CLINICAL UPDATE

Brand Name	Ozempic®
Generic Name	semaglutide
Drug Manufacturer	Novo Nordisk Inc

Clinical Update

TYPE OF CLINICAL UPDATE

New Strength

FDA APPROVAL DATE

March 28, 2022

LAUNCH DATE

March 30, 2022

REVIEW DESIGNATION

Standard

TYPE OF REVIEW

Type 1 - New Molecular Entity; New Drug Application (NDA): 209637

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Ozempic® is a glucagon-like peptide 1 (GLP-1) receptor agonist indicated as:

- an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease.

MECHANISMS OF ACTION

Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. GLP-1 is a physiological hormone that has multiple actions on glucose, mediated by the GLP-1 receptors. The principal mechanism of protraction resulting in the long half-life of semaglutide is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilized against degradation by the DPP-4 enzyme. Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated, and glucagon secretion is inhibited. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase.

CLINICAL UPDATE

DOSAGE FORM(S) AND STRENGTH(S)

Injection: 2 mg/1.5 mL (1.34 mg/mL) available in:

- Single-patient-use pen that delivers 0.25 mg or 0.5 mg per injection

  Injection: 4 mg/3 mL (1.34 mg/mL) available in:

- Single-patient-use pen that delivers 1 mg per injection.

  Injection: 8 mg/3 mL (2.68 mg/mL) available in:

- Single-patient-use pen that delivers 2 mg per injection.

DOSE & ADMINISTRATION

Start at 0.25 mg once weekly. After 4 weeks, increase the dose to 0.5 mg once weekly.

- If additional glycaemic control is needed, increase the dose to 1 mg once weekly after at least 4 weeks on the 0.5 mg dose.
- If additional glycaemic control is needed, increase the dose to 2 mg once weekly after at least 4 weeks on the 1 mg dose

EFFICACY

Ozempic® has been studied as monotherapy and in combination with metformin, metformin and sulfonylureas, metformin and/or thiazolidinedione, and basal insulin in patients with type 2 diabetes mellitus. The efficacy of Ozempic® was compared with placebo, sitagliptin, exenatide extended release (ER), and insulin glargine. Most trials evaluated the use of Ozempic® 0.5 mg, and 1 mg, with the exception of the trial comparing Ozempic® and exenatide ER where only the 1 mg dose was studied. One trial evaluated the use of Ozempic® 2 mg once weekly. In patients with type 2 diabetes mellitus, Ozempic® produced clinically relevant reduction from baseline in HbA1c compared with placebo. The efficacy of Ozempic® was not impacted by age, gender, race, ethnicity, BMI at baseline, body weight (kg) at baseline, diabetes duration and level of renal function impairment.

Monotherapy Use of Ozempic® in Patients with Type 2 Diabetes Mellitus

In a 30-week double-blind trial (NCT02054897), 388 patients with type 2 diabetes mellitus inadequately controlled with diet and exercise were randomized to Ozempic® 0.5 mg or Ozempic® 1 mg once weekly or placebo. Patients had a mean age of 54 years and 54% were men. The mean duration of type 2 diabetes was 4.2 years, and the mean BMI was 33 kg/m2 . Overall, 64% were White, 8% were Black or African American, and 21% were Asian; 30% identified as Hispanic or Latino ethnicity. Monotherapy with Ozempic® 0.5 mg and 1 mg once weekly for 30 weeks resulted in a statistically significant reduction in HbA1c compared with placebo.

The mean baseline body weight was 89.1 kg, 89.8 kg, 96.9 kg in the placebo, Ozempic® 0.5 mg, and Ozempic® 1 mg arms, respectively. The mean changes from baseline to week 30 were -1.2 kg, -3.8 kg and -4.7 kg in the placebo, Ozempic® 0.5 mg, and Ozempic® 1 mg arms, respectively. The difference from placebo (95% CI) for Ozempic® 0.5 mg was -2.6 kg (-3.8, -1.5), and for Ozempic® 1 mg was -3.5 kg (-4.8, -2.2).

Table 1. Results at Week 30 in a Trial of Ozempic® as Monotherapy in Adult Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise

	Placebo	OZEMPIC 0.5 mg	OZEMPIC 1 mg
Intent-to-Treat (ITT) Population (N)[a]	129	128	130
HbA_{1c} (%)			
Baseline (mean)	8.0	8.1	8.1
Change at week 30[b]	-0.1	-1.4	-1.6
Difference from placebo[b] [95% CI]		-1.2 [-1.5, -0.9][c]	-1.4 [-1.7, -1.1][c]
Patients (%) achieving HbA_{1c} <7%	28	73	70
FPG (mg/dL)			
Baseline (mean)	174	174	179
Change at week 30[b]	-15	-41	-44

[a]The intent-to-treat population includes all randomized and exposed patients. At week 30 the primary HbA_{1c} endpoint was missing for 10%, 7% and 7% of patients and during the trial rescue medication was initiated by 20%, 5% and 4% of patients randomized to placebo, OZEMPIC 0.5 mg and OZEMPIC 1 mg, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts.
[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value and country.
[c]$p<0.0001$ (2-sided) for superiority, adjusted for multiplicity.

Combination Therapy Use of Ozempic® in Patients with Type 2 Diabetes Mellitus

Combination with metformin and/or thiazolidinediones

In a 56-week, double-blind trial (NCT01930188), 1231 patients with type 2 diabetes mellitus were randomized to Ozempic® 0.5 mg once weekly, Ozempic® 1 mg once weekly, or sitagliptin 100 mg once daily, all in combination with metformin (94%) and/or thiazolidinediones (6%). Patients had a mean age of 55 years and 51% were men. The mean duration of type 2 diabetes was 6.6 years, and the mean BMI was 32 kg/m2 . Overall, 68% were White, 5% were Black or African American, and 25% were Asian; 17% identified as Hispanic or Latino ethnicity. Treatment with Ozempic® 0.5 mg and 1 mg once weekly for 56 weeks resulted in a statistically significant reduction in HbA1c compared to sitagliptin.

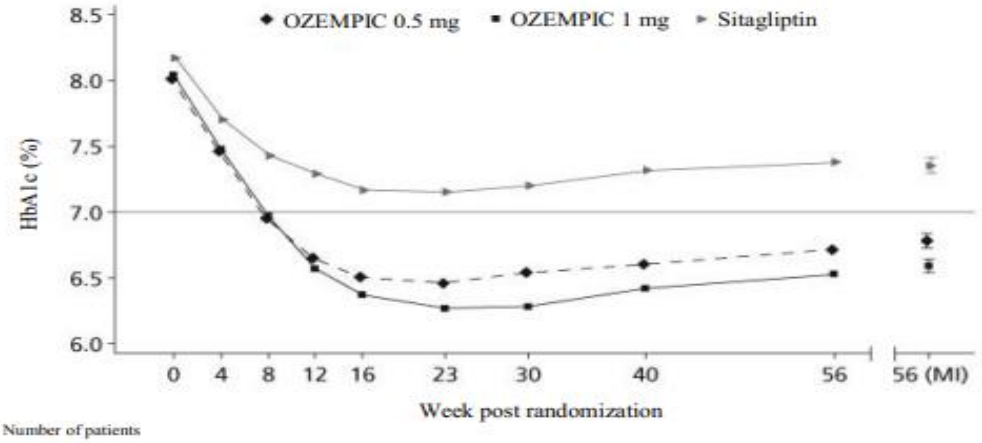
Table 2. Results at Week 56 in a Trial of Ozempic® Compared to Sitagliptin in Adult Patients with Type 2 Diabetes Mellitus in Combination with Metformin and/or Thiazolidinediones

	OZEMPIC 0.5 mg	OZEMPIC 1 mg	Sitagliptin
Intent-to-Treat (ITT) Population (N)[a]	409	409	407
HbA_{1c} (%)			
Baseline (mean)	8.0	8.0	8.2
Change at week 56[b]	-1.3	-1.5	-0.7
Difference from sitagliptin[b] [95% CI]	-0.6 [-0.7, -0.4][c]	-0.8 [-0.9, -0.6][c]	
Patients (%) achieving HbA_{1c} <7%	66	73	40
FPG (mg/dL)			
Baseline (mean)	168	167	173
Change at week 56[b]	-35	-43	-23

[a]The intent-to-treat population includes all randomized and exposed patients. At week 56 the primary HbA_{1c} endpoint was missing for 7%, 5% and 6% of patients and during the trial rescue medication was initiated by 5%, 2% and 19% of patients randomized to OZEMPIC 0.5 mg, OZEMPIC 1 mg and sitagliptin, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts.
[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value and country.
[c]$p<0.0001$ (2-sided) for superiority, adjusted for multiplicity.

The mean baseline body weight was 89.9 kg, 89.2 kg, 89.3 kg in the Ozempic® 0.5 mg, Ozempic® 1 mg, and sitagliptin arms, respectively. The mean changes from baseline to week 56 were -4.2 kg, -5.5 kg, and -1.7 kg for the Ozempic® 0.5 mg, Ozempic® 1 mg, and sitagliptin arms, respectively. The difference from sitagliptin (95% CI) for Ozempic® 0.5 mg was -2.5 kg (-3.2, -1.8), and for Ozempic® 1 mg was -3.8 kg (-4.5, -3.1).

Figure 1. Mean HbA1c (%) over time - baseline to week 56



Observed mean HbA1c at scheduled visits and retrieved dropout multiple imputation (MI) based estimate at week 56 with standard error

Combination with metformin or metformin with sulfonylurea

In a 56-week, open-label trial (NCT01885208), 813 patients with type 2 diabetes mellitus on metformin alone (49%), metformin with sulfonylurea (45%), or other (6%) were randomized to Ozempic® 1 mg once weekly or exenatide 2 mg once weekly. Patients had a mean age of 57 years and 55% were men. The mean duration of type 2 diabetes was 9 years, and the mean BMI was 34 kg/m2 . Overall, 84% were White, 7% were Black or African American, and 2% were Asian; 24% identified as Hispanic or Latino ethnicity. Treatment with Ozempic® 1 mg once weekly for 56 weeks resulted in a statistically significant reduction in HbA1c compared to exenatide 2 mg once weekly.

Table 3. Results at Week 56 in a Trial of Ozempic® Compared to Exenatide 2 mg Once Weekly in Adult Patients with Type 2 Diabetes Mellitus in Combination with Metformin or Metformin with Sulfonylurea

	OZEMPIC 1 mg	Exenatide ER 2 mg
Intent-to-Treat (ITT) Population (N)[a]	404	405
HbA_{1c} (%)		
Baseline (mean)	8.4	8.3
Change at week 56[b]	-1.4	-0.9
Difference from exenatide[b] [95% CI]	-0.5 [-0.7, -0.3][c]	
Patients (%) achieving HbA_{1c} <7%	62	40
FPG (mg/dL)		
Baseline (mean)	191	188
Change at week 56[b]	-44	-34

[a]The intent-to-treat population includes all randomized and exposed patients. At week 56 the primary HbA_{1c} endpoint was missing for 9% and 11% of patients and during the trial rescue medication was initiated by 5% and 10% of patients randomized to OZEMPIC 1 mg and exenatide ER 2 mg, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts.
[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value and country.
[c]$p<0.0001$ (2-sided) for superiority, adjusted for multiplicity.

The mean baseline body weight was 96.2 kg and 95.4 kg in the Ozempic® 1 mg and exenatide ER arms, respectively. The mean changes from baseline to week 56 were -4.8 kg and -2.0 kg in the Ozempic®1 mg and exenatide ER arms, respectively. The difference from exenatide ER (95% CI) for Ozempic® 1 mg was -2.9 kg (-3.6, -2.1).

Combination with metformin or metformin with sulfonylurea

In a 30-week, open-label trial (NCT02128932), 1089 patients with type 2 diabetes mellitus were randomized to Ozempic® 0.5 mg once weekly, Ozempic® 1 mg once weekly, or insulin glargine once daily on a background of metformin (48%) or metformin and sulfonylurea (51%). Patients had a mean age of 57 years and 53% were men. The mean duration of type 2 diabetes was 8.6 years, and the mean BMI was 33 kg/m2 . Overall, 77% were White, 9% were Black or African American, and 11% were Asian; 20% identified as Hispanic or Latino ethnicity.
Patients assigned to insulin glargine had a baseline mean HbA1c of 8.1% and were started on a dose of 10 U once daily. Insulin glargine dose adjustments occurred throughout the trial period based on self-measured fasting plasma glucose before breakfast, targeting 71 to <100 mg/dL. In addition, investigators could titrate insulin glargine at their discretion between study visits. Only 26% of patients had been titrated to goal by the primary endpoint at week 30, at which time the mean daily insulin dose was 29 U per day.
Treatment with Ozempic® 0.5 mg and 1 mg once weekly for 30 weeks resulted in a statistically significant reduction in HbA1c compared with the insulin glargine titration implemented in this study protocol.

Table 4. Results at Week 30 in a Trial of Ozempic® Compared to Insulin Glargine in Adult Patients with Type 2 Diabetes Mellitus in Combination with Metformin or Metformin with Sulfonylurea

	OZEMPIC 0.5 mg	OZEMPIC 1 mg	Insulin Glargine
Intent-to-Treat (ITT) Population (N)[a]	362	360	360
HbA_{1c} (%)			
Baseline (mean)	8.1	8.2	8.1
Change at week 30[b]	-1.2	-1.5	-0.9
Difference from insulin glargine[b] [95% CI]	-0.3 [-0.5, -0.1][c]	-0.6 [-0.8, -0.4][c]	
Patients (%) achieving HbA_{1c} <7%	55	66	40
FPG (mg/dL)			
Baseline (mean)	172	179	174
Change at week 30[b]	-35	-46	-37

[a]The intent-to-treat population includes all randomized and exposed patients. At week 30 the primary HbA_{1c} endpoint was missing for 8%, 6% and 6% of patients and during the trial rescue medication was initiated by 4%, 3% and 1% of patients randomized to OZEMPIC 0.5 mg, OZEMPIC 1 mg and insulin glargine, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts.
[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value, country and stratification factors.
[c]$p<0.0001$ (2-sided) for superiority, adjusted for multiplicity.

The mean baseline body weight was 93.7 kg, 94.0 kg, 92.6 kg in the Ozempic® 0.5 mg, Ozempic® 1 mg, and insulin glargine arms, respectively. The mean changes from baseline to week 30 were -3.2 kg, -4.7 kg and 0.9 kg in the Ozempic® 0.5 mg, Ozempic® 1 mg, and insulin glargine arms, respectively. The difference from insulin glargine (95% CI) for Ozempic® 0.5 mg was -4.1 kg (-4.9, -3.3) and for Ozempic® 1 mg was -5.6 kg (-6.4, -4.8).

Combination with metformin or metformin with sulfonylurea

In a 40-week, double-blind trial (NCT03989232), 961 patients with type 2 diabetes currently treated with metformin with or without sulfonylurea treatment were randomized to Ozempic® 2 mg or Ozempic® 1 mg once weekly. Patients had a mean age of 58.0 years and 58.6% were men. The mean duration of type 2 diabetes was 9.5 years and the mean BMI was 34.6 kg/m2 . At randomization, 53.3% of patients were treated with sulfonylurea and metformin. Overall, 88.1% were White, 4.5% were Black or African American, and 7.2% were

Asian; 11.6% identified as Hispanic or Latino ethnicity. Treatment with Ozempic® 2 mg once weekly for 40 weeks resulted in a statistically significant reduction in HbA1c compared with Ozempic® 1 mg (see Table 5). Patients were stratified by region (Japan/outside Japan) at randomization.

Table 5. Results at Week 40 in a Trial of Ozempic® 2 mg Compared to Ozempic® 1 mg in Adult Patients with Type 2 Diabetes Mellitus in Combination with Metformin or Metformin with Sulfonylurea

	OZEMPIC 1 mg	OZEMPIC 2 mg
Intent-to-Treat (ITT) Population (N)[a]	481	480
HbA_{1c} (%)		
Baseline (mean)	8.8	8.9
Change at week 40[b]	-1.9	-2.1
Difference from OZEMPIC 1 mg [95% CI]		-0.2 [-0.31 ; -0.04][c]
Patients (%) achieving HbA_{1c} <7%[a]	56	64
FPG (mg/dL)		
Baseline (mean)	196	193
Change at week 40[b]	-55	-59

[a] The intent-to-treat population includes all randomized subjects. At week 40 the primary HbA_{1c} endpoint was missing for 3% and 5% of patients randomized to OZEMPIC 1 mg and OZEMPIC 2 mg, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts. For calculation of proportions, imputed values are dichotomized and the denominator is the number of all randomized subjects.

[b] Intent-to-treat analysis using ANCOVA adjusted for baseline value and stratification factor.

[c] $p<0.01$ (2-sided) for superiority, adjusted for multiplicity.

The mean baseline body weight was 98.6 kg and 100.1 kg in the Ozempic® 1 mg and Ozempic® 2 mg arms, respectively. The mean changes from baseline to week 40 were -5.6 kg and -6.4 kg in the Ozempic® 1 mg and Ozempic® 2 mg arms, respectively. The difference between treatment arms in body weight change from baseline at week 40 was not statistically significant.

Combination with basal insulin

In a 30-week, double-blind trial (NCT02305381), 397 patients with type 2 diabetes mellitus inadequately controlled with basal insulin, with or without metformin, were randomized to Ozempic® 0.5 mg once weekly, Ozempic® 1 mg once weekly, or placebo. Patients with HbA1c ≤ 8.0% at screening reduced their insulin dose by 20% at start of the trial to reduce the risk of hypoglycemia. Patients had a mean age of 59 years and 56% were men. The mean duration of type 2 diabetes was 13 years, and the mean BMI was 32 kg/m2. Overall, 78% were White, 5% were Black or African American, and 17% were Asian; 12% identified as Hispanic or Latino ethnicity. Treatment with Ozempic® resulted in a statistically significant reduction in HbA1c after 30 weeks of treatment compared to placebo.

The mean baseline body weight was 89.9 kg, 92.7 kg, and 92.5 kg in the placebo, Ozempic® 0.5 mg, and Ozempic® 1 mg arms, respectively. The mean changes from baseline to week 30 were -1.2 kg, -3.5 kg, and -6.0 kg in the placebo, Ozempic® 0.5 mg, and Ozempic® 1 mg arms, respectively. The difference from placebo (95% CI) for Ozempic® 0.5 mg was -2.2 kg (-3.4, -1.1), and for Ozempic® 1 mg was -4.7 kg (-5.8, -3.6).

Table 6. Results at Week 30 in a Trial of Ozempic® in Adult Patients with Type 2 Diabetes Mellitus in Combination with Basal Insulin with or without Metformin

	Placebo	OZEMPIC 0.5 mg	OZEMPIC 1 mg
Intent-to-Treat (ITT) Population (N)[a]	133	132	131
HbA_{1c} (%)			
Baseline (mean)	8.4	8.4	8.3
Change at week 30[b]	-0.2	-1.3	-1.7
Difference from placebo[b]		-1.1	-1.6
[95% CI]		[-1.4, -0.8][c]	[-1.8, -1.3][c]
Patients (%) achieving HbA_{1c} <7%	13	56	73
FPG (mg/dL)			
Baseline (mean)	154	161	153
Change at week 30[b]	-8	-28	-39

[a]The intent-to-treat population includes all randomized and exposed patients. At week 30 the primary HbA_{1c} endpoint was missing for 7%, 5% and 5% of patients and during the trial rescue medication was initiated by 14%, 2% and 1% of patients randomized to placebo, OZEMPIC 0.5 mg and OZEMPIC 1 mg, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts.

[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value, country and stratification factors.

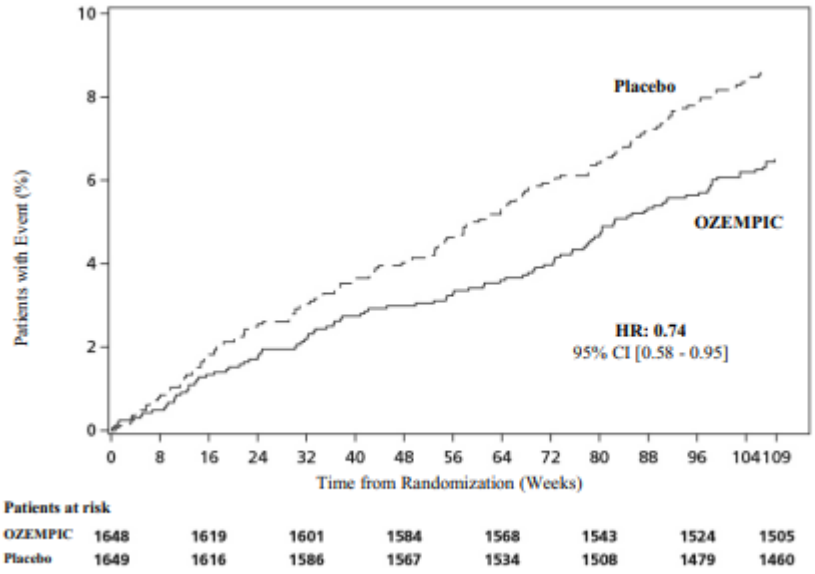
[c]$p<0.0001$ (2-sided) for superiority, adjusted for multiplicity.

Cardiovascular Outcomes Trial of Ozempic® in Patients with Type 2 Diabetes Mellitus and Cardiovascular Disease

SUSTAIN 6 (NCT01720446) was a multi-center, multi-national, placebo-controlled, double-blind cardiovascular outcomes trial. In this trial, 3,297 patients with inadequately controlled type 2 diabetes and atherosclerotic cardiovascular disease were randomized to Ozempic® (0.5 mg or 1 mg) once weekly or placebo for a minimum observation time of 2 years. The trial compared the risk of Major Adverse Cardiovascular Event (MACE) between semaglutide and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and cardiovascular disease. The primary endpoint, MACE, was the time to first occurrence of a three-part composite outcome which included cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. Patients eligible to enter the trial were 50 years of age or older and had established, stable, cardiovascular, cerebrovascular, peripheral artery disease, chronic kidney disease or NYHA class II and III heart failure or were 60 years of age or older and had other specified risk factors for cardiovascular disease. In total, 1,940 patients (58.8%) had established cardiovascular disease without chronic kidney disease, 353 (10.7%) had chronic kidney disease only, and 442 (13.4%) had both cardiovascular disease and kidney disease; 562 patients (17%) had cardiovascular risk factors without established cardiovascular disease or chronic kidney disease. In the trial 453 patients (13.7%) had peripheral artery disease. The mean age at baseline was 65 years, and 61% were men. The mean duration of diabetes was 13.9 years, and mean BMI was 33 kg/m2. Overall, 83% were White, 7% were Black or African American, and 8% were Asian; 16% identified as Hispanic or Latino ethnicity. Concomitant diseases of patients in this trial included, but were not limited to, heart failure (24%), hypertension (93%), history of ischemic stroke (12%) and history of a myocardial infarction (33%). In total, 98.0% of the patients completed the trial and the vital status was known at the end of the trial for 99.6%.

For the primary analysis, a Cox proportional hazards model was used to test for non-inferiority of Ozempic® to placebo for time to first MACE using a risk margin of 1.3. The statistical analysis plan pre specified that the 0.5 mg and 1 mg doses would be combined. Type-1 error was controlled across multiple tests using a hierarchical testing strategy. Ozempic® significantly reduced the occurrence of MACE. The estimated hazard ratio for time to first MACE was 0.74 (95% CI: 0.58, 0.95).

Figure 2 . Kaplan-Meier: Time to First Occurrence of a MACE in the SUSTAIN 6 Trial



The treatment effect for the primary composite endpoint and its components in the SUSTAIN 6 trial is shown in Table below.

Table 7. Treatment Effect for MACE and its Components, Median Study Observation Time of 2.1 Years

	Placebo N=1649 (%)	OZEMPIC N=1648 (%)	Hazard ratio vs Placebo (95% CI)[a]
Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence)	146 (8.9)	108 (6.6)	0.74 (0.58, 0.95)
Non-fatal Myocardial Infarction	64 (3.9)	47 (2.9)	0.74 (0.51, 1.08)
Non-fatal Stroke	44 (2.7)	27 (1.6)	0.61 (0.38, 0.99)
Cardiovascular Death	46 (2.8)	44 (2.7)	0.98 (0.65, 1.48)
Fatal or Non-fatal Myocardial Infarction	67 (4.1)	54 (3.3)	0.81 (0.57, 1.16)
Fatal or Non-fatal Stroke	46 (2.8)	30 (1.8)	0.65 (0.41, 1.03)

[a] Cox-proportional hazards models with treatment as factor and stratified by evidence of cardiovascular disease, insulin treatment and renal impairment.