FDA Draft Definitions for Testing November 9, 2012 'Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials. The clinical likelihood that a suspected event has occurred was individually assessed in the absence of fulfilment of all of the criteria specified in the table, recognizing that information may at times be difficult to interpret due to missing or incomplete data.

Table 2 Phase 3a trials: EAC event definitions and classifications

Event	Definition
Acute Coronary Syndrome	Acute Coronary Syndrome (ACS) conditions include unstable angina pectoris (UAP) requiring hospitalization, non-ST elevation myocardial infarction (MI) (NSTEMI) and ST elevation MI (STEMI).
Acute Myocardial Infarction	**General Considerations** The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. In general, the diagnosis of MI requires the combination of: Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); and Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available. **Criteria for Myocardial Infarction** *a. Clinical Presentation* The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, congestive heart failure, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney

Event	Definition
	disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process. *b. Biomarker Elevations* For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL the laboratory uses to diagnose myocardial infarction (decision limit) should be used. In general, troponins are preferred and take precedence over CKMB when both biomarkers are available. CK-MB should be used if troponins are not available, and total CK may be used in the absence of CK-MB and troponin. Since the prognostic significance of different types of myocardial infarctions (e.g., periprocedural myocardial infarction versus spontaneous myocardial infarction) may be different, all MI events will be categorized by subtype as outlined in the third Universal Definition for Myocardial Infarction (ESC/ACCF/AHA/WHF Expert Consensus Document: Third Universal Definition of Myocardial Infarction. K Thygesen, J S. Alpert, A S. Jaffe, M L. Simoons, B R. Chaitman, H D. White Circulation. 2012;August 24 2012.) c. *Electrocardiogram (ECG) Changes* Electrocardiographic changes can be used to support or confirm a MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves. ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)): o ST elevation New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women. o ST depression and T-wave changes New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or new T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio > 1. The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings. • Criteria for pathological Q-wave o Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3 o Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, and aVF)a. When considering the lateral leads, lead V6, I, and aVL are considered contiguous leads. A The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

Event	Definition
	ECG changes associated with prior myocardial infarction o Pathological Q-waves, as defined above o R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive Twave in the absence of a conduction defect • Criteria for prior myocardial infarction Any one of the following criteria meets the diagnosis for prior MI: o Pathological Q waves (as described above) with or without symptoms in the absence of non-ischemic causes o Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause o Pathological findings of a prior myocardial infarction Under these conditions, any one of the following criteria meets the diagnosis for AMI: Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque fissuring or rupturing. Type 2: MI secondary to ischemia due to imbalance between oxygen demand and supplies, e.g. coronary spasm. Type 3: Sudden cardiac death with symptoms of myocardial ischemia, accompanied by new ST elevation or LBBB, or verified coronary thrombus by angiography, but death occurring before blood samples could be obtained. Type 4a: MI associated with PCI; Type 4b: stent thrombosis documented by angiography or autopsy Type 4c: thrombosis not documented but restenosis is found by angiography or autopsy with no other obvious cause that explains the MI event. Type 5: MI associated with CABG. Criteria for STEMI: New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women. Criteria for NSTEMI: Absence of ECG criteria for STEMI. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.
Unstable Angina Pectoris requiring hospitalization	Unstable angina requiring hospitalization is defined as 1. Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥ 10 minutes in duration occurring at rest, or in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity. AND 2. Prompting an unscheduled hospitalization within 24 hours of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 hour stay (or a change in calendar date if the hospital admission or discharge times are not available). AND 3. At least one of the following: a. New or worsening ST or T wave changes on resting ECG (in the absence of

Event	Definition
	confounders, such as LBBB or LVH) Transient ST elevation (duration < 20 minutes) New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women. ST depression and T-wave changes New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or new T inversion ≥ 0.3 mV in two contiguous leads with prominent R wave or R/S ratio > 1. b. Definite evidence of inducible myocardial ischemia as demonstrated by: - an early positive exercise stress test, defined as ST elevation or ≥ 2 mm ST depression prior to 5 mets □OR - stress echocardiography (reversible wall motion abnormality) OR - myocardial scintigraphy (reversible perfusion defect), OR - MRI (myocardial perfusion deficit under pharmacologic stress). - AND believed to be responsible for the myocardial ischemic symptoms/signs. c. Angiographic evidence of new or worse ≥ 70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs. d. Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge. AND 4. Negative cardiac biomarkers and no evidence of acute MI General Considerations 1. Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of β-blockers, should be considered supportive but not diagnostic of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under category 3, would be insufficient to support classification as hospitalization for unstable angina. 2. If subjects are admitted with suspected unstable angina, and subsequent testing reveals a non-cardiac or non-ischemic etiology, this event should not be recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for myocardial infarction should not be adjudicated as unstable angina. 3. Planned hospitalization or rehospitalization for performance of an elective revascularization in patients who do not fulfill the criteria for unstable angina should not be considered a hospitalization for unstable angina. For example, Hospitalization of a patient with stable exertional angina for coronary angiography and PCI that is prompted by a positive outpatient stress test should not be considered hospitalization for unstable angina. Re-hospitalization of a patient meeting the criteria for unstable angina who was stabilized, discharged, and subsequently readmitted for revascularization, does not

Event	Definition
	constitute a second hospitalization for unstable angina 4. A patient who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for unstable angina endpoint.
Heart Failure Requiring Hospitalization	A Heart Failure Event includes hospitalization for heart failure. A Heart Failure Hospitalization is defined as an event that meets ALL of the following criteria: 1) The patient is admitted to the hospital with a primary diagnosis of HF 2) The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable) 3) The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following: a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea) b. Decreased exercise tolerance c. Fatigue d. Other symptoms of worsened end-organ perfusion or volume overload (must be specified and described by the protocol) 4) The patient has objective evidence of new or worsening HF, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion), including: a. Physical examination findings considered to be due to heart failure, including new or worsened: i. Peripheral edema ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease) iii. Pulmonary rales/crackles/crepitations iv. Increased jugular venous pressure and/or hepatojugular reflux v. S3 gallop vi. Clinically significant or rapid weight gain thought to be related to fluid retention b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including: i. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline. ii. Radiological evidence of pulmonary congestion iii. Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TVI)) OR

Event	Definition
	iv. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m2 Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events. 5) The patient receives initiation or intensification of treatment specifically for HF, including at least ONE of the following: a. Augmentation in oral diuretic therapy b. Intravenous diuretic, inotrope, or vasodilator therapy c. Mechanical or surgical intervention, including: i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device) ii. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)
Cerebrovascular Events (Stroke and TIA)	Introduction These definitions of Transient Ischemic Attack and Stroke apply to a wide range of clinical trials. They are general, overarching, and widely applicable definitions combined with a specific clinical measurement of disability. They are flexible in their application and consistent with contemporary understanding of the pathophysiology of stroke. This approach enables clinical trials to assess the clinically relevant consequences of vascular brain injury for determining the safety or effectiveness of an intervention. The distinction between a Transient Ischemic Attack and an Ischemic Stroke is the presence of infarction. Persistence of symptoms is an acceptable indicator of acute infarction. In trials involving patients with stroke, evidence of vascular central nervous system injury without recognized neurological dysfunction may be observed. Examples include microhemorrhage, silent infarction, and silent hemorrhage. When encountered, the clinical relevance of these findings may be unclear. If appropriate for a given clinical trial, however, they should be precisely defined and categorized. Subdural hematomas are intracranial hemorrhagic events and not strokes. Transient Ischemic Attack Transient ischemic attack (TIA) is defined as a transient episode of focal neurological dysfunction < 24 hours in duration, caused by brain, spinal cord, or retinal ischemia, without imaging evidence of acute infarction Stroke Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Classification: A. Ischemic Stroke Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is

Event	Definition
	an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke. B. Hemorrhagic Stroke Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. C. Undetermined Stroke Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as A or B.
Fatal Events	**Definition of Cardiovascular Death** Cardiovascular death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes. The following definitions will be used. Death due to Acute Myocardial Infarction refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days1 after a MI related to the immediate consequences of the MI, such as progressive heart failure or recalcitrant arrhythmia. We note that there may be assessable mechanisms of cardiovascular death during this time period, but for simplicity, if the cardiovascular death occurs ≤ 30 days of the myocardial infarction, it will be considered a death due to myocardial infarction. Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)), or to treat a complication resulting from MI, should also be considered death due to acute MI. Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure. The 30 day cut-off is arbitrary. For example, If a patient that has a complicated MI requiring intubation and is supported though 30 days but dies shortly thereafter without an intervening symptom free interval, the death should be attributed to the myocardial infarction. Sudden Cardiac Death refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths: a. Death witnessed and occurring without new or worsening symptoms b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review) d. Death after unsuccessful resuscitation from cardiac arrest

Event	Definition
	e. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology f. Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available) General Considerations o Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a patient is seen alive ≤ 24 hours of being found dead, sudden cardiac death (criterion 2f) should be recorded. For patients who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (e.g., a subject found dead in bed, but who had not been seen by family for several days). Death due to Heart Failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF etiology. Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease. Death due to Stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke. Death due to Cardiovascular Procedures refers to death caused by the immediate complications of a cardiac procedure. Death due to Cardiovascular Hemorrhage refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade. Death due to Other Cardiovascular Causes refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease). **Definition of Non-Cardiovascular Death** Non-cardiovascular death is defined as any death with a specific cause that is not thought to be cardiovascular in nature. Detailed recommendations on the classification of non-CV causes of death are beyond the scope of this document. Non-CV causes of death: Pulmonary Renal Gastrointestinal Hepatobiliary Pancreatic Infection (includes sepsis) Non-infectious (e.g., systemic inflammatory response syndrome (SIRS)) Hemorrhage that is neither cardiovascular bleeding or a stroke (see Non-CV procedure or surgery

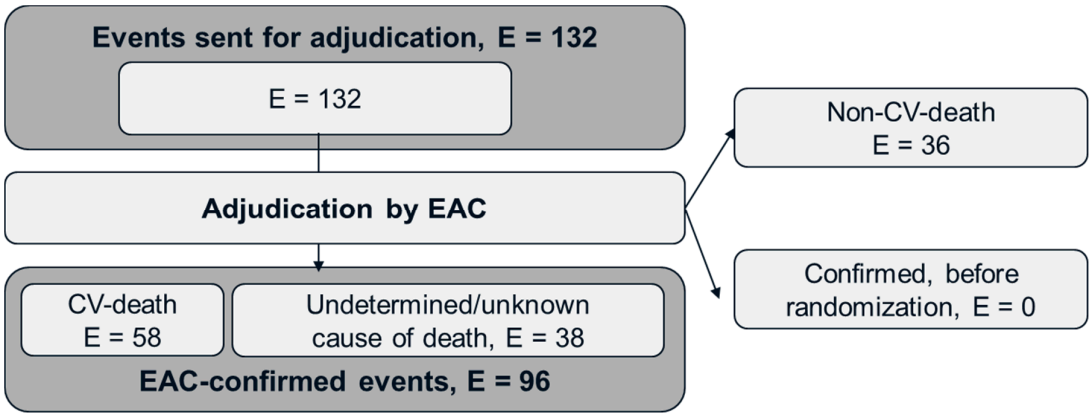
Event	Definition
	Trauma Suicide Non-prescription drug reaction or overdose Prescription drug reaction or overdose Neurological (non-cardiovascular) Malignancy Other non-CV, specify: _____ The definitions of classifications for CV and non-CV death are as follows: Documented—There is documented evidence for classification Probable/Possible —There is good reason and sufficient documentation. Conceivable and cannot be dismissed **Definition of Undetermined Cause of Death** Undetermined Cause of Death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, most deaths should be classifiable as CV or non-CV, and the use of this category of death, therefore, should be used sparingly unless there is absolutely no information that allows the adjudicator to determine causality. All deaths attributed to the category "Undetermined Cause of death" are presumed cardiovascular deaths and as such will be part of the cardiovascular death endpoint.
Pancreatitis or clinical suspicion of pancreatitis	Pancreatitis is an inflammatory process of the pancreas. Two of following diagnostic criteria fulfilling the diagnosis of acute pancreatitis: i. gradual or sudden severe pain in the central part of the abdomen that moves around to the back ii. elevated blood levels of pancreatic enzymes (lipase, amylase) > 3xUNR iii. characteristic imaging finding (ultrasound, CT, MRI) Events of acute pancreatitis will be further classified according to degree of severity based on revised Atlanta criteria. Mild acute pancreatitis (no organ failure and no local or systemic complications) Moderately severe acute pancreatitis (organ failure that resolves within 48 h (transient organ failure) and/or local or systemic complications without persistent organ failure) Severe acute pancreatitis (persistent organ failure (>48 h) (single/multiple organs)) Reference: Banks PA, et al. "Classification of acute pancreatitis -2012: revision of the Atlanta classification and definitions by international consensus" Gut 2013;62:102-111 Chronic pancreatitis will be defined by characteristic imaging finding (ultrasound, CT, MRI) with abnormal pancreatic function tests or characteristic histological findings.
Neoplasm (malignant and benign) (excluding thyroid neoplasm)	Neoplasm is defined as an abnormal growth of tissue. All neoplasms will be captured. Neoplasms will be classified according to the tissue of origin, the organ system and to the malignancy status: Benign Malignant

Event	Definition
	Pre malignant/Carcinoma in situ/borderline Unclassified
Nephropathy	New or worsening nephropathy defined as a new onset of persistent macroalbuminuria, or persistent doubling of serum creatinine level and creatinine clearance per MDRD <45 mL/min/1.73m2, or the need for continuous renal replacement therapy (in the absence of an acute reversible cause) or death due to renal disease. Macroalbuminuria is defined either as a 24-hour urine collection above 300 mg, or as an elevated ratio in a spot sample above 300 mg albumin / g creatinine. To confirm persistent macroalbuminuria or persistent doubling of serum creatinine, a confirmatory measurement should be performed within 12 weeks.
Diabetic retinopathy	Diabetic retinopathy defined as need for retinal photocoagulation or treatment with intravitreal agents or vitreous hemorrhage or diabetes-related-blindness (defined as Snellen visual acuity of 20/200 [6/60] or less or visual field of less than 20 degrees, in the better eye with best correction possible).
Thyroid Disease (if thyroid neoplasm or resulting in thyroidectomy)	All thyroid diseases requiring thyroidectomy, including partial thyroidectomy (e.g. lobectomy, partial lobectomy) will be adjudicated. All thyroid neoplasms will be adjudicated. Medullary carcinoma of the thyroid (MTC) is defined as a distinct thyroid carcinoma that originates in the calcitonin producing parafollicular C cells of the thyroid gland. According to the pathology report, thyroid neoplasms deriving from the C cells will be classified as C-cell hyperplasia, medullary microcarcinoma (carcinoma in situ) and medullary carcinoma.
Coronary Revascularization Procedure	A coronary revascularization procedure is a percutaneous coronary intervention (PCI) or an open surgical procedure designed to improve myocardial blood flow. Percutaneous Coronary Intervention (PCI): Placement of an angioplasty guide wire, balloon, or other device (e.g., stent, atherectomy catheter, brachytherapy delivery device, or thrombectomy catheter) into a native coronary artery or coronary artery bypass graft for the purpose of mechanical coronary revascularization. In the assessment of the severity of coronary lesions with the use of intravascular ultrasound, CFR, or FFR, insertion of a guide wire will NOT be considered PCI.

3 Results of adjudication of deaths and cardiovascular events in SUSTAIN 6 (CVOT)

3.1 Adjudication flow of deaths

The event adjudication process flow for deaths is shown in Figure 1. A total of 132 patients died during the period from randomization to data-base lock (DBL). Of these, a total of 122 patients (3.7%) died during the 2-year in-trial period (Table 3), as based on EAC date of death.



Abbreviations: CV: cardiovascular; E: number of events; EAC: event adjudication committee.

Figure 1 SUSTAIN 6 (CVOT): Event adjudication flow for deaths

Table 3 SUSTAIN 6 (CVOT): EAC-categorization of all-cause death

	Semaglutide 0.5 mg			Semaglutide 1 mg			Placebo		
	N	(%)	R	N	(%)	R	N	(%)	R
Number of patients	826			822			1,649		
Patient years of observation	1,708.4			1,699.8			3,401.1		
All deaths	30	(3.6)	1.8	32	(3.9)	1.9	60	(3.6)	1.8
Cardiovascular death	21	(2.5)	1.2	23	(2.8)	1.4	46	(2.8)	1.4
Non-cardiovascular death	9	(1.1)	0.5	9	(1.1)	0.5	14	(0.8)	0.4

Note: FAS in-trial. Deaths categorized by the EAC as CV deaths included deaths due to undetermined causes.
Abbreviations: N: number of patients; PYO: patient-years of observation; R: rate of events per 100 PYO; %: percentage of patients with event.

Cardiovascular deaths

Of the total of 96 deaths in SUSTAIN 6 (CVOT) categorized as cardiovascular deaths (Figure 1), 90 were determined by the EAC to occur during the in-trial period (Table 4), with the remaining 6 deaths occurring after the in-trial period until DBL. Deaths categorized by the EAC as CV deaths included deaths due to undetermined causes. The most frequent known cause of CV death was sudden cardiac death and death due to acute myocardial infarction (Table 4).

Table 4 SUSTAIN 6 (CVOT): EAC-confirmed cardiovascular death

	Semaglutide 0.5 mg			Semaglutide 1 mg			Placebo		
	N	(%)	R	N	(%)	R	N	(%)	R
Number of patients	826			822			1,649		
Patient years of observation	1,708.4			1,699.8			3,401.1		
All-cause deaths	30	(3.6)	1.8	32	(3.9)	1.9	60	(3.6)	1.8
Cardiovascular death	21	(2.5)	1.2	23	(2.8)	1.4	46	(2.8)	1.4
Sudden cardiac death	9	(1.1)	0.5	6	(0.7)	0.4	12	(0.7)	0.4
Death due to acute MI	5	(0.6)	0.3	4	(0.5)	0.2	4	(0.2)	0.1
Death due to heart failure	2	(0.2)	0.1	2	(0.2)	0.1	5	(0.3)	0.1
Death due to stroke	1	(0.1)	0.1	2	(0.2)	0.1	2	(0.1)	0.1
Other CV causes	0	(0.0)		0	(0.0)		3	(0.2)	0.1
Death, undetermined cause	4	(0.5)	0.2	9	(1.1)	0.5	20	(1.2)	0.6

Note: FAS in-trial. **Abbreviations**: MI: myocardial infarction; N: Number of patients with at least one event, PYO; patient-years of exposure; R: rate of event per 100 PYO; sema: semaglutide; %: percentage of patients with events.

Undetermined cause of death (EAC determination)

A total of 33 deaths occurring during the in-trial period of SUSTAIN 6 (CVOT) (13 with semaglutide and 20 with placebo) had an undetermined cause of death as evaluated by the EAC (Table 4). In addition, 5 deaths occurring after the in-trial period until data-base lock (DBL, 2 with semaglutide and 3 with placebo) had an undetermined cause of death as evaluated by the EAC. Details regarding patients with undetermined cause of death are provided in Table 5. For death classified by the EAC as 'undetermined cause of death', the investigator-reported term pertaining to the adverse event with fatal outcome indicated a cardiovascular cause in the majority of cases. In the analyses of composite cardiovascular endpoints, deaths with undetermined cause are considered cardiovascular deaths.

Table 5 SUSTAIN 6 (CVOT): Patients with undetermined cause of death as adjudicated by EAC

Age/Sex/BMI	EAC day of death	On-treatment/ After in-trial	Preferred term for adverse events with fatal outcome	Reported term for adverse events with fatal outcome
Semaglutide 0.5 mg				
66/M/39.1	576	Y/N	Pulmonary edema	Pulmonary edema
58/F/54.6	226	N/N	Hypoxic-ischemic encephalopathy	Cause of death anoxic encephalopathy
63/F/42.7	751	Y/N	Cardio-respiratory arrest	Cardiopulmonary arrest
72/M/37.9	34	Y/N	Pneumonia; Respiratory failure; Sepsis	Bilateral pneumonia; Respiratory failure, Sepsis
Semaglutide 1 mg				
71/M/21.1	528	N/N	Myocardial ischemia; Pulmonary valve stenosis; Chronic obstructive pulmonary disease	Ischemic heart disease, Pulmonary stenosis; Chronic obstructive airway disease (end-stage)
61/F/24.8	509	Y/N	Death	Death
71/F/38.1	750	Y/N	Death	Death

Age/Sex/BMI	EAC day of death	On-treatment/ After in-trial	Preferred term for adverse events with fatal outcome	Reported term for adverse events with fatal outcome
65/M/31.7	290	Y/N	Ischemic stroke	Repeated ischemic stroke
79/M/35.1	577	N/N	Renal cell carcinoma	Renal cell carcinoma
69/M/28.0	774	N/N	Cerebral infarction	Cerebral infarction
68/M/29.3	291	N/N	Subdural hemorrhage; Cardiac failure congestive	Subdural hematoma; Worsening congestive heart failure
76/F/45.7	832	N/Y	Hemorrhagic stroke	Hemorrhagic stroke
62/M/38.5	687	Y/N	Cardiac arrest	Cardiac arrest
62/M/29.2	507	N/N	Arrhythmia	Fatal cardiac arrhythmia
70/M/31.2	522	N/Y	Death	Death- cause unknown
Placebo				
77/M/29.0	751	N/N	Cardiac failure acute	Acute heart failure
77/M/35.8	96	Y/N	Death	Death
64/M/29.8	345	N/N	Ischemic stroke	Ischemic stroke
58/F/29.2	81	Y/N	Cardiac failure congestive	Congestive cardiac failure
68/M/27.8	468	Y/N	Sudden death	Sudden death
69/F/32.8	243	Y/N	Death	Death due to unknown cause
57/M/22.0	595	N/N	Death	Unknown cause of death
67/M/30.8	772	N/N	Multi-organ failure	Multiple organ failure
72/M/37.0	664	N/N	Cerebral infarction	Subacute left occipital infarct
71/F/35.4	181	N/Y	Death	Death
56/M/48.1	773	Y/N	Hypotension; Cardiac failure congestive, Cardiogenic shock	Hypotension; Exacerbation of congestive heart failure; Cardiogenic shock
69/M/32.4	647	Y/N	Atrioventricular block complete	Complete AV block
65/M/27.6	223	Y/N	Appendicitis	Appendicitis
64/M/27.3	630	Y/N	Septic shock	Septic shock
70/M/28.1	452	N/N	Cerebral ischemia; Splenic abscess	Ischemic cerebrovascular disease; Splenic abscess
66/F/43.1	676	Y/N	Pulmonary embolism	Pulmonary embolism.
58/M/37.5	254	N/Y	Death	Death cause unknown
77/M/29.1	783	N/N	Cerebrovascular accident	Cerebrovascular accident leading to death
76/M/30.3	454	N/N	Death	Unknown cause of death
61/F/33.1	715	N/N	Cerebrovascular accident	Cerebral vascular accident
69/M/39.6	81	Y/N	Death	Death by natural cause
70/F/34.4	626	Y/N	Cardiac arrest	Cardiac arrest
63/M/24.8	701	N/Y	Death	Unknown cause of death

Note: In cases where multiple AEs had a fatal outcome, the event sent for adjudication is presented first.
Abbreviations: ACS: acute coronary syndrome; AE: adverse event; BMI: body mass index; CVE: cerebrovascular event; EAC: event adjudication committee; F: female; Inv.: investigator; M: male; PT: preferred term; TIA: transient ischemic attack.

Non-cardiovascular death

A total of 36 deaths in SUSTAIN 6 (CVOT) were confirmed by the EAC as non-cardiovascular deaths. Of these, 32 deaths occurred during the in-trial period, and 4 deaths occurred after the in-trial period until data-base lock (DBL).

The most frequent causes of non-cardiovascular death were malignancies and infections, with no apparent differences between treatment groups (Table 6).

Table 6 SUSTAIN 6 (CVOT): EAC-confirmed non-cardiovascular death

	Semaglutide 0.5 mg				Semaglutide 1 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of patients	826				822				1,649			
Patient years of observation	1,708.4				1,699.8				3,401.1			
All-cause deaths	30	(3.6)	30	1.8	32	(3.9)	32	1.9	60	(3.6)	60	1.8
Non-cardiovascular death	9	(1.1)	9	0.5	9	(1.1)	9	0.5	14	(0.8)	14	0.4
Malignancy	2	(0.2)	2	0.1	6	(0.7)	6	0.4	6	(0.4)	6	0.2
Infection (includes sepsis)	2	(0.2)	2	0.1	3	(0.4)	3	0.2	4	(0.2)	4	0.1
Gastrointestinal	2	(0.2)	2	0.1	0	(0.0)			0	(0.0)		
Pulmonary	0	(0.0)			0	(0.0)			2	(0.1)	2	0.1
Hemorrhage that is neither CV bleeding or a stroke	0	(0.0)			0	(0.0)			1	(0.1)	1	<0.1
Neurological (non-CV)	1	(0.1)	1	0.1	0	(0.0)			0	(0.0)		
Non-CV procedure or surgery	1	(0.1)	1	0.1	0	(0.0)			0	(0.0)		
Renal	1	(0.1)	1	0.1	0	(0.0)			0	(0.0)		
Trauma	0	(0.0)			0	(0.0)			1	(0.1)	1	<0.1

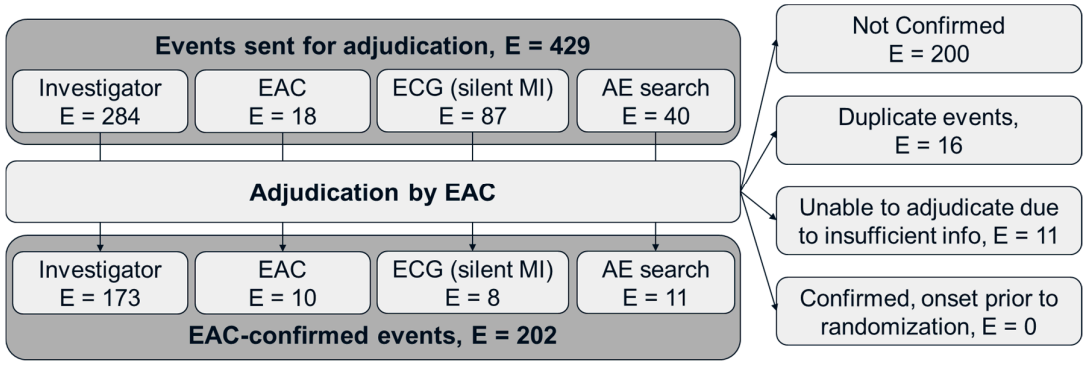
Note: FAS in-trial
Abbreviations: CV: cardiovascular; E: events; N: number of patients with at least one event; PYO: patient-years of exposure; R: rate of events per 100 PYO; sema: semaglutide; %: percentage of patients with at least one event.

3.2 Adjudication flow of cardiovascular events

All events with fatal outcome and events potentially related to acute coronary syndrome, cerebrovascular events, coronary revascularization procedures and heart failure requiring hospitalization were pre-defined as applicable for adjudication; see Sections 1 and 2).

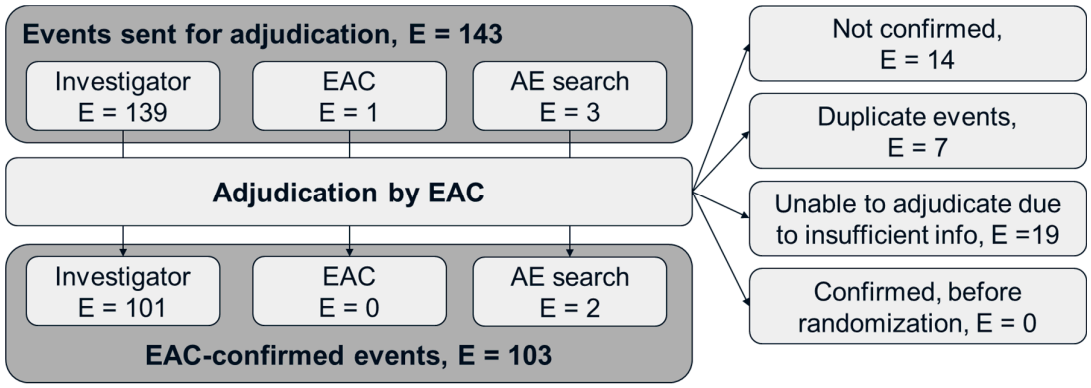
An overview of the event adjudication process numbers related to cardiovascular events is presented below; acute coronary syndrome (Figure 1), cerebrovascular events (Figure 3), coronary revascularization procedures (Figure 4) and heart failure requiring hospitalization (Figure 5). Overall, the majority of adjudicated events were identified by the investigators.

The EAC confirmation rate of events of acute coronary syndrome, cerebrovascular events, coronary revascularization procedures and heart failure requiring hospitalization were highest among events identified by investigators. EAC confirmation rates did not differ between semaglutide and placebo across reporting methods.



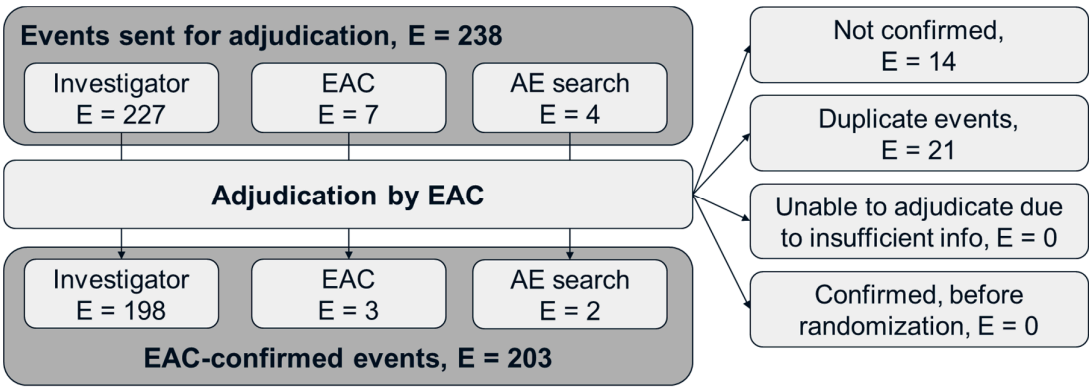
Abbreviations: AE: adverse event; CV: cardiovascular; E: number of events; EAC: event adjudication committee; ECG: electrocardiogram; MI: myocardial infarction.

Figure 2 SUSTAIN 6 (CVOT): Event adjudication process flow for acute coronary syndrome



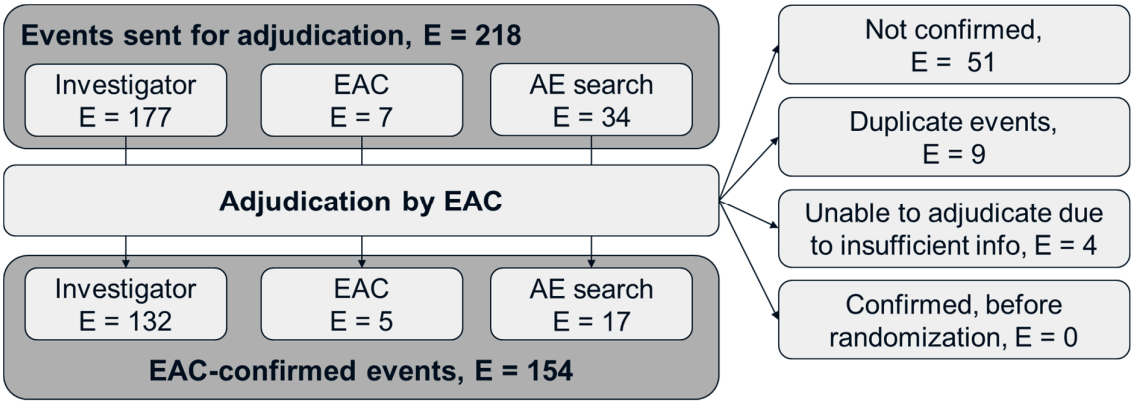
Abbreviations: AE: adverse event; CV: cardiovascular; E: number of events; EAC: event adjudication committee.

Figure 3 SUSTAIN 6 (CVOT): Event adjudication process flow for cerebrovascular events



Abbreviations: AE: adverse event; CV: cardiovascular; E: number of events; EAC: event adjudication committee.

Figure 4 SUSTAIN 6 (CVOT): Event adjudication process flow for coronary revascularization procedures



Abbreviations: AE: adverse event; CV: cardiovascular; E: number of events; EAC: event adjudication committee.

Figure 5 SUSTAIN 6 (CVOT): Event adjudication process flow for heart failure requiring hospitalization

A total of 34 events could not be adjudicated by the EAC due to insufficient information including 11 potential events of acute coronary syndrome (Figure 2), 19 potential cerebrovascular events (Figure 3), and 4 potential events of heart failure requiring hospitalization (Figure 5). Details of all 34 events are provided in Table 7. The right-hand column of the table describes EAC-confirmed cardiovascular events for the respective patients, including their temporal relation to the event that could not be adjudicated.

Table 7 SUSTAIN 6 (CVOT): Patients with cardiovascular events where EAC was unable to adjudicate due to lack of information

Age/Sex/BMI	Event source	EAC category	Preferred term/ Reported term for the adverse event	Other confirmed cardiovascular events
Semaglutide 0.5 mg				
62/M/31.34	Inv.	Heart failure	Cardiac failure/ Decompensated heart failure	No
65/M/40.01	Inv.	CVE	Lacunar infarction/ Lacunar infarct finding in brain CT – chronic	No
53/M/35.29	Inv.	ACS	Angina unstable/ Unstable angina	Prior unstable angina (ACS)
61/F/41.09	Inv.	ACS	Coronary artery disease/ Worsening of coronary artery disease	Prior coronary revascularization
58/F/54.63	Inv.	CVE	Cerebrovascular accident/ Stroke	Subsequent CV death (~4 months later)
	Inv.	CVE	Hypoxic-ischemic encephalopathy/ Anoxic encephalopathy	Subsequent CV death (~4 months later)
Semaglutide 1 mg				
79/F/30.59	Inv.	CVE	Ischemic stroke/ Ischemic stroke	No
65/M/31.74	Inv.	CVE	Ischemic stroke/ Repeated ischemic stroke	Prior CVE and subsequent CV death (4 days later)
63/M/27.76	AE	ACS	Angina pectoris/	Subsequent CVE (37 days later)

Age/Sex/BMI	Event source	EAC category	Preferred term/ Reported term for the adverse event	Other confirmed cardiovascular events
	search		Worsening of stable angina pectoris	
54/M/27.14	Inv.	ACS	Coronary artery disease/ Worsening of coronary artery disease	Coronary revascularization on the same day
	Inv.	Heart failure	Cardiac failure congestive/ Congestive heart failure	Coronary revascularization on the same day
76/M/28.42	Inv.	CVE	Transient ischemic attack/ TIA (previously documented as slurred speech)	No
69/M/28.03	Inv.	CVE	Cerebral infarction/ Cerebral infarction	Subsequent CV death (51 days later)
76/F/45.72	Inv.	CVE	Hemorrhagic stroke/ Hemorrhagic stroke	CV death on the same day. Also, prior CVE.
Placebo				
64/M/29.76	Inv.	CVE	Ischemic stroke/ Ischemic stroke	Subsequent CV death (38 days later)
51/F/35.02	AE search	Heart failure	Pulmonary congestion/ Pulmonary congestion	No
53/M/23.77	Inv.	CVE	Ischemic stroke/ Ischemic stroke	No
65/M/27.63	Inv.	ACS	Acute myocardial infarction/ Acute myocardial infarction	No
61/M/33.33	Inv.	ACS	Myocardial ischemia/ Acute myocardial ischemia	Prior events of ACS and heart failure. Subsequent CV death (6 days later)
67/M/25.86	Inv.	CVE	Ischemic stroke/ Ischemic stroke	No
63/F/32.43	Inv.	ACS	Coronary artery disease/ Worsening of coronary artery disease	Subsequent coronary revascularization (13 days later)
	ECG	ACS	-	Coronary revascularization (temporal relation unknown)
75/M/26.22	Inv.	CVE	Cerebral infarction/ Infarction in the left posterior cerebral artery area	No
60/M/31.83	Inv.	ACS	Acute myocardial infarction/ Acute myocardial infarction	CV death on the same day
58/M/37.53	Inv.	CVE	Hemorrhagic stroke/ Hemorrhagic stroke	Subsequent CV death (~4 months later)
70/F/28.64	Inv.	ACS	Non-cardiac chest pain/ Non-cardiac chest pain	No
79/F/21.49	Inv.	CVE	Drop attacks/ Drop attack	No
77/M/29.12	Inv.	CVE	Cerebrovascular accident/ Cerebrovascular accident leading to death	Prior heart failure (~14 months earlier. Subsequent CV death (6 days later)
61/F/33.12	Inv.	CVE	Cerebrovascular accident/ Stroke	Prior heart failure (~11 months earlier). Subsequent CV death (~6 months later)
	Inv.	ACS	Myocardial infarction/ Myocardial infarction	Prior heart failure (~11 months earlier). Subsequent CV death

Age/Sex/BMI	Event source	EAC category	Preferred term/ Reported term for the adverse event	Other confirmed cardiovascular events
				(~6 months later)
	Inv.	CVE	Cerebrovascular accident/ Cerebral vascular accident	Prior heart failure (~17 months earlier). CV death on the same day.
72/M/44.1	Inv.	CVE	Cerebrovascular accident/ Cerebrovascular event-stroke	Prior ACS (~9 months earlier)
56/M/48.11	Inv.	Heart failure	The AE (which was one of 3 causes of death on death certificate) was later deleted from the CRF by the investigator, with reason for deletion noted as 'changed information'.	Heart failure events and CV death (temporal relation to non-adjudicatable event unknown)
51/F/48.54	Inv.	CVE	Cerebral infarction/ Left middle cerebral artery infarct	No

Abbreviations: ACS: acute coronary syndrome; AE: adverse event; CVE: cerebrovascular event; DB: database; EAC: event adjudication committee; F: female; Inv.: investigator; M: male; PT: preferred term; TIA: transient ischemic attack.

3.3 EAC-confirmed cardiovascular events

The EAC performed adjudication of all potential cardiovascular events within event categories included in the MACE and expanded MACE definitions, i.e., events of acute coronary syndrome, cerebrovascular events, coronary revascularizations, and heart failures requiring hospital admission; for details see Table 1. A total of 662 such cardiovascular events were confirmed by the EAC in SUSTAIN 6 (CVOT) (Figure 5), of which 650 events occurred during the in-trial period (Table 8). Please note that the table includes both first events and recurrent events within each cardiovascular category. For all types of EAC-confirmed cardiovascular events, the proportion of patients with events as well as event rates were lower or similar with semaglutide relative to placebo.

Table 8 SUSTAIN 6 (CVOT): EAC-confirmed cardiovascular events

	Semaglutide 0.5 mg				Semaglutide 1 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of patients	826				822				1,649			
Patient years of observation	1,708.4				1,699.8				3,401.1			
Acute coronary syndrome	40	(4.8)	50	2.93	33	(4.0)	41	2.41	92	(5.6)	107	3.15
Acute MI	28	(3.4)	35	2.05	23	(2.8)	28	1.65	60	(3.6)	72	2.12
Silent MI	2	(0.2)	2	0.12	2	(0.2)	2	0.12	7	(0.4)	7	0.21
UAP req. hospitalization	12	(1.5)	13	0.76	10	(1.2)	11	0.65	27	(1.6)	28	0.82
Cerebrovascular events	21	(2.5)	22	1.29	18	(2.2)	19	1.12	58	(3.5)	60	1.76
Stroke	17	(2.1)	17	1.00	13	(1.6)	13	0.76	46	(2.8)	46	1.35
Transient ischemic attack	5	(0.6)	5	0.29	5	(0.6)	6	0.35	13	(0.8)	14	0.41
Coronary revascularization	39	(4.7)	48	2.81	31	(3.8)	32	1.88	103	(6.2)	119	3.50
Hosp. for heart failure	37	(4.5)	51	2.99	22	(2.7)	30	1.76	54	(3.3)	71	2.09

Note: FAS in-trial.
Abbreviations: E: number of events; R: events per 100 years of observation; EAC: event adjudication committee; hosp: hospitalization; N: number of patients with at least one event; MI: myocardial infarction; PYO: patient-years of observation; UAP: unstable angina pectoris; req.: requiring; %: percentage of patients with at least one event.

3.4 Time to first MACE - Primary endpoint

The primary endpoint was the time from randomization to first occurrence of a composite of the following cardiovascular endpoints: EAC-confirmed cardiovascular death (including undetermined cause of death), non-fatal myocardial infarction or non-fatal stroke, together defined as major adverse cardiovascular events (MACE).

Events with EAC-confirmed onset date between randomization and end of the in-trial observation period were included in the analyses. When events had the same date of onset the priority for selecting the first event was: cardiovascular death (incl. undetermined cause of death) > non-fatal myocardial infarction > non-fatal stroke. A schematic overview exemplifying how patients contribute to time to first MACE analyses for both the primary composite endpoint and for the analyses of the individual components is provided in Figure 6.

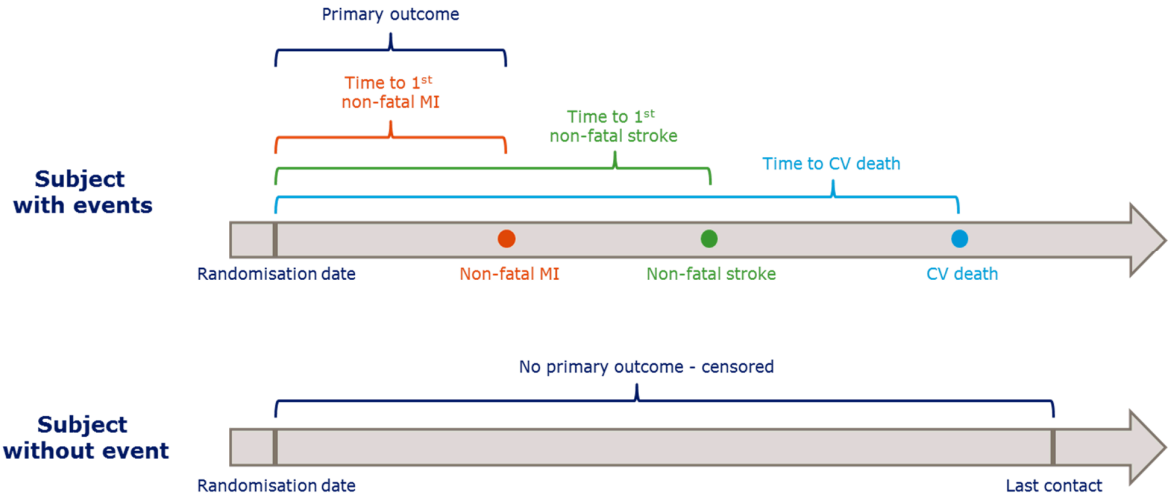


Figure 6 SUSTAIN 6 (CVOT): Example of how patients contribute to time to first MACE analyses

4 Adjudication of diabetic retinopathy complications in SUSTAIN 6 (CVOT)

Adverse events related to diabetic retinopathy were selected for adjudication, and the events confirmed by the EAC fulfilling at least one of the following four criteria refer to an event of diabetic retinopathy complications:

- Need for retinal photocoagulation
- Need for treatment with intravitreal agents
- Vitreous hemorrhage

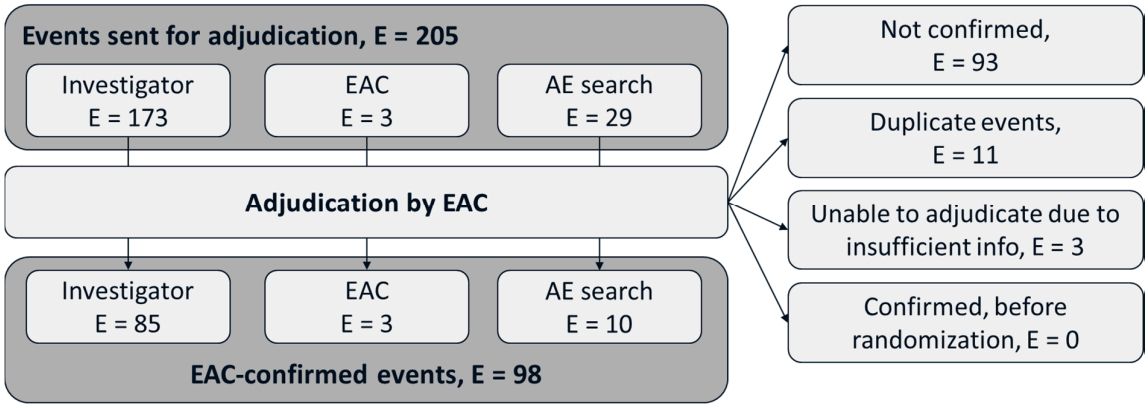
- Onset of diabetes-related blindness (defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of less than 20 degrees, in the better eye with best correction possible)

A patient could have recurrent events fulfilling any of the above criteria as well as several events fulfilling more than one criterion.

Time to first EAC-confirmed event of diabetic retinopathy complications was a secondary endpoint. The composite time-to-event endpoint was analyzed using the same method as the primary analysis. The analysis was based on the FAS using the in-trial observation period.

Adjudication flow of diabetic retinopathy complications

The process flow of events of diabetic retinopathy complications is shown in Figure 7. A total of 98 events of diabetic retinopathy complications were confirmed by the EAC; the majority of the confirmed events were identified by the investigator. Please note that the table shows the number of events and that each event could fulfil more than one criterion.



Abbreviations: AE: adverse event; E: events; EAC: event adjudication committee.

Figure 7 SUSTAIN 6 (CVOT): Adjudication flow for diabetic retinopathy complications

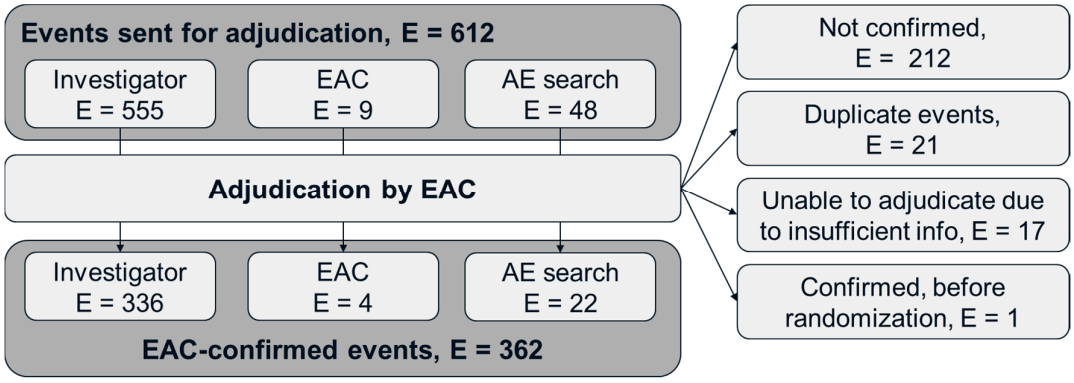
The overall EAC confirmation rate of events of diabetic retinopathy complications was 47.8%, with the highest rates among events identified by the EAC and investigators. More events were sent for adjudication among those patients treated with semaglutide, but with similar confirmation rates across treatment groups.

5 Adjudication of potential neoplasms in SUSTAIN 6 (CVOT)

5.1 Adjudication flow of neoplasms

5.1.1 Neoplasm events (excluding thyroid)

A process overview of the neoplasm events (excluding thyroid) sent for adjudication and those confirmed by the EAC is depicted in Figure 8. A total of 612 neoplasm events (excluding thyroid) were sent for adjudication in SUSTAIN 6 (CVOT) and of these, 362 were confirmed. In addition, 4 thyroid neoplasms were confirmed (see Section 5.1.2) giving a total of 366 confirmed neoplasms. Out of the total of 366 neoplasms, 364 events had onset during the in-trial period. One (1) event of malignant lung neoplasm was confirmed with semaglutide 1 mg with an onset date during the period after end-of-trial until data-base lock (DBL). One (1) patient had an EAC-confirmed benign colorectal neoplasm (colon adenoma) with onset at day -2 i.e. prior to randomization to placebo.



Note: Confirmed events with onset prior to randomization are included in number of EAC-confirmed events.
Abbreviations: AE: adverse event; E: number of events; EAC: event adjudication committee.

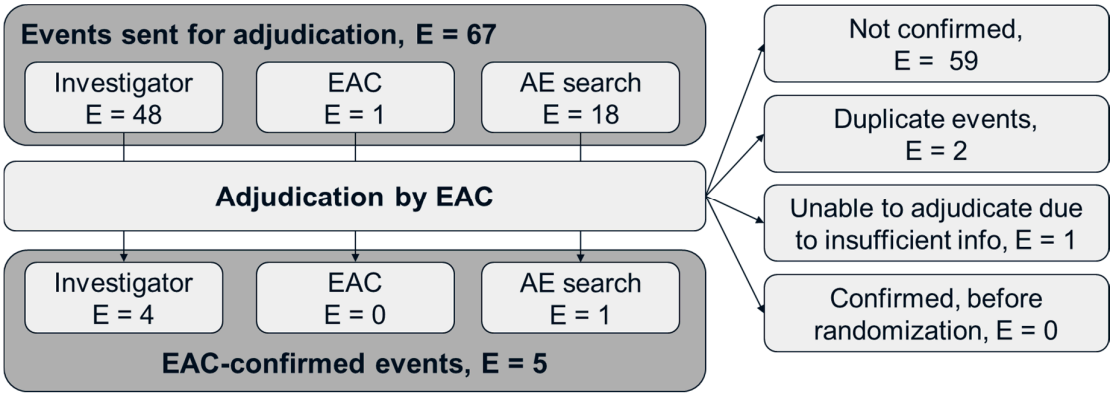
Figure 8 SUSTAIN 6 (CVOT): Event adjudication process flow for neoplasms (excluding thyroid)

The overall EAC confirmation rate of neoplasm events was 59.2%, with the highest rate among events identified by the investigators. Overall EAC confirmation rates were slightly higher with semaglutide than with placebo.

5.1.2 Thyroid events

A process overview of the thyroid events sent for adjudication and those confirmed by the EAC is depicted in Figure 9. A total of 67 thyroid events were sent for adjudication, 5 of these were confirmed by the EAC. The majority had been identified by the investigators. Four (4) of the 5 EAC-confirmed thyroid events were thyroid neoplasms and 1 event was a thyroidectomy.

The EAC confirmation rate of thyroid events was low (7.5%), with the highest rate among events identified by the investigators.



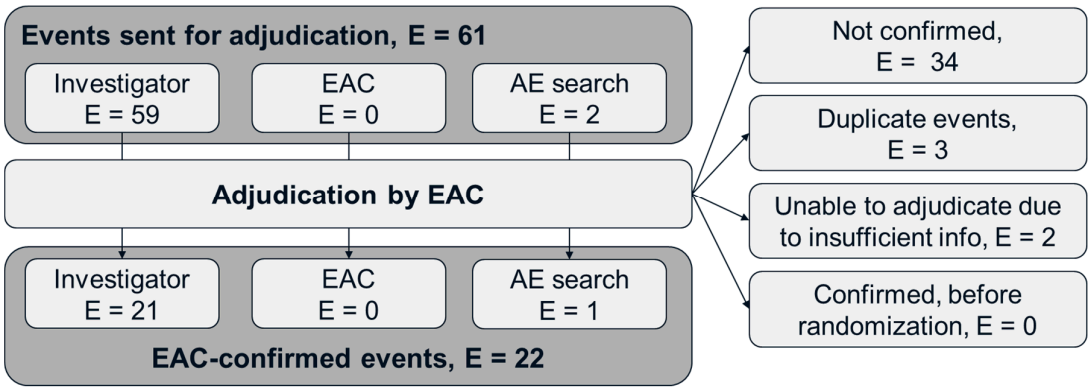
Note: Confirmed events with onset prior to randomization are included in number of EAC-confirmed events.

Abbreviations: E: number of events; EAC: event adjudication committee.

Figure 9 SUSTAIN 6 (CVOT): Event adjudication process flow for thyroid neoplasms and events leading to thyroidectomy

6 Adjudication of potential pancreatitis in SUSTAIN 6 (CVOT)

A process overview of the events sent for adjudication is depicted in Figure 10. A total of 22 events of pancreatitis were confirmed by the EAC in SUSTAIN 6 (CVOT). Of the 22 confirmed events, 18 events occurred during the on-treatment observation period, and additional 3 events during the in-trial observation period. The last event occurred after the in-trial observation period. The EAC was unable to adjudicate 2 investigator-reported events due to insufficient information, 1 with semaglutide 0.5 mg and 1 with placebo. The 34 EAC non-confirmed events were mainly reported as elevated pancreatic enzymes, suspicion of pancreatitis, or abdominal pain; the terms were evenly distributed across the treatment groups.



Notes: Diagram presents all events reported from randomization to data base lock. One (1) event pre-evaluated as pancreatitis, but adjudicated as a pancreatic neoplasm is not included in this diagram.

Abbreviations: AE: adverse event; E: number of events; EAC: (external) event adjudication committee.

Figure 10 SUSTAIN 6 (CVOT): Event adjudication process flow for pancreatitis

Semaglutide s.c. OW

Treatment to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus

NDA 209637

Briefing Document
Appendix 3
Subgroup analyses of MACE in SUSTAIN 6 (CVOT)

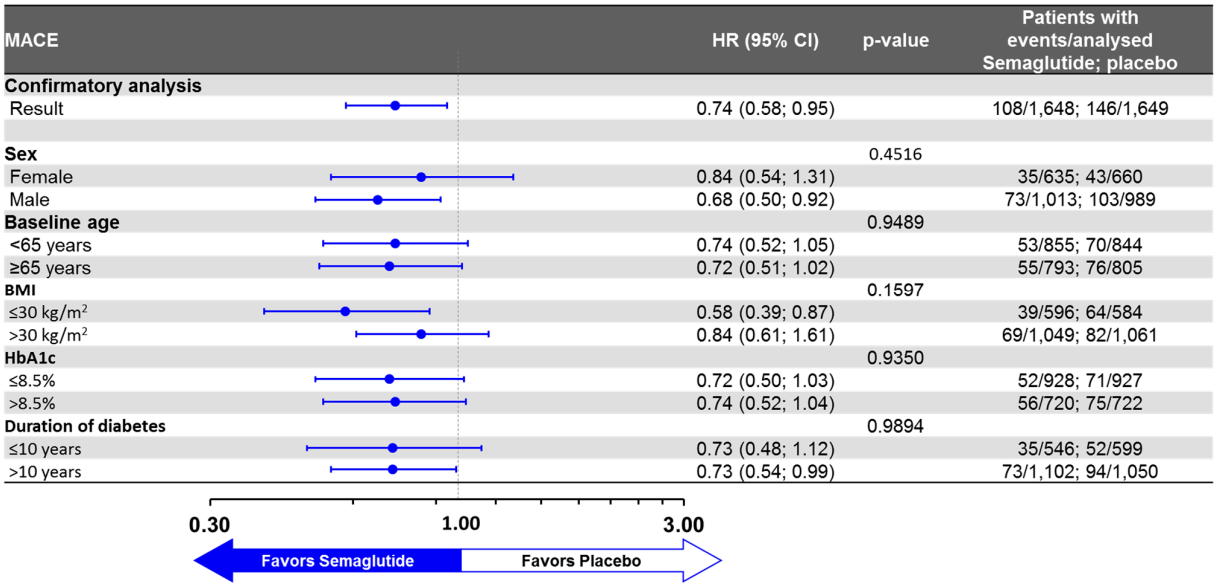
Endocrinologic and Metabolic Drug Advisory Committee

October 18, 2017

Advisory Committee Briefing Materials: Available for Public Release

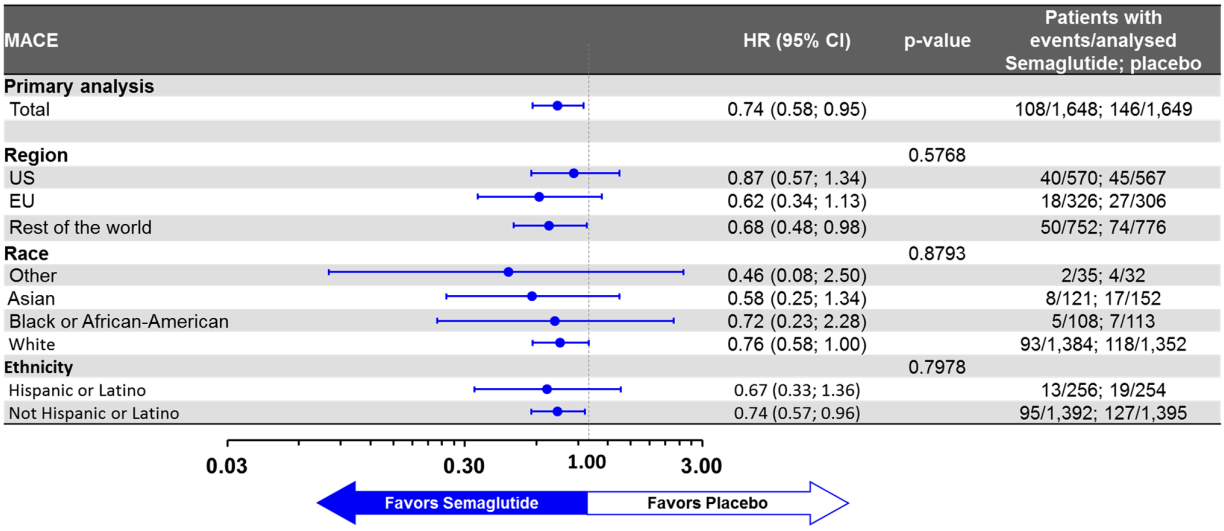
List of in-text figures

Page



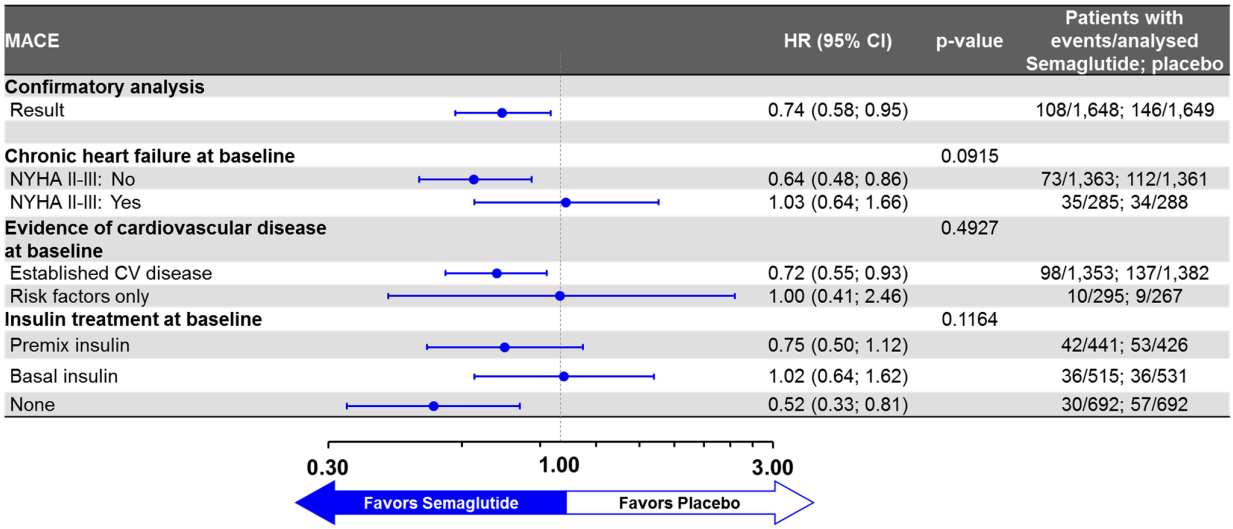
Notes: FAS in-trial. Estimated HRs and associated CIs are from a Cox proportional hazards model with an interaction between treatment and the relevant subgroup as fixed factor. The p-value is from the Wald test of no-interaction.
Abbreviations: BMI: body mass index; CI: confidence interval; EAC: event adjudication committee; HR: hazard ratio.

Figure 1 SUSTAIN 6 (CVOT): Forest plot on time to first EAC-confirmed MACE, pre-planned subgroup analyses for sex, age, BMI, HbA_{1c}, and duration of diabetes



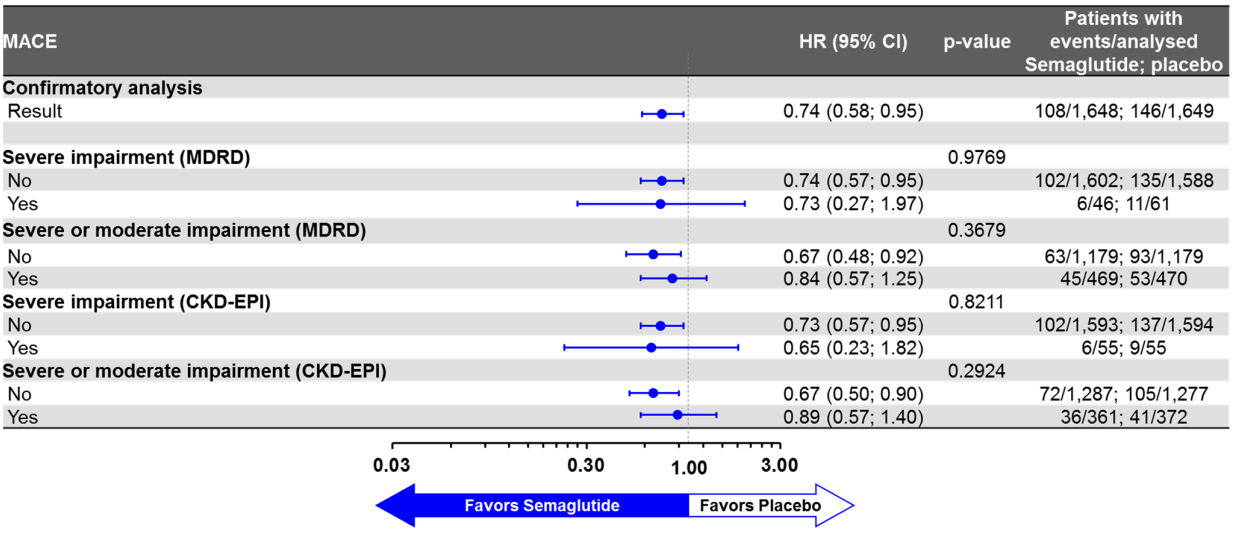
Notes: FAS in-trial. Estimated HRs and associated CIs are from a Cox proportional hazards model with an interaction between treatment and the relevant subgroup as fixed factor. The p-value is from the Wald test of no-interaction.
Abbreviations: CI: confidence interval; EAC: event adjudication committee; HR: hazard ratio.

Figure 2 SUSTAIN 6 (CVOT): Forest plot on time to first EAC-confirmed MACE, preplanned subgroup analyses for region, race, and ethnicity



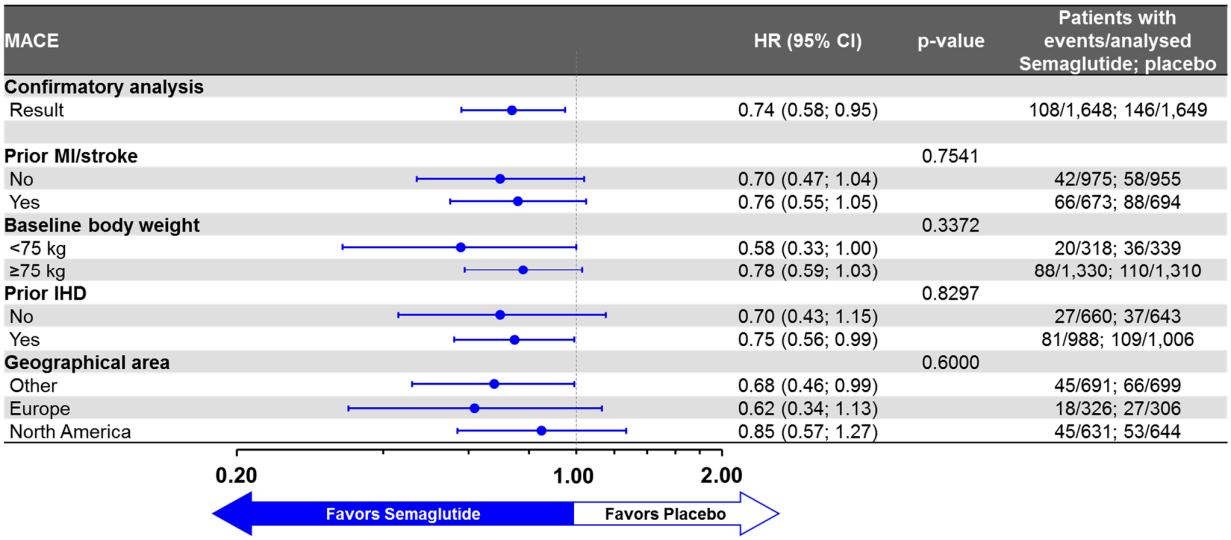
Notes: FAS in-trial. Estimated HRs and associated CIs are from a Cox proportional hazards model with an interaction between treatment and the relevant subgroup as fixed factor. The p-value is from the Wald test of no-interaction
Abbreviations: CI: confidence interval; CV: cardiovascular; EAC: event adjudication committee; HR: hazard ratio.

Figure 3 SUSTAIN 6 (CVOT): Forest plot on time to first EAC-confirmed MACE, preplanned subgroup analyses for chronic heart failure class II-III, evidence of cardiovascular disease, and insulin treatment at baseline



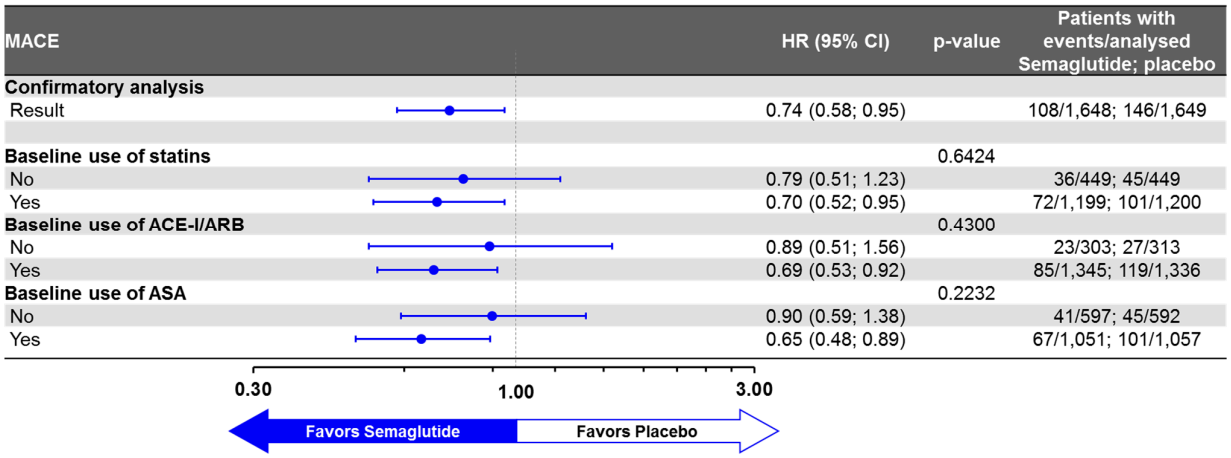
Notes: FAS in-trial. Estimated HRs and associated CIs are from a Cox proportional hazards model with an interaction between treatment and the relevant subgroup as fixed factor. The p-value is from the Wald test of no-interaction.
Abbreviations: CI: confidence interval; CKD-Epi: chronic kidney disease epidemiology collaboration; EAC: event adjudication committee; HR: hazard ratio; MDRD: modification of diet in renal disease.

Figure 4 SUSTAIN 6 (CVOT): Forest plot on time to first EAC-confirmed MACE, preplanned subgroup analyses for renal impairment



Notes: FAS in-trial. Estimated HRs and associated CIs are from a Cox proportional hazards model with an interaction between treatment and the relevant subgroup as fixed factor. The p-value is from the Wald test of no-interaction
Abbreviations: CI: confidence interval; CKD-Epi: chronic kidney disease epidemiology collaboration; EAC: event adjudication committee; HR: hazard ratio; IHD: ischemic heart disease; MDRD: modification of diet in renal disease.

Figure 5 SUSTAIN 6 (CVOT): Forest plot on time to first EAC-confirmed MACE, *post hoc* subgroup analyses for prior MI/stroke, baseline body weight, prior ischemic heart disease, and geographical area



Notes: FAS in-trial. Estimated HRs and associated CIs are from a Cox proportional hazards model with an interaction between treatment and the relevant subgroup as fixed factor. The p-value is from the Wald test of no-interaction.
Abbreviations: ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; ASA: acetylsalicylic acid; CI: confidence interval; EAC: event adjudication committee; HR: hazard ratio.

Figure 6 SUSTAIN 6 (CVOT): Forest plot on time to first EAC-confirmed MACE, *post hoc* subgroup analyses for baseline use of statins, ACE-inhibitors/Angiotensin receptor blockers, and acetylsalicylic acid