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CADTH COMMON DRUG REVIEW

Clinical Review Report

Semaglutide (Ozempic)

(Novo Nordisk Canada Inc.)

Indication: For the treatment of adult patients with type 2 diabetes mellitus to improve glycemic control, in combination with metformin (second-line treatment), and in combination with metformin and sulfonylurea (third-line treatment).

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Table of Contents

Tables

Figures

Abbreviations

A1C	glycated hemoglobin
ADA	American Diabetes Association
AE	adverse event
BMI	body mass index
CFB	change from baseline
CI	confidence interval
CoV	coefficient of variance
CVOT	cardiovascular outcome trial
CV	cardiovascular
DB	double-blind
DBP	diastolic blood pressure
DIC	deviance information criterion
DPP-4	dipeptidyl peptidase-4
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DUL	dulaglutide
EAC	Event Adjudication Committee
eGFR	estimated glomerular filtration rate
EXE	exenatide
FAS	full analysis set
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
DCCPG	Diabetes Canada Clinical Practice Guidelines
HDL	high-density lipoprotein
HR	hazard ratio
HRQoL	health-related quality of life
IG	insulin glargine
ITC	indirect treatment comparison
ITT	intention-to-treat
LDL	low-density lipoprotein
LOCF	last observation carried forward
MACE	major adverse cardiovascular event
MAR	missing at random
MD	mean difference
MET	metformin
MI	myocardial infarction
MMRM	mixed model for repeated measurement
MTC	medullary thyroid carcinoma
NI	non-inferiority
NMA	network meta-analysis
OAD	oral antidiabetic drug
OL	open label
PP	per-protocol
RCT	randomized controlled trial

SAE	serious adverse event
SAS	safety analysis set
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SE	standard error
SEM	semaglutide
SF-36	Short Form (36) Health Survey
SGLT2	sodium-glucose cotransporter-2
SIT	sitagliptin
SU	sulfonylurea
TEAE	treatment-emergent adverse event
TZD	thiazolidinedione

Drug	Semaglutide (Ozempic)
Indication	The once-weekly treatment of adult patients with type 3 diabetes mellitus to improve glycemic control, in combination with: • Diet and exercise in patients for whom metformin is inappropriate due to contraindication or intolerance. • Metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control. • Metformin and a sulfonylurea (SU), when diet and exercise plus dual therapy with metformin and a SU do not achieve adequate glycemic control. • Basal insulin with metformin, when diet and exercise plus basal insulin with metformin do not achieve adequate glycemic control.
Reimbursement Request	• In combination with metformin for patients who have not achieved adequate glycemic control with metformin alone (second-line treatment). • In combination with metformin plus sulfonylurea for patients who have not achieved adequate glycemic control with metformin in combination with sulfonylurea (third-line treatment).
Dosage Form(s)	0.5 mg once-weekly injection 1 mg once-weekly injection
NOC Date	January 4, 2018
Manufacturer	Novo Nordisk Canada Inc.

Executive Summary

Introduction

Diabetes mellitus is a metabolic disease that is characterized by persistent elevations in blood glucose or hyperglycemia. Type 2 diabetes mellitus (T2DM) accounts for approximately 90% of cases of diabetes mellitus.[1] It has a significant impact on both individuals and societies. In Canada, this is one of the most common chronic diseases. Diabetes Canada estimated that 3.5 million people (9% of the population) were living with diabetes in 2018, and that this number will increase to 4.7 million people (11%) by 2028.[2]

Numerous pharmacological treatment options and combination therapy strategies are available when blood glucose levels are not adequately controlled by lifestyle modifications alone.[3] Metformin (MET) is considered first-line therapy and is indicated for most patients. A second or third agent may be added in addition to MET. Injectable agents such as glucagon-like peptide-1 (GLP-1) receptor agonists, and insulin and insulin analogues may also be added to MET, or patients can be switched to insulin.[4]

Semaglutide (SEM) is a selective long-acting GLP-1 receptor agonist that mimics or acts on the same receptor as endogenous hormone incretin.[5] It received Health Canada Notice of Compliance (NOC) on January 4, 2018. SEM is indicated for the improvement of glycemic control in adult patients with type 2 diabetes mellitus (T2DM) via once-weekly treatment, in combination with diet and exercise when MET is inappropriate due to contraindications or intolerance, or when adequate glycemic control has not been achieved with diet and exercise plus the maximum tolerated dose of MET, dual therapy with MET and a sulfonylurea (SU), or dual therapy with basal insulin and MET.[6]

The objective of this review was to perform a systematic review of the beneficial and harmful effects of semaglutide (SEM) at the recommended dose for the treatment of adult patients with T2DM.

Results and Interpretation

Included Studies

A total of eight phase III randomized controlled trials (RCTs), SUSTAIN-1 to SUSTAIN-7, and the Seino study, met the inclusion criteria for this systematic review (N = 308 to 3,297 per trial).

These trials evaluated the efficacy and safety of SEM 0.5 mg or 1 mg once weekly, alone or in combination with oral antidiabetic drugs (OADs) such as MET or MET plus a SU, or insulin, compared with placebo or active comparators in adults with T2DM and inadequate glycemic control with background therapy. All three placebo-controlled trials (SUSTAIN-1, 5, and 6)[7-9] and one active-controlled trial (SUSTAIN-2)[10] included a randomized double-blind treatment period, and all other active-controlled trials had an open-label design (SUSTAIN-3, 4, 7, and the Seino study).[11-14] The primary objective of the included trials was to compare the effect of SEM once-weekly treatment with the comparators on change in A1C from baseline, except for SUSTAIN-6 and the Seino study. “Time from randomization to first occurrence of major adverse cardiovascular event (MACE)” was the primary outcome in SUSTAIN-6. The occurrence of treatment-emergent adverse event (TEAE) was the primary outcome in the Seino study. The occurrence of diabetes-related comorbidities (macrovascular and microvascular) was also measured in the only cardiovascular outcomes trial (CVOT), SUSTAIN-6. Change in body weight, body mass index (BMI), blood pressure, and blood lipid profile were evaluated in all trials. Health-related quality of life (HRQoL) was evaluated in all trials but SUSTAIN-1 and the Seino study. Non-inferiority (NI) of treatment with SEM versus active comparators (SUSTAIN-2, 3, 4, and 7) on glycemic control was assessed in four SUSTAIN trials, based on pre-defined NI margin of 0.3% or 0.4%. NI of treatment with SEM compared with placebo on increase in cardiovascular (CV) events was assessed in patients who had prior or concomitant CV conditions in SUSTAIN-6. In SUSTAIN-2, 3, 4, 6, and 7, superiority of SEM compared with placebo or active treatment for either change in A1C or change in body weight was tested if NI test criterion for the primary end point was met. Treatment duration of the included trials ranged from 30 weeks to 104 weeks.

Baseline characteristics were generally similar between groups within trials although some differences in the proportion of males and average body weight were noted in SUSTAIN-1, as well as differences in the duration of diabetes in SUSTAIN-4.

Efficacy

SEM used as first-line, second-line, or third-line therapy was associated with statistically significant reductions in A1C after 30 to 56 weeks compared with placebo or active treatment. SEM 1 mg was more likely to be related to greater reduction in A1C compared with SEM 0.5 mg.

First-line therapy (add-on to diet and exercise):

- When compared with placebo, the between-group difference in A1C reduction was –1.43% to –1.53% (SUSTAIN-1).

Second-line therapy (add-on to MET):

- When compared with sitagliptin (SIT), the between-group difference in A1C reduction was [redacted] (subgroup data from SUSTAIN-2).
- When compared with EXE, the between-group difference in A1C reduction was [redacted] (subgroup data from SUSTAIN-3).
- When compared with insulin glargine, the between-group difference in A1C reduction was [redacted](subgroup data from SUSTAIN-4).
- When compared with DUL, the between-group difference in A1C reduction was –0.40% to –0.41% (SUSTAIN-7).

Third-line therapy (add-on to MET + SU or MET + thiazolidinedione [TZD]):

- When compared with SIT, the between-group difference in A1C reduction was [redacted](subgroup data from SUSTAIN-2).
- When compared with EXE, the between-group difference in A1C reduction was [redacted] (subgroup data from SUSTAIN-3).
- When compared with insulin glargine, the between-group difference in A1C reduction was [redacted](subgroup data from SUSTAIN-4).

In addition, results for glycemic control were reported for patients received SEM as add-on to one or two OADs background antidiabetic therapy: the difference between SEM (add-on to standard of care, basal insulin alone, or basal insulin plus MET) and placebo in A1C reduction was –0.66% to –1.75%, $P < 0.0001$; the difference between SEM (add-on to diet and exercise or diet and exercise plus one OAD) and SIT in A1C reduction was –1.13% to –1.14%, $P < 0.0001$. The change in A1C versus placebo or an active control was considered clinically relevant by the clinical expert consulted for this review. SUSTAIN-2, 3, 4, and 7 were NI trials, and the results suggested that SEM was noninferior and superior to the active control for the change from baseline in A1C based on a pre-defined NI margin of 0.3% or 0.4%.

SEM used as first-line, second-line, or third-line therapy was also associated with statistically significant reductions in weight after 30 to 56 weeks compared with placebo or active treatment. SEM 1 mg was more likely to be related to greater reduction in weight compared with SEM 0.5 mg.

First-line therapy (add-on to diet and exercise):

- When compared with placebo, the between-group difference in weight reduction was –2.75 kg to 3.56 kg (SUSTAIN-1).

Second-Line therapy (add-on to MET):

- When compared with SIT, the between-group difference in weight reduction was [redacted](subgroup data from SUSTAIN-2).
- When compared with EXE, the between-group difference in weight reduction was [redacted](subgroup data from SUSTAIN-3).
- When compared with insulin glargine, the between-group difference in weight reduction was [redacted](subgroup data from SUSTAIN-4).
- When compared with DUL, the between-group difference in weight reduction was –2.26 kg to –3.55 kg (SUSTAIN-7).

Third-line therapy (add-on to MET + SU or MET + TZD):

- When compared with SIT, the between-group difference in weight reduction was [redacted] (subgroup data from SUSTAIN-2).
- When compared with EXE, the between-group difference in weight reduction was [redacted] (subgroup data from SUSTAIN-3).
- When compared with insulin glargine, the between-group difference in weight reduction was [redacted] (subgroup data from SUSTAIN-4).

In addition, results for weight reduction were also reported for patients received SEM as add-on to one or two OADs background antidiabetic therapy: the difference between SEM (add-on to standard of care, basal insulin alone, or basal insulin plus MET) and placebo in weight reduction was –2.31 kg to –5.06 kg, $P < 0.0001$; the difference between SEM (add-on to diet and exercise or diet and exercise plus one OAD) and SIT in weight reduction was –2.22 kg to –3.88 kg, $P < 0.0001$. The change in weight versus placebo or an active control was considered clinically relevant by the clinical expert consulted for this review.

When compared with placebo or active controls, SEM used as first-line, second-line, or third-line therapy was generally not associated with any statistically significant improvements in blood pressure or blood lipids in the full population of the trials. In addition, the between-group differences in blood pressure or blood lipids were not considered clinically important as per the clinical expert.

Risk of cardiovascular (CV) events was examined in patients with existing CV disease in the two-year trial SUSTAIN-6. The results showed that the proportion of patients with first MACE (CV death, non-fatal myocardial infarction [MI], and non-fatal stroke) was lower with SEM therapy (6.6%) compared with placebo (8.9%). Treatment with either dose of SEM was also associated with numerically lower events of non-fatal MI and non-fatal stroke, while the number of deaths from CV causes was similar across treatment groups. The estimated hazard ratio (HR) was 0.74 (95% confidence interval [CI] 0.58 to 0.95, below the NI margin of 1.8), indicating that SEM statistically significantly reduced the risk of experiencing a MACE by 26% when compared with placebo, in patients with existing CV disease. *P* value was 0.0167 for the superiority test. Treatment with SEM was also associated with numerically lower events of revascularization, unstable angina pectoris requiring hospitalization, or hospitalization for heart failure. Furthermore, proportions of new or worsening nephropathy were numerically lower in the SEM groups than in the placebo groups, while proportions of diabetic retinopathy complications were numerically higher in the SEM groups than in the placebo groups: [redacted] with SEM 0.5 mg, [redacted] with SEM 1 mg, [redacted] with placebo 0.5 mg, and [redacted] with placebo 1 mg.

SEM was compared with GLP-1 receptor agonist and DPP-4 inhibitors in the SUSTAIN trials. However, direct evidence is lacking for other comparisons. The manufacturer submitted three separate indirect treatment comparisons (ITCs) in patients inadequately control on one OAD that compared SEM to other GLP-1 agonists, SGLT2 inhibitors, and SU. Results of these ITCs suggested a reduction in A1C and body weight with SEM versus the comparators; however, the data should be interpreted with caution, due to the use of separate networks for each drug class rather than one connected network that included all drugs relevant to the decision-making comparator set, and the relatively poor quality of these ITCs.

Harms

The adverse event profile of SEM appears to be similar to other drugs in the class and no new safety signals were identified based on the included trials. The overall frequency of AEs was similar between treatment groups within trials. In the placebo-controlled trials (except for SUSTAIN-6), AEs were reported by 56% to 69% of patients treated with SEM, and by 54% to 58% of patients treated with placebo. In the active-controlled trials, AEs were reported by 68% to 75% of patients with SEM, and 62% to 76% of patients with other active treatments. Serious adverse events (SAEs) were reported by 4% to 7% of patients received placebo, 5% to 9% of patients received SEM (2% to 3% of these SAEs were gastrointestinal [GI] disorders), and 2% to 8% of patient received other active treatments. The rates of AEs leading to treatment discontinuation were 4% to 7% in the placebo group, 3% to 10% in the SEM group, and 1% to 7% in other active treatment groups. The frequency of GI disorders was higher in the SEM group, compared with placebo, or active comparator which was not a GLP-1 receptor agonist, such as SIT or insulin. The frequency of hypoglycemia was highest in the insulin glargine group in SUSTAIN-4 (39.4%). The risk of hypoglycemia for SEM was comparable to the other GLP-1 receptor agonists such as EXE and DUL, and it was lower than SIT and insulin glargine. Severe hypoglycemia was reported infrequently in the included trials.

Patients in the CV outcome trial (SUSTAIN-6) reported higher AE rates compared with the other SUSTAIN trials. The incidence of TEAEs was 88% to 89%. The rates of SAEs were 32.1%, 29.3%, and 34.9% in patients who received SEM 0.5 mg, SEM 1 mg, and placebo, respectively. The rates of AEs leading to premature treatment discontinuation were 11.5% to 14.5% in the SEM groups and 6.7% in the placebo group.

The ITC that examined all-cause mortality among patients with T2DM treated with GLP-1 agonists, DPP-4 inhibitors, or SGLT2 inhibitors suggested that the risk of death among those who received SEM was similar to other therapies with the exception of empagliflozin. These data should be interpreted with caution due to potential heterogeneity in-trial and patient characteristics of the included studies that was not adequately explored in the ITC.

Potential Place in Therapy[1]

The first-line therapy for most patients with T2DM remains MET. The place for SEM is as second- or third-line therapy for patients not achieving their glycemic target.

The Diabetes Canada Clinical Practice Guidelines (DCCPG) recommend that, for patients with clinical CV disease, the preferred choice for second-line therapy is an agent with demonstrated CV benefit. The DCCPG list empagliflozin (Grade A, Level 1A), liraglutide (Grade A, Level 1A) or canagliflozin (Grade C, Level 2) as agents meeting this criterion. SEM would be an additional agent that could be included in this category, and it would be the only once-weekly medication in this group. For patients without clinical CV disease, the DCCPG recommend choosing the second-line therapy best suited to the individual. In particular, avoidance of hypoglycemia or weight gain is a priority for many patients, so DPP-4 inhibitors, GLP-1 receptors agonists, or SGLT2 inhibitors can be considered as potential agents. SEM would be one more within this already extensive category. For all patients, continuing escalation of therapy by the addition of third- or fourth-line agents may be needed to achieve glycemic targets.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Only about 50% of T2DM patients in Canada achieve glycemic targets,[15] which represents the primary unmet medical need for this population. Continuing escalation of therapy with more and more add-on agents is burdensome for patients, increases their exposure to potential adverse effects, and may impair their adherence with therapy. Although insulin is particularly effective at improving glycemia, treatment intensification in the real world is often limited by hypoglycemia, as well patient reluctance to take multiple daily injections. SEM may in part fulfill this unmet need, as the data suggest that it is particularly efficacious at lowering A1C, it does not lead to hypoglycemia or weight gain, and although it is an injectable, it is only administered once per week (rather at least once per day for insulin). Thus, patients taking SEM may be able to achieve lower A1C levels without hypoglycemia than those on other agents, reducing the need for intensification with further add-on therapy.

The patients who will receive this drug in practice are patients with type 2 diabetes who require intensification of therapy to meet glycemic targets and who are willing to take a once-weekly injectable medication. These will include patients with clinical cardiovascular disease, but also a substantial proportion of the much larger population of patients without clinical cardiovascular disease. There will be no barriers to identifying such patients.

Conclusions

In patients with type 2 diabetes and inadequate glycemic control on previous antidiabetic treatment, semaglutide 0.5 mg or 1 mg as monotherapy, or as add-on therapy to metformin, or metformin plus another antidiabetic agent, was associated with statistically significant reductions in A1C and body weight as compared with placebo plus add-on therapies. Semaglutide 0.5 mg or 1 mg was superior to active treatments, such as DPP-4 inhibitors, other GLP-1 receptor agonists, or insulin glargine, in reduction in A1C and body weight.

In patients who have type 2 diabetes and existing cardiovascular disease, semaglutide 0.5 mg or 1 mg as add-on to standard of care, does not increase the risk of certain cardiovascular events (measured with MACE) and may reduce the risk of cardiovascular events as compared with placebo.

HRQoL was improved for all treatment groups within trials, but statistically significant differences between treatment groups were not always observed. In addition, treatment with semaglutide was associated with lowered systolic blood pressure and diastolic blood pressure, and improved blood lipid profile, compared with placebo or other active treatments. However, statistically significant differences were not always observed.

The results of the manufacturer-provided ITCs suggested a reduction in A1C and weight with semaglutide versus other GLP-1 agonists, SGLT2 inhibitors, and SU in patients inadequately controlled on one OAD. However, the data were analyzed as separate networks for each drug class, rather than one connected network that included all drugs relevant to the decision-making comparator set. The restricted scope of the comparisons limited the evidence included in each analysis, excluded comparisons with the DPP-4 inhibitor class, and limited the applicability of the findings. No conclusions could be drawn from the indirect comparisons of semaglutide versus other GLP-1 agonists or SGLT2 inhibitors as add-on to 1 or 2 OAD due to fundamental limitations of these analyses.

The adverse event profile of SEM appears to be similar to other drugs in the class and no new safety signals were identified based on the included trials.

It is unclear whether semaglutide fills a specific unmet clinical need for patients with type 2 diabetes. It is the fifth GLP-1 receptor agonist approved for the management of type 2 diabetes in Canada; and given the availability of a number of antihyperglycemics from other drug classes, semaglutide represents an additional treatment option.

Table 1: Summary of Primary Outcomes

Population/ Study	Treatment	N	Baseline A1C, % Mean (SD)	Change from Baseline A1C, % Mean (SE)	Between-Group Difference, Mean (95% CI)	*P* value
First-Line Therapy						
SUSTAIN-1	SEM 0.5 mg	128	8.09 (0.89)	–1.45 (0.10)	–1.43 (–1.71 to –1.15)	*P* < 0.0001
	SEM 1 mg	130	8.12 (0.81)	–1.55 (0.10)	–1.53 (–1.81 to –1.25)	*P* < 0.0001
	Placebo	129	7.95 (0.85)	–0.02 (0.10)	–	
Second-Line Therapy (add-on to MET)						
SUSTAIN-2	SEM 0.5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SEM 1 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SIT	[redacted]	[redacted]	[redacted]	[redacted]	
SUSTAIN-3	SEM 1 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE	[redacted]	[redacted]	[redacted]	[redacted]	
SUSTAIN-4	SEM 0.5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SEM 1 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	IG	[redacted]	[redacted]	[redacted]	[redacted]	
SUSTAIN-7	SEM 0.5 mg	301	8.3 (0.96)	–1.51 (0.06)	–0.40 (–0.55 to –0.25)	*P* < 0.0001
	SEM 1 mg	300	8.2 (0.92)	–1.78 (0.06)	–0.41 (–0.57 to –0.25)	*P* < 0.0001
	DUL 0.75 mg	299	8.2 (0.91)	–1.11 (0.05)	–	
	DUL 1.5 mg	299	8.2 (0.89)	–1.37 (0.06)	–	
Third-Line Therapy (add-on to MET + SU or MET + TZD)						
SUSTAIN-2	SEM 0.5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SEM 1 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SIT	[redacted]	[redacted]	[redacted]	[redacted]	
SUSTAIN-3	SEM 1 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	EXE	[redacted]	[redacted]	[redacted]	[redacted]	
SUSTAIN-4	SEM 0.5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SEM 1 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	IG	[redacted]	[redacted]	[redacted]	[redacted]	

CI = confidence interval; DUL = dulaglutide; EXE = exenatide; A1C = glycated hemoglobin; IG = insulin glargine; MET = metformin; NA = not applicable; SD = standard deviation; SE = standard error; SEM = semaglutide; SIT = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

Source: Clinical Study Reports of SUSTAIN-1[7] and SUSTAIN-7;[13] additional information of subgroup analyses in SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4 provided in Submission.[16]

Table 2: Summary of Harms

Study	Treatment	N	Patients with ≥ 1 AE, n (%)	Patients with ≥ 1 SAE, n (%)	AEs leading to premature treatment discontinuation, n (%)	Death, n (%)	GI disorders, n (%)	Severe hypoglycemia, n (%)
SUSTAIN-1	SEM 0.5 mg	128	82 (64.1)	7 (5.5)	8 (6.3)	0	49 (38.3)	0
	SEM 1 mg	130	73 (56.2)	7 (5.4)	7 (5.4)		50 (38.5)	
	placebo	129	69 (53.5)	5 (3.9)	3 (2.3)		19 (14.7)	
SUSTAIN-2	SEM 0.5 mg	409	306 (74.8)	30 (7.3)	33 (8.1)	2 (0.5)	178 (43.5)	0
	SEM 1 mg	409	292 (71.4)	30 (7.3)	39 (9.5)	1 (0.2)	163 (39.9)	0
	SIT	407	292 (71.7)	29 (7.1)	12 (2.9)	3 (0.7)	96 (23.6)	2 (0.5)
SUSTAIN-3	SEM 1 mg	404	303 (75.0)	38 (9.4)	38 (9.4)	2 (0.5)	169 (41.8)	1 (0.2)
	EXE	405	309 (76.3)	24 (5.9)	29 (7.2)	0	135 (33.3)	0
SUSTAIN-4	SEM 0.5 mg	362	253 (69.9)	22 (6.1)	20 (5.5)	4 (1.1)	149 (41.2)	2 (0.6)
	SEM 1 mg	360	264 (73.3)	17 (4.7)	27 (7.5)	0	156 (43.3)	5 (1.4)
	IG	360	235 (65.3)	18 (5.0)	4 (1.1)	2 (0.6)	54 (15.0)	5 (1.4)
SUSTAIN-5	SEM 0.5 mg	132	91 (68.9)	8 (6.1)	6 (4.5)	0	36 (27.3)	0
	SEM 1 mg	131	84 (64.1)	12 (9.2)	8 (6.1)		45 (34.4)	2 (1.5)
	placebo	133	77 (57.9)	9 (6.8)	1 (0.8)		21 (15.8)	1 (0.8)
SUSTAIN-6	SEM 0.5 mg	823	732 (88.9)	264 (32.1)	95 (11.5)	30 (3.6)	552 (67.1)	14 (1.7)
	SEM 1 mg	819	722 (88.2)	240 (29.3)	119 (14.5)	32 (3.9)	658 (80.4)	9 (1.1)
	placebo	1,644	1,453 (88.4)	574 (34.9)	110 (6.7)	60 (3.6)	516 (31.4)	26 (1.6)
SUSTAIN-7	SEM 0.5 mg	301	204 (67.8)	17 (5.6)	24 (8.0)	1 (0.3)	129 (42.9)	0
	SEM 1 mg	300	207 (69.0)	23 (7.7)	29 (9.7)	1 (0.3)	133 (44.3)	1 (0.3)
	DUL 0.75 mg	299	186 (62.2)	24 (8.0)	14 (4.7)	2 (0.7)	100 (33.4)	1 (0.3)
	DUL 1.5 mg	299	221 (73.9)	22 (7.4)	20 (6.7)	2 (0.7)	143 (47.8)	2 (0.7)
Seino	SEM 0.5 mg	103	77 (74.8)	6 (5.8)	3 (2.9)	0	37 (35.9)	0
	SEM 1 mg	102	73 (71.6)	2 (2.0)	11 (10.8)		41 (34.2)	1 (1.0)
	SIT	103	68 (66.0)	2 (1.9)	2 (1.9)		6 (5.8)	0

AE = adverse event; DUL = dulaglutide; EXE = exenatide; GI = gastrointestinal; IG = insulin glargine; SAE = serious adverse event; SEM = semaglutide; SIT = sitagliptin.

Source: Clinical Study Reports of SUSTAIN-1 to SUSTAIN-7[7-13] and the Seino study.[14]

Introduction

Disease Prevalence and Incidence

Diabetes mellitus is a metabolic disease that is characterized by persistent elevations in blood glucose or hyperglycemia. There are two main subtypes of diabetes mellitus: type 1 diabetes mellitus, which is caused by inadequate secretion of insulin from pancreatic beta cells, and type 2 diabetes mellitus (T2DM), which results from cells that are unresponsive to the insulin that is produced. T2DM is more common than type 1, accounting for approximately 90% of cases of diabetes mellitus.[1]

The etiology of diabetes mellitus is associated with genetic factors and environmental triggers are believed to play a role in the development of disease.[17] Onset of T2DM typically occurs around 40 years of age or older,[18] although this is changing with the increase in obesity and sedentary behaviours leading to more frequent diagnosis of T2DM in children and younger people.[19] Poor diet, minimal exercise, and associated weight gain are considered major risk factors for T2DM.[20] Patients with T2DM who in the initial stages of their disease are able to secrete insulin but who are hyperinsulinemic, may progress to a stage where insulin secretion is reduced, similar to type 1 diabetes mellitus. As described by the patient input received for this report (Appendix 1), common symptoms of diabetes include extreme fatigue, unusual thirst, frequent urination, and weight change. More serious complications may present for patients with poor blood glucose control. For example, low blood glucose may cause confusion, coma, or seizures. High levels of glucose may lead to more long-term issues such as damage to the nerves and blood vessels, which increases the risk of blindness, heart disease, kidney disease, and damage to the extremities. Patients also report that diabetes has a great impact on patients' emotional, social, and economic status.

Diabetes has a significant impact on both individuals and societies. The prevalence of diabetes is increasing at a dramatic rate around the world. In a report produced by the World Health Organization, there was an estimated 422 million adults living with diabetes globally in 2014, up from 108 million in 1980.[19] Further, this number is projected to increase to 693 million by 2045 if the current trends continue.[17] Diabetes is also a significant problem in Canada, as one of the most common chronic diseases in the country. Diabetes Canada estimated that 3.5 million people (9% of the population) were living with diabetes in 2018, and that this number will increase to 4.7 million people (11%) by 2028.[2] People with diabetes are more likely to be hospitalized and to experience complications requiring care by a specialist. It is estimated that, by 2020, the direct and indirect costs of diabetes for the Canadian health care system will increase to C$16.9 billion per year.[18]

Standards of Therapy

Treatment regimens and therapeutic targets should be individualized in patients with T2DM due to the heterogeneous nature of the disease. Initial treatment often consists of lifestyle modifications through diet and exercise. When blood glucose levels are not adequately controlled by lifestyle modifications alone, pharmacological treatment becomes necessary.[3] There are many classes of antihyperglycemic agents used to treat T2DM, which include both insulin and noninsulin therapies.[3] Metformin (MET) is considered first-line therapy and is indicated for most patients. If treatment through lifestyle modifications and MET monotherapy fail to achieve adequate glycemic control, a second or third agent may be added in addition to MET.

There are several oral antidiabetic drugs (OADs) that may be used with MET, such as sulfonylureas (SU), meglitinides, thiazolidinediones (TZD), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter-2 (SGLT2) inhibitors. Injectable agents, such as glucagon-like peptide-1 (GLP-1) receptor agonists, and insulin and insulin analogues (rapid-acting, intermediate, or long-acting forms), may also be considered as an add-on to MET, or patients can be switched to insulin.[4] However, according to the 2018 Diabetes Canada Clinical Practice Guidelines (DCCPG), it is recommended that DPP-4 inhibitors, GLP-1 receptor agonists, or SGLT2 inhibitors be considered first as hypoglycemia and weight gain are less of an issue with these agents, provided contraindications, accessibility, and affordability are considered.[3]

Although there are currently numerous therapeutic options and combination therapy strategies available, none of the available therapies are curative and many patients still have difficulty achieving adequate glycemic control.[21] Further, there are certain disadvantages to consider with some of the options, such as weight gain or hypoglycemia associated with the use of TZDs, SUs, and insulin.[3,22] In contrast, some agents, such as SGLT2 inhibitors and GLP-1 receptor agonists, may be advantageous in terms of cardiovascular (CV) effects, which is a particular concern as CV effects are common and a leading cause of death among those with diabetes.[4,23,24]

It is recommended that the selection of a second agent is patient specific, and based on the efficacy and safety profile of available agents.[3] This includes various factors, such as the effectiveness of an agent at lowering blood glucose and glycated hemoglobin (A1C), concerns regarding hypoglycemia, effects on body weight, and the ability to reduce the risk of diabetic microvascular and/or CV complications.[3] Additional considerations include patient's renal function, other comorbidities, planning pregnancy, cost and coverage, ease of administration, and patient preference.[3]

Drug

Semaglutide (SEM) is a selective long-acting GLP-1 receptor agonist that mimics or acts on the same receptor as endogenous hormone incretin.[5] In doing so, SEM increases glucose-dependent insulin secretion and decreases glucagon secretion, while also slowing gastric emptying. Overall, this increases first- and second-phase insulin secretion with the expectation of improved glycemic control.[5,6,25] SEM received Health Canada Notice of Compliance (NOC) in January 4, 2018. As per the Health Canada–approved product monograph, SEM is indicated for the improvement of glycemic control in adult patients with T2DM via once-weekly treatment, in combination with diet and exercise when MET is inappropriate due to contraindications or intolerance, or when adequate glycemic control has not been achieved with diet and exercise plus: the maximum tolerated dose of MET, dual therapy with MET and a sulfonylurea (SU), or dual therapy with basal insulin and MET.[6]

The recommended route of administration for SEM is subcutaneously in the abdomen, thigh, or upper arm.[6,25] It is available as a pre-filled multi-dose pen delivering doses of 0.25 mg or 0.5 mg, as well as a pre-filled pen that delivers a dose of 1 mg.[6] It is recommended that a patient begins with a once-weekly sub-therapeutic dose of 0.25 mg, followed by an increase to 0.5 mg per week after four weeks. For patients that require additional glycemic control after four weeks, the dose may be increased to 1 mg once weekly, which is the maximum recommended dose.[6,25]

Other GLP-1 receptor agonists currently approved in Canada are dulaglutide, exenatide, liraglutide, and lixisenatide.

Key characteristics of currently available antihyperglycemic therapies are presented in Table 3.

Table 3: Key Characteristics of Available Antihyperglycemic Agents

	GLP-1 Analogues	DPP-4 Inhibitors	Insulin/Insulin Analogues	TZD	SGLT2 Inhibitors	MET	SU
Mechanism of Action	Mimic GLP-1, which: • leads to insulin secretion • delays glucagon release • delays gastric emptying • reduces food intake	Increase GLP-1 by inhibiting the DPP-4 enzyme, which inactivates GLP-1 and: • leads to insulin secretion • inhibits glucagon release • delays gastric emptying • reduces food intake	Substitute for endogenously secreted insulin	PPAR-gamma agonists: • increase uptake of free fatty acid • increase uptake of glucose • reduce glucose synthesis	Inhibits the SGLT2 transporter in the kidney, leading to increased glucose excretion	Reduces gluconeogenesis, increases conversion of glucose to glycogen, and increases degradation of glucose	Promotes insulin secretion by binding to the SU receptor
Indication[a]	T2DM that cannot be adequately controlled by diet and exercise alone Monotherapy (not EXE and LIX), or in combination with MET, or SU (EXE and LIX only), or PIO (LIX only), or MET + SU, or MET + PIO (LIX only), or insulin ± MET Add-on in patients with established CV disease (LIR only)	T2DM that cannot be adequately controlled by diet and exercise alone Monotherapy (not SAX), or in combination with MET, or SU (not SIT), or PIO (ALO and SIT only), or MET + SU (not ALO), or MET + PIO (ALO and SIT only), or insulin ± MET (not LIN)	Patients with DM who require insulin for control of hyperglycemia	T2DM that cannot be adequately controlled by diet /exercise alone, or when all other OADs (in monotherapy or in combination) fail to adequately control blood glucose, or are inappropriate due to contraindications or intolerance	T2DM that cannot be adequately controlled by diet and exercise alone Monotherapy, or in combination with MET, or SU (CAN and DAP only), or SIT (DAP only), or PIO (EMP only), or MET + SU (not ERT), or MET + SIT (not EMP), or MET + PIO (CAN and EMP only), or insulin ± MET (not ERT) Add-on in patients with established CV disease (CAN and EMP only)	T2DM that cannot be controlled by proper dietary management, exercise, and weight reduction, or when insulin therapy is not appropriate. Treatment of obese patients with diabetes.	T2DM in adults, alone or in combination with other anti-hyperglycemic agents, as an adjunct to exercise and diet.
Route of Administration	SC	Oral	SC	Oral	Oral	Oral	Oral
Recommended Dose	Varies by drug	Varies by drug	Titrated, depending on regimen can be	4 mg to 8 mg per day, taken once daily	Varies by drug, taken once daily	850 mg to 1,000 mg twice daily,	Varies by drug, taken once or twice daily

	GLP-1 Analogues	DPP-4 Inhibitors	Insulin/Insulin Analogues	TZD	SGLT2 Inhibitors	MET	SU
			given from 1 to 4 or more times per day			maximum of 2,550 mg daily	
Serious Side Effects / Safety Issues	**Warnings/ precautions** • Thyroid C-cell Tumours • prolonged PR interval • pancreatitis • GI disorders **Contraindications** • Personal or family history of MTC or in patients with MEN2 • During pregnancy or breast-feeding women • ESRD or severe renal impairment (creatinine clearance < 30 mL/min), including patients receiving dialysis	**Warnings/ precautions** • Severe hepatic impairment • Pancreatitis • HF • Immune suppression • hypersensitivity reactions • bullous pemphigoid **Contraindications** • Diabetic ketoacidosis	**Warnings/ precautions** • Hypoglycemia • Immune responses	**Serious warning** • Bone fractures in women • Exacerbation of fluid retention and congestive HF • Increasing risk of cardiac ischemia **Warnings/Precautions** • Bladder cancer • HF • Hepatitis /hepatic failure **Contraindications** • Patients with HF • Serious hepatic impairment • Pregnancy	**Serious warning** • Diabetic ketoacidosis **Warnings/Precautions** • Reduced intravascular volume • Hypoglycemia when combined with antihyperglycemics • Increase in LDL-C • Hyperkalemia • Impaired renal function • Genital mycotic infections • Urinary tract infection • Lower limb amputation • Fractures **Contraindications** • Patients who experience renal impairment with eGFR < 30 to 60 mL/min/1.73 m2 (drug dependent), ESRD, or patients on dialysis	**Serious warning** • Lactic acidosis (rare) • Use in patients with excessive alcohol intake **Contraindications** • Acute or chronic metabolic acidosis including ketoacidosis • Severe hepatic dysfunction • Impaired or unknown renal function • Excessive alcohol intake • CV collapse and in disease states related to hypoxemia • During stress conditions • Severe dehydration or shock	**Precautions** • Hypoglycemia **Contraindications** • Ketoacidosis • Severe liver, thyroid, or renal impairment

ALO = alogliptin; CAN = canagliflozin; CV = cardiovascular; DAP = dapagliflozin; DM = diabetes mellitus; DPP-4 = dipeptidyl peptidase-4; DUL = dulaglutide; eGFR = estimated glomerular filtration rate; EMP = empagliflozin; ERT = ertugliflozin; ESRD = end-stage renal disease; EXE = exenatide; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; HF = heart failure; IG = insulin glargine; LDL-C = low-density lipoprotein cholesterol; LIN = linagliptin; LIR = liraglutide; LIX = lixisenatide; MET = metformin; MEN2 = multiple endocrine neoplasia type 2; MTC = medullary thyroid carcinoma; OAD = oral antidiabetic drug; PIO = pioglitazone; PPAR = peroxisome proliferator-activated receptor; SAX = saxagliptin; SC = subcutaneous; SEM = semaglutide; SGLT2 = sodium-glucose cotransporter-2; SIT = sitagliptin; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione.

[a] Health Canada indication.

Source: e-CPS and lixisenatide product monograph.[25,26]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of semaglutide injection (1.34 mg/mL) for the treatment of adult patients with T2DM.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CADTH Common Drug Review (CDR) and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient Population	Adult patients with T2DM who have inadequate glycemic control with diet or exercise alone, or on therapy with metformin alone, sulfonylurea in combination with metformin, or basal insulin in combination with metformin, as adjunct to diet and exercise. **Subgroups** • Baseline A1C • BMI and/or body weight • Background diabetes therapy (drug naive vs. oral antidiabetic drug vs. insulin) • History of cerebrovascular or cardiovascular disease • Renal function
Intervention	Semaglutide SC injection 0.5 mg or 1 mg once weekly, as monotherapy or add-on therapy with one or more antidiabetic drugs
Comparators	One or more of the following: • Metformin • Sulfonylureas • SGLT2 inhibitors (i.e., canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) • Other GLP-1 analogues (i.e., dulaglutide, liraglutide, lixisenatide, exenatide) • DPP-4 inhibitors (i.e., alogliptin, linagliptin, sitagliptin, saxagliptin) • Thiazolidinediones (i.e., pioglitazone, rosiglitazone) • Meglitinides (i.e., repaglinide) • Alpha-glucosidase inhibitors (i.e., acarbose) • Insulin/insulin analogues (including basal and prandial regimens) or • placebo

Outcomes	**Efficacy outcomes:**
	• Glycemic control (e.g., A1C)[a]
	• Mortality (all-cause, cardiovascular related)
	• Diabetes-related morbidity[a]
	  ○ Macrovascular, i.e., CVD, cerebrovascular disease, or peripheral vascular disease, MI, stroke, etc.
	  ○ Microvascular, i.e., retinopathy, neuropathy, or nephropathy
	• Hospitalization (all-cause, cardiovascular related)
	• HRQoL[a]
	• Blood pressure
	• BMI and/or body weight[a]
	• Lipid profile

Outcomes	**Harms outcomes:** • AEs • SAEs

	• WDAEs • Mortality • Notable harms: GI AEs, hypoglycemia (including severe hypoglycemia), injection site reactions, anaphylaxis, pancreatitis, MTC
Study Design	Published and unpublished phase III or IV RCTs

A1C = glycated hemoglobin; AE = adverse event; BMI = body mass index; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; HRQoL = health-related quality of life; MI = myocardial infarction; MTC = medullary thyroid carcinoma; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Ozempic (semaglutide).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on December 21, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on April 10, 2019. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trial Registries, and Databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Results

Findings from the Literature

A total of eight studies were identified from the literature for inclusion in the systematic review (Figure 1). An overview of the included RCTs is provided in Table 5. Details of these trials are presented in Table 6 and Table 7. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

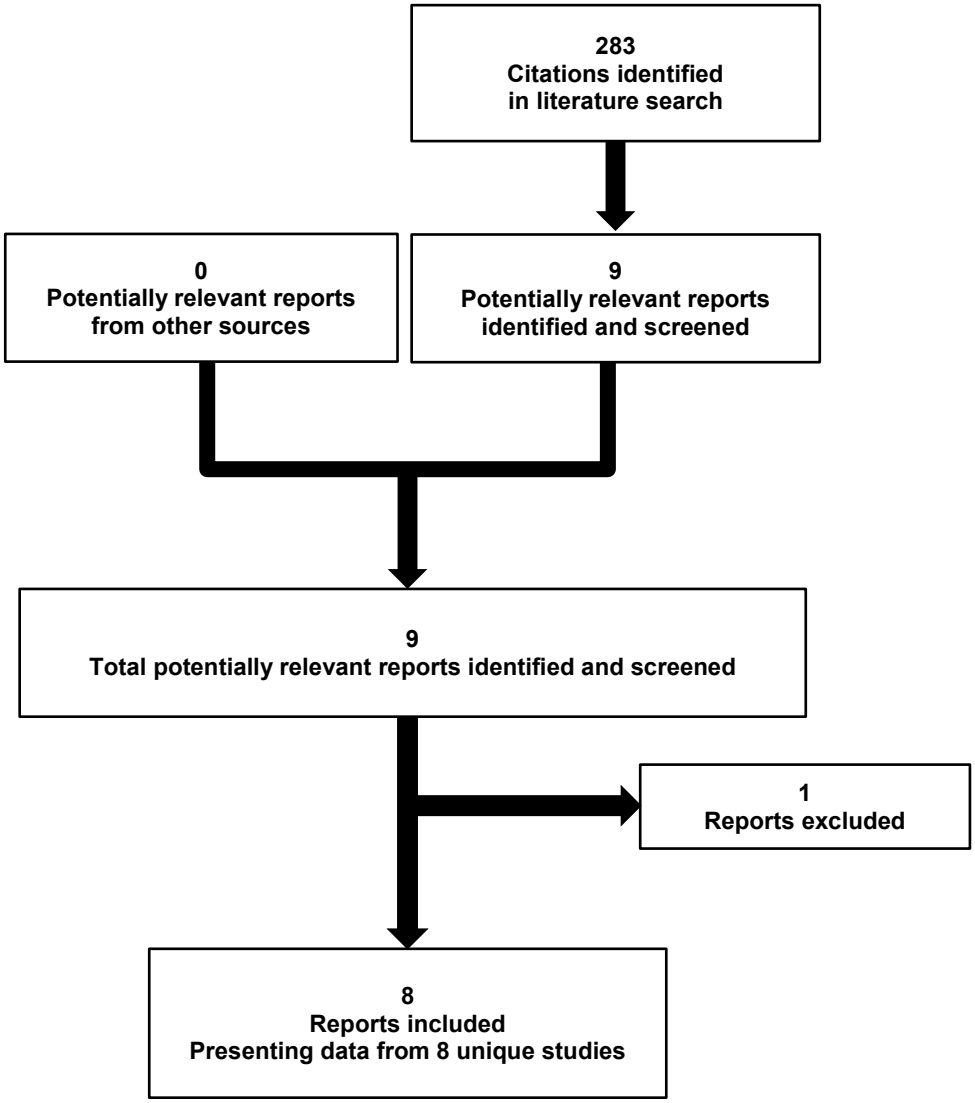


Table 5: Overview of Included Clinical Trials

	SUSTAIN-1	SUSTAIN-2	SUSTAIN-3	SUSTAIN-4	SUSTAIN-5	SUSTAIN-6	SUSTAIN-7	Seino
Stratification at Randomization	Not stratified	Not stratified	Not stratified	Stratified based on: • background OAD (MET vs. MET+ SU)	Stratified based on: • baseline A1C level • use of MET (yes vs. no)	Stratified based on: • Extent of CV disease • Insulin therapy • Renal function	Not stratified	Stratified based on: • Pre-trial treatment (diet/exercise vs. diet/exercise + OAD)
Population	Drug-naive T2DM patients N = 388	T2DM patients with inadequate glycemic control on treatment with MET, TZD or MET + TZD. N = 1,231	T2DM patients on stable diabetes treatment with 1 to 2 OADs of the following: MET, TZD, SU N = 813	T2DM patients, insulin-naive, inadequate glycemic control on stable diabetes treatment with MET or MET + SU N = 1,089	T2DM patients, inadequate glycemic control on stable diabetes treatment with basal insulin alone or basal insulin + MET N = 397	T2DM patients at high risk for CV events N = 3,297	T2DM patients with inadequate glycemic control on treatment with MET N = 1,201	Japanese T2DM patients treated with diet/exercise only, or diet/exercise in addition to OAD monotherapy N = 308
Intervention	SEM 0.5 mg SEM 1 mg (First-line)	SEM 0.5 mg SEM 1 mg (Second- or third-line)	SEM 1 mg (Second- or third-line)	SEM 0.5 mg SEM 1 mg (Second- or third-line)	SEM 0.5 mg SEM 1 mg (Third-line)	SEM 0.5 mg SEM 1 mg (Third-line)	SEM 0.5 mg SEM 1 mg (Second-line)	SEM 0.5 mg SEM 1 mg (First- or second-line)
Comparators	Placebo	SIT	EXE	IG	Placebo	Placebo	DUL	SIT
Background Therapy	Diet and exercise only	1 to 2 OADs of the following: MET TZD MET + TZD	1 to 2 OADs of the following: MET SU TZD	MET alone MET + SU	Basal insulin alone Basal insulin + MET	OAD naive 1 to 2 OADs Basal or pre-mix insulin alone, or combined with 1 to 2 OADs	MET alone	Diet and exercise only Diet and exercise + OAD
Per Cent of Background Therapy	Diet and exercise only 100%	MET 94% MET + TZD 5% Other 1%	MET 49% MET + SU 45%	MET 48% MET + SU 51%	Insulin 17% Insulin + MET 83%	T2DM treatment-naive 1.6% MET 73%[a]	MET 100%	Diet and exercise only 70%

	SUSTAIN-1	SUSTAIN-2	SUSTAIN-3	SUSTAIN-4	SUSTAIN-5	SUSTAIN-6	SUSTAIN-7	Seino
			Other 6%	Other 0.1%		Insulin 58%[a] SU 42.7%[a]		Diet and exercise + OAD (MET, SU, IG, TZD, DPP-4 inhibitors, etc.) 30%

A1C = glycated hemoglobin; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; DUL = dulaglutide; EXE = exenatide; IG = insulin glargine; MET = metformin; OAD = oral antihyperglycemic drug; SEM = semaglutide; SIT = sitagliptin; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione.

[a] Background therapy with MET, insulin, and SU were not mutually exclusive, therefore the sum of these percentage exceeded 100%.

Sources: Clinical Study Reports of SUSTAIN-1 to SUSTAIN-7,[7-13] and the Seino study.[14]

Table 6: Details of Included Studies (Placebo-Controlled RCTs)

		SUSTAIN-1	SUSTAIN-5	SUSTAIN-6
DESIGNS & POPULATIONS	**Study Design**	Phase III DB RCT	Phase III DB RCT	Phase III DB, NI RCT
	Locations	72 sites in Europe, Asia, Africa, and North America including Canada	90 sites in Europe, Asia, and the US	229 sites in Europe, Asia, North America including Canada, South America, Africa, Australia
	Randomized (N)	388	397	3,297
	Inclusion Criteria[a]	Adult patients with T2DM and treated with diet and exercise for ≥ 30 days prior to screening, with A1C 7.0% to 10.0%.	Adult patients with T2DM and on stable diabetes treatment with basal insulin alone or basal insulin + MET for 90 days prior to screening, with A1C 7.0% to 10.0%.	Adult patients with T2DM, and: • age ≥ 50 years at screening and clinical evidence of CV disease, or age ≥ 60 years at screening and subclinical evidence of CV disease; • antidiabetic drug naive, 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); • A1C ≥ 7.0% at screening.
	Exclusion Criteria	• Known or suspected hypersensitivity to trial product(s) or related products • Any chronic disorder or severe disease that might jeopardize a patient's safety or adherence with the protocol • History of chronic or acute pancreatitis • Screening calcitonin ≥ 50 ng/L • Personal or family history of MTC or MEN2 • Acute coronary or cerebrovascular event < 90 days prior to randomization • Heart failure (New York Heart Association Class IV) • Known proliferative retinopathy or maculopathy requiring acute treatment • Diagnosis of malignant neoplasm in the previous 5 years.		
	Additional Exclusion Criteria	Any glucose-lowering agents < 90 days prior to screening; impaired renal function (eGFR < 30 mL/min/1.73 m^2).	Glucose-lowering drugs other than those stated in Inclusion Criteria < 90 days before screening, severely impaired renal function (eGFR < 30 mL/min/1.73 m^2), Experienced > 3 episodes of severe hypoglycemia within 6 months prior to screening, and/or hypoglycemia unawareness.	Type 1 diabetes; use of GLP-1 RA or pramlintide < 90 days prior to screening; use of any DPP-4 inhibitor < 30 days prior to screening; treatment with insulin other than basal and pre-mixed insulin, < 90 days prior to screening; acute decompensation of glycemic control requiring immediate intensification of treatment to prevent acute complications of diabetes (e.g., diabetic ketoacidosis) < 90 days prior to screening; currently planned coronary, carotid, or peripheral artery revascularization; chronic hemodialysis or chronic peritoneal dialysis; end-stage liver disease; prior solid organ transplant or awaiting solid organ transplant; any acute condition or exacerbation of chronic condition that would interfere with the initial trial visit schedule and procedures.

		SUSTAIN-1	SUSTAIN-5	SUSTAIN-6
DRUGS	**Intervention**	SEM 0.5 mg SC q.w. SEM 1 mg SC q.w.	SEM 0.5 mg SC q.w. SEM 1 mg SC q.w.	SEM 0.5 mg SC q.w. SEM 1 mg SC q.w.
	Comparator(s)	Placebo 0.5 mg SC q.w. Placebo 1 mg SC q.w.		
DURATION	**Phase**			
	Screening	2 weeks		
	Double-blind	30 weeks	30 weeks	104 weeks
	Follow-up	5 weeks		
OUTCOMES	**Primary End Point**	Change in A1C		Time from randomization to first occurrence of a MACE (CV death, non-fatal MI, or non-fatal stroke)
	Other End Points	Change in: • body weight • BMI • SBP and DBP • blood lipids Safety	Change in: • body weight • BMI • SBP and DBP • blood lipids HRQoL Safety	Expanded composite CV outcome and its individual components; Composite microvascular outcome and its individual components; Change in: • A1C • body weight • BMI • SBP and DBP • blood lipids HRQoL Safety
NOTES	**Publications**	Sorli 2017[27]	Rodbard 2018[28]	Marso 2016[29]

A1C = glycated hemoglobin; BMI = body mass index; CV = cardiovascular; DB = double-blind; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HRQoL = health-related quality of life; MACE = major adverse cardiovascular event; MEN2 = multiple endocrine neoplasia type 2; MET = metformin; MI = myocardial infarction; MTC = medullary thyroid carcinoma; NI = non-inferiority; OAD = oral antidiabetic drug; q.w. = once weekly; RCT = randomized controlled trial; SBP = systolic blood pressure; SC = subcutaneous; SEM = semaglutide; T2DM = type 2 diabetes mellitus.

[a] In SUSTAIN-1, "diet/exercise" was specified as background therapy, however, this was not indicated for patients in SUSTAIN-5 and SUSTAIN-6.

Note: Three additional reports were included (Submission,[30] Health Canada Reviewer's Report,[31] and the FDA Medical Review[32]).

Source: Clinical Study Reports of SUSTAIN-1, 5, and 6.[7-9]

Table 7: Details of Included Studies (Active-Controlled RCTs)

		SUSTAIN-2	SUSTAIN-3	SUSTAIN-4	SUSTAIN-7	Seino
Designs & Populations	**Study Design**	Phase III, DB, NI RCT	Phase III, OL, NI RCT	Phase III, OL, NI RCT	Phase III, OL, NI RCT	Phase III, OL RCT
	Locations	124 sites in Asia, Europe, South America, and Mexico	141 sites in Europe, South America, and the US	196 sites in Europe, Asia, Africa, North America (not including Canada) and South America	196 sites in Europe, Asia, and the US	Multiple sites in Japan
	Randomized (N)	1,231	813	1,089	1,201	308
	Inclusion Criteria	Adult patients diagnosed with T2DM, insufficient glycemic control (A1C 7% to 10.5%) while on stable antihyperglycemic treatment for ≥ 90 days prior to screening.	Adult patients diagnosed with T2DM, insufficient glycemic control (A1C 7% to 10.5%) while on stable antihyperglycemic treatment for ≥ 90 days prior to screening.	Adult patients diagnosed with T2DM, insulin-naive, A1C 7% to 10%, while on stable antihyperglycemic treatment for ≥ 90 days prior to screening.	Adult patients diagnosed with T2DM, insufficient glycemic control (A1C 7% to 10.5%) while on stable antihyperglycemic treatment for ≥ 90 days prior to screening.	Adult patients (≥ 20 years) diagnosed with T2DM and treated with diet/exercise in addition to OAD monotherapy when A1C 6.5% to 9.5%, or treated with diet/exercise only if A1C 7% to 10.5%, at least 30 days before screening.
	Additional Inclusion Criteria[a]	Background antihyperglycemic treatment with MET, TZD, or MET + TZD	Background antihyperglycemic treatment with 1 to 2 OADs (MET ± TZD or MET ± SU)	Background antihyperglycemic treatment with MET ± SU	Background antihyperglycemic treatment with MET	Background treatment with diet/exercise, or diet/exercise + OAD
	Exclusion Criteria	• Known or suspected hypersensitivity to trial product(s) or related products • Any chronic disorder or severe disease that might jeopardize a patient's safety or adherence with the protocol • History of chronic or idiopathic acute pancreatitis • Screening calcitonin ≥ 50 ng/L • Personal or family history of MTC or MEN2 • eGFR < 60 mL/min/1.73 m^2 (< 30 mL/min/1.73 m^2 in SUSTAIN-4) • Acute coronary or cerebrovascular event < 90 days (< 180 days in SUSTAIN-7) before randomization or heart failure (New York Heart Association Class IV) • Known proliferative retinopathy or maculopathy requiring acute treatment				
	Additional Exclusion Criteria	Glucose-lowering drugs other than those stated in Inclusion Criteria < 90 days before screening.	Glucose-lowering agents other than those stated in Inclusion Criteria < 90 days of screening.	Glucose-lowering drugs other than those stated in Inclusion Criteria < 90 days before screening. Experienced > 3 episodes of severe hypoglycemia within 6 months prior to screening, and/or hypoglycemia unawareness.	Treatment with any medication for diabetes or obesity other than stated in Inclusion Criteria < 90 days before screening.	Glucose-lowering drugs (except for pre-trial OAD) < 60 days before screening.

		SUSTAIN-2	SUSTAIN-3	SUSTAIN-4	SUSTAIN-7	Seino
DRUGS	**Intervention**	SEM 0.5 mg SC q.w. SEM 1 mg SC q.w.	SEM 1 mg SC q.w.	SEM 0.5 mg SC q.w. SEM 1 mg SC q.w.	SEM 0.5 mg SC q.w. SEM 1 mg SC q.w.	SEM 0.5 mg SC q.w. SEM 1 mg SC q.w.
	Comparator(s)	SIT 100 mg p.o. q.d.	EXE 2 mg SC q.w.	IG SC q.d. (initial dose 10 IU, then adjusted according to widely accepted titration algorithm for IG)	DUL 0.75 mg SC q.w. DUL 1.5 mg SC q.w.	SIT 100 mg p.o. q.d.
DURATION	**Phase**					
	Screening	2 weeks				2 weeks for diet/exercise only; or 8 weeks washout if patients received pre-trial OAD monotherapy.
	Treatment	56 weeks		30 weeks	40 weeks	30 weeks
	Follow-up	5 weeks				
OUTCOMES	**Primary End Point**	Change in A1C				Number of TEAEs
	Other End Points	Change in: • body weight • BMI • SBP and DBP • blood lipids • HRQoL Safety				Change in: • A1C • body weight • BMI • SBP and DBP • blood lipids Other safety endpoints
NOTES	**Publications**	Ahren 2017[33]	Ahmann 2018[34]	Aroda 2017[35]	Pratley 2018[36]	Seino 2018[14]

A1C = glycated hemoglobin; b.i.d. = twice daily; BMI = body mass index; DB = double-blind; DBP = diastolic blood pressure; DUL = dulaglutide; eGFR = estimated glomerular filtration rate; EXE = exenatide; HRQoL = health-related quality of life; IG = insulin glargine; MEN2 = multiple endocrine neoplasia type 2; MET = metformin; MTC = medullary thyroid carcinoma; NI = non-inferiority; OAD = oral antihyperglycemic drug; OL = open label; p.o. = orally; q.d. = once daily; q.w. = once weekly; RCT = randomized controlled trial; SBP = systolic blood pressure; SC = subcutaneous; SEM = semaglutide; SIT = sitagliptin; SU = sulfonylurea; TEAE = treatment-emergent adverse event; TZD = thiazolidinedione; T2DM = type 2 diabetes mellitus.

[a] In the Seino study, "diet/exercise" was specified as background therapy all study participants; however, this was not indicated for patients in SUSTAIN-2, 3, 4, and 7.

Note: Three additional reports were included (CDR Submission,[30] FDA medical review,[32] Health Canada Reviewer's Report[31]).

Source: Clinical Study Reports of SUSTAIN-2,[10] SUSTAIN-3,[11] SUSTAIN-4,[12] SUSTAIN-7,[13] and Seino 2018.[14]

Included Studies

Description of Studies

A total of eight phase III RCTs met the inclusion criteria (SUSTAIN-1 to 7 and the Seino study).[7-14]

These trials evaluated the efficacy and safety of SEM 0.5 mg or 1 mg once weekly (alone or in combination with oral antidiabetic drug [OAD] such as MET or MET plus an SU, or insulin), compared with placebo or active comparators in adults with T2DM and inadequate glycemic control with background therapy. All three placebo-controlled trials (SUSTAIN-1, 5,

and 6)[7-9] and one active-controlled trial (SUSTAIN-2)[10] included a randomized double-blind treatment period, and all other active-controlled trials had an open-label design (SUSTAIN-3, 4, 7, and the Seino study).[11-14] In all trials, the patients who met the inclusion criteria and were assigned to the treatment with either dose of SEM underwent a dose escalation period. Randomization was conducted using an interactive voice or interactive Web response system (IV/WRS). Patients were stratified based on their background therapy (SUSTAIN-4, 5, and 6), baseline A1C level (SUSTAIN-5), their extent of cardiovascular (CV) disease (SUSTAIN-6) or renal function (SUSTAIN-6) in some trials (Table 5). There was no stratification for randomization in other trials. The primary objective of the included trials was to compare the effect of SEM once weekly treatment with the comparators on change in A1C from baseline, except for SUSTAIN-6 and the Seino study. "Time from randomization to first occurrence of major adverse cardiovascular event (MACE)" was the primary outcome in SUSTAIN-6. The occurrence of treatment-emergent adverse event (TEAE) was the primary outcome in the Seino study. The occurrence of diabetes-related comorbidities (macrovascular and microvascular) was also measured in the only cardiovascular outcomes trial (CVOT) SUSTAIN-6. Change in body weight, body mass index (BMI), blood pressure, and blood lipid profile were evaluated in all trials. Health-related quality of life (HRQoL) was evaluated in all trials but SUSTAIN-1 and the Seino study. Non-inferiority (NI) of treatment with SEM versus active comparators (SUSTAIN-2, 3, 4, and 7) on glycemic control was assessed in four SUSTAIN trials. NI of treatment with SEM compared with placebo on increase in CV events was assessed in patients who had prior or concomitant CV conditions in SUSTAIN-6. SUSTAIN-1 and 5 and the Seino study evaluated the superiority of two dose levels (0.5 mg and 1.0 mg) of SEM versus placebo on glycemic control or safety in patients with T2DM.

All the trials had a 2-week screening period. In the Seino study, patients were required to undergo an 8-week washout period if they received pre-trial OAD monotherapy. Patients on stable doses of background therapies who met the inclusion criteria were randomly assigned to treatment with SEM or the comparators. The treatment duration varied from 30 to 56 weeks in the majority of the trials, while the study participants in SUSTAIN-6 received 104 weeks of treatment with the study drugs. Patients had a 5-week follow-up period after the last dose of the study drug.

For all trials, an independent external Event Adjudication Committee (EAC) was established to perform ongoing adjudication, standardization, and assessment of selected outcomes, such as CV death, pancreatitis, and neoplasms, according to pre-defined diagnostic criteria. The purpose of the adjudication was to confirm events in a consistent manner according to standardized criteria using independent external medical experts.

Details of the trial characteristics are presented in Table 6 and Table 7.

Populations

Inclusion and Exclusion Criteria

Patients enrolled in the SUSTAIN trials were adults (greater than and equal to 18 years of age) with T2DM, while patients enrolled from Japan (Seino study) were greater than and equal to 20 years of age. They were required to have inadequate glycemic control with previous antihyperglycemic treatments, such as diet or exercise, or stable diabetes drug treatment (e.g., MET, SU, TZD, or insulin). Stable diabetes treatment was defined as "unchanged medication and unchanged dose" in SUSTAIN-2, 3, 4, and "+/- 20% change in total daily dose with basal insulin alone or in combination with metformin" in SUSTAIN-5. In the Seino study, stable OAD monotherapy was defined as "receiving half-maximum or below

dose according to Japanese labelling for 30 days prior to screening." Each trial had specific inclusion criteria related to A1C levels and background medications at screening (Table 6 and Table 7). The required A1C levels at baseline ranged from 7% to 10% in the majority of the trials. MET monotherapy or combination of MET plus SU or MET plus insulin were common background medications in the included trials. In SUSTAIN-1, all study participants were drug naive at baseline. Some patients in SUSTAIN-6 (1.6%) and the Seino study (70%) did not receive prior antihyperglycemic treatment (Table 5).

Eligible patients in SUSTAIN-6 were required to have clinical or subclinical evidence of CV disease, defined as meeting at least one of the following criteria presented in the table below.

Clinical Evidence of CV Disease	Subclinical Evidence of CV Disease
• Prior MI	• Persistent microalbuminuria (30 mg/g to 299 mg/g) or proteinuria
• Prior stroke or TIA	• Hypertension and left ventricular hypertrophy by ECG or imaging
• Prior coronary, carotid, or peripheral arterial revascularization	• Left ventricular systolic or diastolic dysfunction by imaging
• > 50% stenosis on angiography or imaging of coronary, carotid, or lower extremity arteries	• Ankle/brachial index < 0.9
• History of symptomatic coronary heart disease documented by e.g., positive exercise stress test or any cardiac imaging, or unstable angina with ECG changes	
• Asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or stress echocardiogram or any cardiac imaging	
• Chronic heart failure (NYHA class II to III)	
• Chronic renal impairment, documented (prior to screening) by eGFR < 60 mL/min/1.73m^2	

CV = cardiovascular; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; NYHA = New York Heart Association; TIA = transient ischemic attack.

Exclusion criteria were similar across trials and those with recent cardiovascular events or heart failure (NYHA class IV), history of acute or chronic pancreatitis, impaired renal function, or any chronic disorder or severe disease that might jeopardize patient's safety or compliance with the protocol, were not eligible for enrolment. In SUSTAIN-4 and SUSTAIN-5, patients were excluded if they experienced more than three episodes of severe hypoglycemia within six months prior to screening, or if they experienced hypoglycemia unawareness (Table 6 and Table 7).

Baseline Characteristics

The proportion of patients who were male ranged from 43% to 79% per treatment group and the mean age per treatment group was from 53 years to 65 years (Table 8, Table 9, and Table 10). In the SUSTAIN trials, the patients enrolled were predominantly white (61% to 84%) with a mean BMI per group ranging from 32 kg/m^2 to 34 kg/m^2, and with body weight ranging from 89 kg to 97 kg. The patient's baseline characteristics in the Japanese study (Seino) differed from the SUSTAIN trials, in that the average BMI was 25 kg/m^2 to 26 kg/m^2 and the average body weight was 68 kg to 71 kg. The baseline A1C in all trials ranged from 8.0% to 8.7%. The mean duration of diabetes varied across trials and was lowest for SUSTAIN-1 (6.4 years to 6.7 years), and highest for SUSTAIN-6 (13.2 years to 14.3 years). The mean eGFR at baseline was above 90 mL/min/1.73 m^2 for all trials except for SUSTAIN-6, where the average eGFR ranged from 75.6 mL/min/1.73 m^2 to 77.2 mL/min/1.73 m^2.

Baseline characteristics were generally similar between groups within trials although some differences in the average body weight were noted in SUSTAIN-1, as well as differences in the duration of diabetes in SUSTAIN-1 and SUSTAIN-4.

Table 8: Summary of Baseline Characteristics (Placebo-Controlled RCTs; FAS)

Characteristics	SUSTAIN-1			SUSTAIN-5		
	SEM 0.5 mg N = 128	SEM 1.0 mg N = 130	Placebo N = 129	SEM 0.5 mg N = 132	SEM 1 mg N = 131	Placebo N = 133
Age, years, mean (SD)	54.6 (11.1)	52.7 (11.9)	53.9 (11.0)	59.1 (10.3)	58.5 (9.0)	58.8 (10.9)
Sex, n (%)						
male	60 (46.9)	80 (61.5)	70 (54.3)	74 (56.1)	77 (58.8)	71 (53.4)
female	69 (53.1)	50 (38.5)	59 (45.7)	58 (43.9)	54 (41.2)	62 (46.6)
Race, n (%)						
White	83 (64.8)	88 (67.7)	78 (60.5)	108 (81.8)	98 (74.8)	101 (75.9)
Black / African American	11 (8.6)	11 (8.5)	9 (7.0)	4 (3.0)	9 (6.9)	8 (6.0)
Asian	26 (20.3)	25 (19.2)	32 (24.8)	19 (14.4)	23 (17.6)	24 (18.0)
American Indian / Alaska Native	0	0	1 (0.8)	0	0	0
Native Hawaiian /Other Pacific Islander	0	0	0	1 (0.8)	0	0
Other	8 (6.3)	6 (4.6)	9 (7.0)	0	1 (0.8)	0
Duration of diabetes, years, mean (SD)	4.85 (6.11)	3.65 (4.89)	4.06 (5.48)	12.91 (7.59)	13.74 (7.82)	13.30 (7.98)
BMI, kg/m^2, mean (SD)	32.46 (7.62)	33.92 (8.43)	32.40 (6.86)	32.77 (6.01)	32.00 (6.41)	31.77 (6.05)
Body weight, kg, mean (SD)	89.81 (22.96)	96.87 (25.59)	89.05 (22.16)	92.74 (19.57)	92.49 (22.23)	89.88 (21.06)
A1C, %, mean (SD)	8.09 (0.89)	8.12 (0.81)	7.95 (0.85)	8.36 (0.83)	8.31 (0.82)	8.42 (0.88)
eGFR, mL/min/1.73 m^2, mean (SD)	95.91 (26.23)	100.9 (27.74)	100.2 (24.97)	91.88 (26.30)	91.06 (23.41)	90.97 (25.37)
Background therapy, n (%)						
MET	Drug naive			110 (83.3)	110 (84.0)	110 (82.7)
SU				0	0	1 (0.8)
TZD				NR		
Basal insulin				132 (100)	131 (100)	133 (100)

A1C = glycated hemoglobin; BMI = body mass index; eGFR = estimated glomerular filtration rate; FAS = full analysis set; MET = metformin; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SEM = semaglutide; SU = sulfonylurea; TZD = thiazolidinedione.

Source: Clinical Study Reports of SUSTAIN-1[7] and SUSTAIN-5.[8]

Table 9: Summary of Baseline Characteristics (Active-Controlled RCTs; FAS)

Characteristics	SUSTAIN-2			SUSTAIN-3		SUSTAIN-4			SUSTAIN-7				Seino		
	SEM 0.5 mg N = 409	SEM 1 mg N = 409	SIT N = 407	SEM 1 mg N = 404	EXE N = 405	SEM 0.5 mg N = 362	SEM 1 mg N = 360	IG N = 360	SEM 0.5 mg N = 301	SEM 1 mg N = 300	DUL 0.75 mg N = 299	DUL 1.5 mg N = 299	SEM 0.5 mg N = 103	SEM 1 mg N = 102	SIT N = 103
Age, years, mean (SD)	54.8 (10.2)	56.0 (9.4)	54.6 (10.4)	56.4 (10.3)	56.7 (11.1)	56.5 (10.3)	56.7 (10.4)	56.2 (10.6)	56 (10.9)	55 (10.6)	55 (10.4)	56 (10.6)	58.8 (10.4)	58.1 (11.6)	57.9 (10.1)
Sex, n (%)															
Male	207 (50.6)	205 (50.1)	208 (51.1)	219 (54.2)	228 (56.3)	197 (54.4)	182 (50.6)	195 (54.2)	169 (56.1)	162 (54.0)	160 (53.5)	171 (57.2)	79 (76.7)	75 (73.5)	81 (78.6)
Female	202 (49.4)	204 (49.9)	199 (48.9)	185 (45.8)	177 (43.7)	165 (45.6)	178 (49.4)	165 (45.8)	132 (43.9)	138 (46.0)	139 (46.5)	128 (42.8)	24 (23.3)	27 (26.5)	22 (21.4)
Race, n (%)															
White	279 (68.2)	279 (68.2)	281 (69.0)	341 (84.4)	338 (83.5)	279 (77.1)	279 (77.5)	276 (76.7)	233 (77.4)	243 (81.0)	232 (77.6)	220 (73.6)	0		
Black / African American	18 (4.4)	24 (5.9)	17 (4.2)	28 (6.9)	30 (7.4)	32 (8.8)	34 (9.4)	33 (9.2)	17 (5.6)	18 (6.0)	17 (5.7)	18 (6.0)			
Asian	106 (25.9)	99 (24.2)	102 (25.1)	8 (2.0)	6 (1.5)	42 (11.6)	39 (10.8)	38 (10.6)	50 (16.6)	38 (12.7)	48 (16.1)	55 (18.4)	100%		
American Indian/ Alaska Native	0			2 (0.5)	1 (0.2)	1 (0.3)	0	1 (0.3)	0				0		
Native Hawaiian/ Other Pacific Islander	0			0	2 (0.5)	0			0						
Other	6 (1.5)	7 (1.7)	7 (1.7)	3 (0.7)	5 (1.2)	3 (0.8)	3 (0.8)	5 (1.4)	1 (0.3)	1 (0.3)	2 (0.7)	6 (2.0)			
Duration of diabetes, years, mean (SD)	6.44 (4.66)	6.70 (5.56)	6.60 (5.08)	9.02 (5.95)	9.40 (6.71)	7.77 (5.14)	9.34 (7.17)	8.61 (6.29)	7.7 (5.92)	7.3 (5.66)	7.0 (5.48)	7.6 (5.65)	8.0 (5.2)	7.8 (6.9)	8.1 (6.7)
BMI, kg/m^2, mean (SD)	32.43 (6.22)	32.50 (6.61)	32.45 (5.81)	33.97 (7.23)	33.57 (6.23)	33.11 (6.45)	32.96 (6.51)	32.95 (6.51)	33.7 (7.12)	33.6 (6.49)	33.6 (6.90)	33.1 (6.57)	25.1 (3.8)	26.1 (5.2)	25.1 (3.6)
Body weight, kg, mean (SD)	89.93 (20.39)	89.21 (20.74)	89.29 (19.67)	96.21 (22.50)	95.37 (20.46)	93.73 (21.39)	94.00 (22.48)	92.61 (21.52)	96.4 (24.38)	95.5 (20.90)	95.6 (23.01)	93.4 (21.79)	67.8 (11.7)	70.8 (16.4)	69.4 (12.9)
A1C, %, mean (SD)	8.01 (0.92)	8.04 (0.93)	8.17 (0.92)	8.36 (0.95)	8.33 (0.96)	8.13 (0.85)	8.25 (0.94)	8.13 (0.88)	8.3 (0.96)	8.2 (0.92)	8.2 (0.91)	8.2 (0.89)	8.2 (1.0)	8.0 (0.9)	8.2 (0.9)
eGFR, mL/min/ 1.73 m^2, mean (SD)	99.12 (24.87)	99.86 (21.65)	100.9 (22.73)	100.5 (24.68)	100.5 (22.54)	97.89 (25.94)	97.95 (27.55)	99.66 (26.46)	Mean NR. Per cent of patients with normal renal function was 221 (73.4%), 225 (75.0%), 205 (68.6%) and 209 (69.9%), respectively.				NR		

Characteristics	SUSTAIN-2			SUSTAIN-3		SUSTAIN-4			SUSTAIN-7				Seino		
	SEM 0.5 mg N = 409	SEM 1 mg N = 409	SIT N = 407	SEM 1 mg N = 404	EXE N = 405	SEM 0.5 mg N = 362	SEM 1 mg N = 360	IG N = 360	SEM 0.5 mg N = 301	SEM 1 mg N = 300	DUL 0.75 mg N = 299	DUL 1.5 mg N = 299	SEM 0.5 mg N = 103	SEM 1 mg N = 102	SIT N = 103
Background Therapy, n (%)															
MET	403 (98.5)	406 (99.3)	405 (99.5)	391 (96.8)	390 (96.3)	362 (100)	360 (100)	359 (99.7)	301 (100)	300 (100)	299 (100)	299 (100)	12 (11.7)	13 (12.7)	12 (11.7)
SU	1 (0.2)	0	1 (0.2)	181 (44.8)	208 (51.4)	186 (51.4)	185 (51.4)	187 (51.9)	0				5 (4.9)	2 (2.0)	5 (4.9)
TZD	23 (5.6)	20 (4.9)	23 (5.7)	13 (3.2)	6 (1.5)	NR			0				2 (1.9)	2 (2.0)	3 (2.9)
DPP-4 inhibitors	NR			NR		NR			0				8 (7.8)	7 (6.9)	6 (5.8)

A1C = glycated hemoglobin; BMI = body mass index; DUL = dulaglutide; eGFR = estimated glomerular filtration rate; EXE = exenatide; FAS = full analysis set; IG = insulin glargine; MET = metformin; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SEM = semaglutide; SIT = sitagliptin; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione.

Source: Clinical Study Reports of SUSTAIN-2, 3, 4, and 7;[10-13] Seino 2017.[14]

Compared with other trials, patients in SUSTAIN-6 were older, had longer history of diabetes, and poorer renal function. Among the patients enrolled in the trial, approximately 60% had ischemic heart disease, more than 40% had prior arterial revascularization, more than 30% had prior myocardial infarction or >50% artery stenosis, and more than 90% had hypertension. Neuropathy (41%) and nephropathy (44%) were common microvascular comorbidities in the study population. In SUSTAIN-6, the most commonly used antidiabetic medication at baseline was MET (approximately 73%) followed by insulin treatment (58% of patients were treated with basal insulin or pre-mix insulin; 42% were insulin-naive at baseline) and SUs (42.8%: 26.8% without insulin and 15.9% in combination with insulin). Less than 2% of patients did not use any diabetes medication at baseline (Table 10).

Table 10: Summary of Baseline Characteristics (CV Outcome RCT)

Characteristics	SUSTAIN-6			
	SEM 0.5 mg N = 826	SEM 1 mg N = 822	Placebo 0.5 mg N = 824	Placebo 1 mg N = 825
Age, years, mean (SD)	**64.6 (7.3)**	**64.7 (7.1)**	**64.8 (7.6)**	**64.4 (7.5)**
Sex, n (%)				
Male	495 (59.9)	518 (63.0)	482 (58.5)	507 (61.5)
Female	331 (40.1)	304 (37.0)	342 (41.5)	318 (38.5)
Race, n (%)				
White	693 (83.9)	691 (84.1)	676 (82.0)	676 (81.9)
Black / African American	54 (6.5)	54 (6.6)	54 (6.6)	59 (7.2)
Asian	63 (7.6)	58 (7.1)	80 (9.7)	72 (8.7)
American Indian / Alaska Native	2 (0.2)	1 (0.1)	4 (0.5)	3 (0.4)
Native Hawaiian /other Pacific Islander	0	3 (0.4)	0	0
Other	14 (1.7)	15 (1.8)	10 (1.2)	15 (1.8)
Duration of diabetes, years, mean (SD)	14.29 (8.21)	14.06 (8.19)	13.97 (8.54)	13.23 (7.45)
BMI, kg/m^2, mean (SD)	32.71 (6.29)	32.90 (6.18)	32.93 (6.35)	32.66 (5.97)
Body weight, kg, mean (SD)	91.80 (20.25)	92.86 (21.05)	91.83 (20.35)	91.90 (20.75)
A1C, %, mean (SD)	8.67 (1.39)	8.73 (1.51)	8.70 (1.49)	8.70 (1.45)
SBP, mm Hg, mean (SD)	136.1 (17.97)	135.8 (16.96)	135.8 (16.16)	134.8 (17.45)
DBP, mm Hg, mean (SD)	77.10 (9.78)	76.88 (10.21)	77.54 (9.85)	76.66 (10.21)
HDL cholesterol, mmol/L, mean (SD)	1.19 (0.34)	1.16 (0.32)	1.19 (0.33)	1.16 (0.32)
LDL cholesterol, mmol/L, mean (SD)	2.32 (1.01)	2.32 (0.89)	2.31 (0.99)	2.36 (0.98)
eGFR, mL/min/1.73 m^2, mean (SD)	75.60 (25.81)	76.15 (25.97)	75.55 (26.65)	77.22 (27.71)
History of CV disease				
Ischemic heart disease	493 (59.7)	495 (60.2)	510 (61.9)	496 (60.1)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI	266 (32.2)	264 (32.1)	267 (32.4)	275 (33.3)
Heart failure	201 (24.3)	180 (21.9)	190 (23.1)	206 (25.0)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	772 (93.5)	771 (93.8)	756 (91.7)	760 (92.1)
Ischemic stroke	89 (10.8)	89 (10.8)	96 (11.7)	109 (13.2)
Hemorrhagic stroke	28 (3.4)	24 (2.9)	27 (3.3)	29 (3.5)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	SUSTAIN-6			
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background CV medication, n (%)				
Anti-hypertensive drugs	773 (93.6)	780 (94.9)	757 (91.9)	772 (93.6)
Diuretics	318 (38.5)	306 (37.2)	306 (37.1)	330 (40.0)
Lipid lowering drugs	634 (76.8)	629 (76.5)	618 (75.0)	640 (77.6)
Anti-thrombotic medication	625 (75.7)	627 (76.3)	625 (75.8)	637 (77.2)
Background antidiabetic therapy, n (%)				
Drug naive	9 (1.1)	14 (1.7)	18 (2.2)	11 (1.3)
MET	617 (74.7)	594 (72.3)	586 (71.1)	617 (74.8)
SU ± other antidiabetics ± insulin	349 (42.3)	349 (42.5)	363 (44.1)	349 (42.3)
Insulin (long-acting) ± other antidiabetics	479 (58.0)	477 (58.0)	478 (58.0)	479 (58.1)
TZD	14 (1.7)	21 (2.6)	18 (2.2)	23 (2.8)

A1C = glycated hemoglobin; BMI = body mass index; CABG = coronary artery bypass graft; CV = cardiovascular; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MET = metformin; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SBP = systolic blood pressure; SD = standard deviation; SU = sulfonylurea; TIA = transient ischemic attack; TZD = thiazolidinedione.

Source: Clinical Study Report of SUSTAIN-6.[9]

Interventions

All placebo-controlled trials and one active-controlled trial (SUSTAIN-2) had double-blind design. The manufacturer, investigators, and patients were blinded to treatment allocation. SUSTAIN-3, 4, 7, and the Seino study were open-label RCTs.

The treatment period included a dose escalation period followed by a maintenance period. SEM was initiated at 0.25 mg subcutaneously once weekly. The maintenance dose of SEM 0.5 mg subcutaneously once weekly was started after four doses (4 weeks) of 0.25 mg. The maintenance dose of SEM 1.0 mg subcutaneously once weekly was started after four doses (4 weeks) of 0.25 mg, followed by four doses (four weeks) of 0.5 mg. In SUSTAIN-1, 2, 5, and 6, SEM placebo was administered using the same strategy as SEM. After the maintenance dose was reached, the dose was not to be changed during the remainder of the trial. If the maintenance dose was not tolerated, treatment could be discontinued and in such cases, treatment was not re-initiated, except in cases where suspicion of acute pancreatitis led to discontinuation of treatment, but later acute pancreatitis was ruled out.

In SUSTAIN-1 to 5 and SUSTAIN-7, rescue medications were offered to patients with unacceptable hyperglycemia during the treatment with study drugs. Unacceptable hyperglycemia was determined when any of the fasting plasma glucose (FPG) levels measured at scheduled visits and a confirmatory FPG obtained by the local or central laboratory exceeded the following limits and no inter-current cause of the hyperglycemia could be identified:

- 15 mmol/L from baseline to week 6 (or to week 7 in SUSTAIN-7)
- 13.3 mmol/L from week 6 to week 12 (or from week 8 to week 13 in SUSTAIN-7)
- 11.1 mmol/L from week 12 (or from week 14 in SUSTAIN-7) to end-of-trial

Rescue medication referred to intensification of the existing background medication or initiation of new medication, and it was prescribed as add-on to randomized treatment. In SUSTAIN-1, MET was the first choice of rescue medication unless contraindicated. In

SUSTAIN-5, increasing the basal insulin dose was the first choice. In these six trials, GLP receptor agonists, DPP-4 inhibitors, and pramlintide or amylin analogues were not allowed or preferred not to be used as rescue medications. There was no description on the use of rescue medication in the study populations in SUSTAIN-6 and the Seino study.

In SUSTAIN-6, approximately 58% of the patients received concomitant insulin therapy. If their A1C was > 8% at screening, reductions in insulin doses were allowed in case of increased episodes of hypoglycemia. Patients treated with insulin and who had A1C ≤ 8.0% at screening were to have the insulin dose reduced by 20% at start of study drug to limit the potential risk of episodes of hypoglycemia induced by the combined therapy of insulin and SEM.

Outcomes

Glycemic Control

Change from baseline to end of study (week 30 to week 56 across studies) in A1C was a primary outcome in all included trials, except for SUSTAIN-6 and the Seino study. In SUSTAIN-6 and the Seino study, change from baseline to week 30 in A1C was a secondary end point. Note that in SUSTAIN-6, change in A1C was assessed at week 30, instead of end of study.

Mortality (all-cause, cardiovascular related)

This outcome was assessed in all included trials, and the cases of death required to be confirmed by EAC.

Diabetes-Related Morbidity and Mortality

This outcome was assessed in the only CVOT (SUSTAIN-6). In this trial, the primary end point was time from randomization to the first EAC-confirmed MACE, defined as CV death, non-fatal MI, or non-fatal stroke. In addition, the secondary end points in SUSTAIN-6 included:

1. Time from randomization to first occurrence of an expanded composite CV outcome (defined as either EAC-confirmed MACE, revascularization (coronary and peripheral), unstable angina requiring hospitalization or hospitalization for heart failure);
2. Time from randomization to each individual component of the expanded composite CV outcome;
3. Time from randomization to first occurrence of all-cause death, non-fatal MI, or non-fatal stroke.

All of the above outcomes except peripheral revascularization were EAC-confirmed.

Hospitalization (All-cause, Cardiovascular Related)

This outcome was not measured in any of the included trials.

Health-Related Quality of Life

Patient's HRQoL was evaluated using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) or Short Form (36) Health Survey (SF-36). The DTSQ was used to assess patient satisfaction with treatment (six items) and perception of change in hyperglycemia and hypoglycemia (2 items).[37] The DTSQ has two versions that have eight items each: the DTSQ original status version (DTSQs) and the DTSQ change version (DTSQc). Six of the eight items measure treatment satisfaction (satisfaction with current treatment, convenience, flexibility, satisfaction with own understanding of diabetes, and likelihood of continuing on or recommending current treatment). The item scores range from "very satisfied" (score of 6) to "very unsatisfied" (score of 0), and the sum of these items is taken to generate a DTSQs score, ranging from 0 to 36. Higher DTSQs scores indicate greater satisfaction with treatment. For the two items measuring perceived frequency of hyperglycemia and frequency of hypoglycemia, the items are scored on 7-point response scales ranging from "most of the time" (score of 6) to "none of the time" (score of 0). Lower DTSQs scores indicate more ideal blood glucose levels in this case. No minimal clinically important difference (MCID) was identified for the change in DTSQs scores. The psychometric properties of different language versions of the DTSQs were assessed in a study of type 1 and type 2 diabetes patients treated with insulin or poorly controlled on SUs who then started on insulin treatment. The DTSQs was shown to be consistently reliable in all languages studied and significantly sensitive to change in type 1 diabetes patients at weeks 8, 20, 24, and at last available visit.[38] However, it has also been observed that because patients tend to report satisfaction with current treatment in the absence of experience with alternatives for comparison, the DTSQs often exhibits a ceiling effect.[37] Change in DTSQs from baseline to end of study was measured in SUSTAIN-2, 3, 4, 5, and 7.

The SF-36 is a 36-item, generic health status instrument that has been used extensively in clinical trials in many disease areas.[39] It consists of eight health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The eight domains are aggregated to create two component summaries: the physical component summary (PCS) and the mental component summary (MCS), with scores ranging from zero to 100 with higher scores indicating better health status. However, previous research suggested a lack of improvement in SF-36 scores (deteriorated or remained stable) following interventions demonstrating modest improvement in A1C levels, blood lipid, and blood pressure in patients with T2DM.[40] The MCID for either the PCS or MCS of the SF-36 for the change from baseline is typically between 2.5 and 5 points. SF-36 was measured in SUSTAIN-2 to SUSTAIN-7.

Blood Pressure

Change from baseline to end of study in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were secondary efficacy end points in all included trials. In SUSTAIN-1 to SUSTAIN-7, it was indicated that measurements were taken in a sitting position, after the patient had been sitting for at least five minutes.

BMI and Body Weight

Change from baseline to end of study in body weight and BMI were secondary efficacy end points in all included trials.

Lipid Profile

Fasting blood lipids (e.g., total cholesterol, HDL cholesterol, and LDL cholesterol) was a secondary efficacy end point in all included trials.

Safety

An adverse event (AE) was defined as any untoward medical occurrence in a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with his treatment. It can be any unfavourable and unintended sign, symptom, or disease, or any worsening of a pre-existing condition temporally associated with the use of a product, whether or not considered related to the product. A TEAE was defined as an event with onset that occurs on or after the first day of study medication administration and no later than the follow-up visit.

A serious adverse event (SAE) was defined as an event that resulted in death, was life threatening, resulted in hospitalization or prolongation of existing hospitalization, persistent or significant disability, was a congenital anomaly or birth defect, or other important medical events.

In addition, AEs leading to premature treatment discontinuation was measured in the included trials. Safety areas of special interest, such as gastrointestinal (GI) disorders, severe hypoglycemia, pancreatitis, or injection site reaction were explored, based on the known and potential risks of GLP-1 receptor agonists, experience from using GLP-1 receptor agonists in patients with T2DM and in weight management, and regulatory requirements for the development of treatments for T2DM. Hypoglycemic episodes were classified according to the Novo Nordisk classification of hypoglycemia and the American Diabetes Association (ADA) classification of hypoglycemia. According to the ADA classification, severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal was considered sufficient evidence that the event was induced by a low plasma glucose concentration.[41] Novo Nordisk definition of severe or blood glucose (BG)-confirmed symptomatic hypoglycemia referred to an episode that was severe according to the ADA classification or BG-confirmed by a plasma glucose value less than 3.1 mmol/L with symptoms consistent with hypoglycemia.

In the Seino study, TEAE was the primary outcome measure.

Statistical Analysis

No interim analyses were planned or performed for any of the included trials.

Three observation periods were described in data analyses in SUSTAIN-1 to 7 (no information was provided with respected to the observation periods used in the Seino study).

- “On-treatment without rescue medication” period was the primary observation period when selecting data related to efficacy (a subset of the ‘on-treatment’ observation period. It included observations recorded at, or after the date of first dose of study medication and not after the first occurrence of the following: the end date of the ‘on-treatment’ observation period, or initiation of rescue medication);

- "On-treatment" period was primary observation period when selecting data related to safety evaluation (a subset of the 'in-trial' observation period, namely the portion where the patient was considered to be exposed to study medication);
- "In-trial" period was used for supportive analyses of both efficacy and safety considered supportive (included observations recorded at, or after randomization, and not after the last patient-investigator contact [phone or on-site visit], which was scheduled to take place five weeks after the planned last dose of study medication at the follow-up visit, or the death of the patient during the trial, whichever occurred first).

In SUSTAIN-6, only two observation periods were used: the "in-trial" observation period, and "on-treatment" observation period (a subset of the in-trial observation period, which represents the time period where patients were considered exposed to study medication).

In all trials but SUSTAIN-6, the primary statistical analysis for the primary efficacy outcome (e.g., A1C) was based on full analysis set (FAS), using data from "on-treatment without rescue medication" observation period. A Mixed Model for Repeated Measurements (MMRM) approach was adopted where treatment and country were included as fixed factors and baseline A1C as a covariate. The model assumed that data were missing at random (MAR). The change from baseline in body weight, BMI, blood pressure, and blood lipids were analyzed using similar methods across all trials. In SUSTAIN-6, the continuous efficacy data such as A1C, body weight, BMI, blood pressure and blood lipids were analyzed using data from the "in-trial" observation period. In SUSTAIN-6, the primary objective was to confirm that SEM treatment did not excessively increase the CV risk as compared with placebo. The primary outcome (time to first EAC-confirmed MACE) was evaluated using a stratified Cox hazards model with treatment group as fixed factor (Table 11). The model was stratified by all possible combinations of the three stratification factors used in the randomization procedure (in total nine levels). From this model the hazard ratio (HR) (SEM/placebo) together with the 2-sided 95% CI were estimated. The non-inferiority (NI) in increased CV risk between SEM and placebo was concluded if the upper bound of the two-sided 95% CI of the for SEM versus placebo was less than 1.8 for time to first occurrence of MACE, in accordance with the FDA guidance on the development of a new antidiabetic therapy to treat T2DM.[42]

Missing data were imputed with various approaches, such as the last observation carried forward (LOCF) method, or with the MMRM model or ANCOVA model. Methods of missing data handling are listed in Table 11.

Sensitivity analyses were conducted for the primary and the confirmatory secondary end point (body weight in the SUSTAIN trials) to assess the impact of missing data. Various approaches were used, such as per-protocol (PP) analysis, complete case analysis, LOCF-based analysis, the comparator-based imputation analysis, and MMRM-based "in-trial" analysis. Details are provided in Table 11.

All trials except the Seino study used a pre-specified ordered testing procedure to control for inflated type I1 error rates. To advance to the next test (i.e., from test 1 to test 2, from test 2 to test 3, etc.), the preceding test criterion must be met (i.e., the corresponding null hypothesis must be rejected). If the corresponding null hypothesis was not rejected, the testing was to stop, and no further conclusions could be drawn. Details on the statistical testing procedure and power estimates are listed in Table 12.

Subgroup analyses were performed in some SUSTAIN trials to examine the consistency of the primary analysis results across subgroup levels. In SUSTAIN-5, subgroup analysis based on renal function was explored. In SUSTAIN-6, the subgroups of interest of this review included baseline A1C levels, BMI, and renal function. In SUSTAIN-2 to 4, post hoc subgroup analyses were carried out based on background antidiabetic therapy; in addition, interaction between treatment and background OAD therapy was examined in these posts hoc subgroup analyses.

Table 11: Summary of Statistical Testing Methods

Study	Outcome	Statistical Model	Imputation of Missing Data	Sensitivity Analyses
SUSTAIN-1	Change from baseline in A1C to week 30	Primary statistical analysis was based on FAS using observed data from "on-treatment without rescue medication" period. An MMRM model was used where all post-baseline A1C measurements obtained at all planned visits were entered as dependent variables, and treatment and country were included as fixed factors and baseline A1C as covariate, and all nested within visit. The model assumed that data were MAR.	LOCF MMRM imputation	• Complete case analysis • LOCF-based analysis • Comparator-based imputation analysis • "In-trial" analysis
SUSTAIN-2	Change from baseline in A1C to week 56	Primary statistical analysis was based on FAS using observed data from "on-treatment without rescue medication" period. An MMRM model was used where all post-baseline A1C measurements obtained at all planned visits were entered as dependent variables, and treatment and country were included as fixed factors and baseline A1C as covariate, and all nested within visit. The model assumed that data were MAR. The NI analysis set was based on FAS and supplemented by an analysis with the PP analysis.	LOCF MMRM imputation ANCOVA imputation (for PRO data)	• PP analysis • Complete case analysis • LOCF-based analysis • Comparator-based imputation analysis • "In-trial" analysis
SUSTAIN-3	Change from baseline in A1C to week 56	Primary statistical analysis was based on FAS using observed data from "on-treatment without rescue medication" period. An MMRM model was used where treatment and country were included as fixed factors and baseline A1C as covariate, and all nested within visit. The model assumed that data were MAR. The NI analysis set was based on FAS and supplemented by an analysis with the PP analysis.	LOCF MMRM imputation ANCOVA imputation (for PRO data)	• PP analysis • Complete case analysis • LOCF-based analysis • Comparator-based imputation analysis • "In-trial" analysis
SUSTAIN-4	Change from baseline in A1C to week 30	Primary statistical analysis was based on FAS using observed data from "on-treatment without rescue medication" period. An MMRM model was used where treatment, country, and pre-trial OAD (MET or MET + SU) were included as fixed factors and baseline A1C as	LOCF MMRM imputation	• PP analysis • Complete case analysis • LOCF-based analysis • Comparator-based imputation analysis

Study	Outcome	Statistical Model	Imputation of Missing Data	Sensitivity Analyses
		covariate, and all nested within visit. The model assumed that data were MAR. Stratification factor: • background OAD: MET vs. MET + SU The NI analysis set was based on FAS and supplemented by an analysis with the PP analysis.	ANCOVA imputation (for PRO data)	• "In-trial" analysis
SUSTAIN-5	Change from baseline in A1C to week 30	Primary statistical analysis was based on FAS using observed data from "on-treatment without rescue medication" period. An MMRM model was used where treatment, country, and stratification variable were included as fixed factors and baseline A1C as covariate, and all nested within visit. The model assumed that data were MAR. Stratification variables: • A1C at screening: ≤ 8% vs. > 8% • use of MET: yes vs. no.	LOCF MMRM imputation ANCOVA imputation (for PRO data)	• Complete case analysis • LOCF-based analysis • Comparator-based imputation analysis • "In-trial" analysis
SUSTAIN-6	Time to first occurrence of MACE	Primary objective was to confirm that SEM did not excessively increase the CV risk as compared with placebo. The primary analysis was based on FAS using data from "in-trial" observation period. The primary end point was analyzed using a stratified Cox proportional hazards model with treatment group as fixed factor. The model was stratified by all possible combinations of the three stratification factors used in the randomization procedure (nine levels in total). Stratification factors: • evidence of CV disease at baseline: clinical vs. subclinical • insulin treatment at baseline: none vs. basal insulin vs. pre-mixed insulin • renal impairment: presence vs. absence.	MMRM imputation	• Analysis on all time to first MACE using alternative data-censoring strategies for exposure to treatment • Analysis on all time to first MACE using alternative patient selection
SUSTAIN-7	Change from baseline in A1C to week 40	Primary statistical analysis was based on FAS using data from "on-treatment without rescue medication" observation period. An MMRM model was used where all post-baseline A1C measurements obtained at all planned visits were entered as dependent variables, and treatment and country were included as fixed factors and baseline A1C as covariate, and all nested within visit. The model assumed that data were MAR.	LOCF	• Tipping point analysis • PP analysis • Complete case analyses • LOCF-based analysis • Retrieved dropout analysis

Study	Outcome	Statistical Model	Imputation of Missing Data	Sensitivity Analyses
Seino study	Number of TEAEs	Analysis of the primary end point was based on FAS using data from "in-trial" observation period. Main efficacy analysis was based on FAS using observed data from "on-treatment without rescue medication" period. An MMRM model was used where treatment and pre-trial treatment at screening were included as fixed factors and baseline A1C as covariate, and all nested within visit.	Missing (efficacy) data were imputed from a MMRM. Amount of missing data were expected to be small.	• Complete case analyses • ANCOVA using the LOCF imputation • Comparator-based multiple imputation • MMRM-based "in-trial" analysis

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CV = cardiovascular; FAS = full analysis set; A1C = glycated hemoglobin; LOCF = last observation carried forward; MACE = major adverse cardiovascular event; MAR = missing at random; MET = metformin; MMRM = Mixed Model for Repeated Measurements;
NI = non-inferiority; OAD = oral antidiabetic drug; PP = per-protocol; PRO = patient-reported outcome; SEM = semaglutide; SU = sulfonylurea; TEAE = treatment-emergent adverse event.

Source: Clinical Study Reports of SUSTAIN-1 to SUSTAIN-7[7-13] and the Seino study.[14]

Table 12: Statistical Testing Hierarchy and Power Estimates

Study	Statistical Testing Hierarchy	Statistical Power
SUSTAIN-1	Change from baseline to week 30 in the following outcomes were tested in order as listed below for SEM 1 mg versus placebo first, then SEM 0.5 mg versus placebo second: 1. Superiority in change in A1C for SEM 1 mg vs. placebo 2. Superiority in change in A1C for SEM 0.5 mg vs. placebo 3. Superiority in change in body weight for SEM 1 mg vs. placebo 4. Superiority in change in body weight for SEM 0.5 mg vs. placebo Superiority for either change in A1C or change in body weight was claimed if the upper limit of the 2-sided 95% CI for the estimated difference was below 0% or 0 kg, respectively.	Planned enrolment of 129 patients per treatment group at week 30 (20% dropout for SEM; 30% dropout for placebo) would have ≥ 90% power to detect: 1. a 0.5% difference in change from baseline to week 30 in A1C (SD = 1.1%) 2. a 2.5 kg in change in body weight at week 30 (SD = 4 kg) between SEM and placebo, based on a 1-sided CI with a confidence level of 97.5%. The two placebo groups were pooled in data analysis.
SUSTAIN-2	Change from baseline to week 56 in the following outcomes were tested in order as listed below for SEM 1 mg versus SIT first, then SEM 0.5 mg versus SIT second: 1. Non-inferiority in change in A1C for SEM 1 mg vs. SIT 2. Non-inferiority in change in A1C for SEM 0.5 mg vs. SIT 3. Superiority in change in A1C for SEM 1 mg vs. SIT 4. Superiority in change in body weight for SEM 1 mg vs. SIT 5. Superiority in change in body weight for SEM 0.5 mg vs. SIT 6. Superiority in change in A1C for SEM 0.5 mg vs. SIT Non-inferiority was concluded if the upper limit of the two-sided 95% CI for the estimated difference in A1C between SEM and SIT was < 0.3%. Superiority for either change in A1C or change in body weight was claimed if the upper limit of the 2-sided 95% CI for the estimated difference was below respectively 0% or 0 kg.	Planned enrolment of 399 patients per treatment group at week 56 (30% dropout) would have ≥ 90% power to detect: 1. a non-inferiority margin of 0.3%, a true difference of 0 in change from baseline to week 56 in A1C (SD = 1.1%) 2. a 1.5 kg in change in body weight at week 56 (SD = 4 kg) between SEM and SIT, based on a 1-sided CI with a confidence level of 97.5%. The two SIT treatment arms were pooled in data analyses.
SUSTAIN-3	Change from baseline to week 56 in the following outcomes were tested in order as listed below for SEM versus EXE: 1. Non-inferiority on change in A1C 2. Superiority on change in A1C 3. Superiority on change in body weight. Non-inferiority was concluded if the upper limit of the two-sided 95% CI for the estimated difference in A1C between SEM and EXE was < 0.3%. Superiority for either change in A1C or change in body weight was claimed if the upper limit of the 2-sided 95% CI for the estimated difference was below 0% or 0 kg, respectively.	Planned enrolment of 399 patients per treatment group at week 56 (30% dropout) would have ≥ 90% power to detect: 1. a non-inferiority margin of 0.3%, a true difference of 0 in change from baseline to week 56 in A1C (SD = 1.1%) 2. a 1.5 kg in change in body weight at week 56 (SD = 4 kg) between SEM and EXE, based on a 1-sided CI with a confidence level of 97.5%.

Study	Statistical Testing Hierarchy	Statistical Power
SUSTAIN-4	Change from baseline to week 30 in the following outcomes were tested in order as listed below for SEM 1 mg versus IG first, then SEM 0.5 mg versus IG second: 1. Non-inferiority in change in A1C for SEM 1 mg vs. IG 2. Superiority in change in body weight for SEM 1 mg vs. IG 3. Non-inferiority in change in A1C for SEM 0.5 mg vs. IG 4. Superiority in change in A1C for SEM 1 mg vs. IG 5. Superiority in change in body weight for SEM 0.5 mg vs. IG 6. Superiority in change in A1C for SEM 0.5 mg vs. IG Non-inferiority was concluded if the upper limit of the two-sided 95% CI for the estimated difference in A1C between SEM and IG was < 0.3%. Superiority for either change in A1C or change in body weight was claimed if the upper limit of the 2-sided 95% CI for the estimated difference was below respectively 0% or 0 kg.	Planned enrolment of 349 patients per treatment group (279 patients in the PP set) at week 30 (20% dropout) would have 80% power to detect: 1. a non-inferiority margin of 0.3%, a true difference of 0 in change from baseline to week 30 in A1C (SD = 1.1%) 2. a 1.5 kg in change in body weight at week 30 (SD = 4 kg) between SEM and IG, based on a 1-sided CI with a confidence level of 97.5%.
SUSTAIN-5	Change from baseline to week 30 in the following outcomes were tested in order as listed below for SEM 1 mg versus placebo first, then SEM 0.5 mg versus placebo second: 1. Superiority in change in A1C for SEM 1 mg vs. placebo 2. Superiority in change in A1C for SEM 0.5 mg vs. placebo 3. Superiority in change in body weight for SEM 1 mg vs. placebo 4. Superiority in change in body weight for SEM 0.5 mg vs. placebo Superiority for either change in A1C or change in body weight was claimed if the upper limit of the 2-sided 95% CI for the estimated difference was below 0% or 0 kg, respectively.	Planned enrolment of 130 patients per treatment group at week 30 (20% dropout) would have 82% power to detect: 1. a 0.5% difference in change from baseline to week 30 in A1C (SD = 1.1%) 2. a 2.5 kg in change in body weight at week 30 (SD = 4 kg) between SEM and placebo, based on a 1-sided CI with a confidence level of 97.5%. The two placebo groups were pooled in data analysis.
SUSTAIN-6	Change from baseline to study end points in the following outcomes were tested in order as listed below for SEM 1 mg versus placebo first, then SEM 0.5 mg versus placebo second: 1. Non-inferiority of SEM vs. placebo for the primary end point 2. Superiority of SEM 1 mg vs. placebo in change in body weight at week 104 3. Superiority of SEM 0.5 mg vs. placebo in change in body weight at week 104 4. Superiority of SEM 1 mg vs. placebo in change in A1C at week 30 for patients on pre-mix insulin at baseline 5. Superiority of SEM 0.5 mg vs. placebo in change in A1C at week 30 for patients on pre-mix insulin at baseline 6. Superiority of SEM 1 mg vs. placebo in change in A1C at week 30 for patients on SU monotherapy at baseline	Sample size calculation was based on the assumptions of a mean time in the trial of 2.10 years, an annual primary-event rate of 1.98%, a lost to follow-up rate of less than 10.0% and a true HR of 1.00. The total sample size required was set to 3,260, to determine the primary outcome in at least 122 patients and provide a power of 90% to reject a HR of at least 1.80 at the 0.05 level of significance.

Study	Statistical Testing Hierarchy	Statistical Power
	7. Superiority of SEM 0.5 mg vs. placebo in change in A1C at week 30 for patients on SU monotherapy at baseline Non-inferiority of SEM versus placebo was considered to be confirmed if the upper limit of the two-sided 95% CI for the HR was below 1.8 or equivalent if the *P* value for the one-sided test of: H0: HR ≥ 1.8 against Ha: HR < 1.8 was less than 2.5% (or equivalent to 5% for a two-sided test).	
SUSTAIN-7	Change from baseline to week 40 in the following outcomes were tested in order as listed below for SEM 0.5 mg versus DUL first, then SEM 1 mg versus IG second: 1. A1C non-inferiority of SEM 0.5 mg vs. DUL 0.75 mg (margin of 0.4%) 2. Body weight superiority of SEM 0.5 mg vs. DUL 0.75 mg 3. A1C superiority of SEM 0.5 mg vs. DUL 0.75 mg 4. A1C non-inferiority of SEM 1 mg vs. DUL 1.5 mg (margin of 0.4%) 5. Body weight superiority of SEM 1 mg vs. DUL 1.5 mg 6. A1C superiority of SEM 1 mg vs. DUL 1.5 mg Non-inferiority and/or superiority were confirmed if the mean treatment difference was supporting the corresponding hypothesis and the two-sided *P* value was strictly below its local two-sided significance level.	Planned enrolment of 299 patients per treatment group at week 40 (25% dropout) would have 90% power to detect: 1. a non-inferiority margin of 0.4%, a difference of 0 in change from baseline to week 40 in A1C (SD = 1.1%) 2. a 1.5 kg in change in body weight at week 40 (SD = 4 kg) between SEM and DUL, based on a 1-sided CI with a confidence level of 97.5%. The following assumptions were used: 1) treatment difference in A1C of SEM relative to DUL at week 40 within both dose levels (SEM 0.5 mg vs. DUL 0.75 mg; SEM 1 mg vs. DUL 1 mg) was zero; 2) the assumed treatment difference in body weight of SEM relative to DUL at week 40 within both dose levels was 1.5 kg; 3) the SD for A1C was assumed to be 1.1% and the SD for body weight was assumed to be 4 kg.
Seino study	No information.	Planned number of randomized patients was 306. Treatment discontinuation was expected to be 20%. No details for power calculation.

A1C = glycated hemoglobin; CI = confidence interval; DUL = dulaglutide; EXE = exenatide; HR = hazard ratio; IG = insulin glargine; PP = per-protocol; SD = standard deviation; SEM = semaglutide; SIT = sitagliptin.

Source: Clinical Study Reports of SUSTAIN-1 to 7[7-13] and the Seino study[14]

Table 13: Patient Disposition (Placebo-Controlled RCTs)

Characteristics	SUSTAIN-1			SUSTAIN-5		
	SEM 0.5 mg	SEM 1 mg	Placebo	SEM 0.5 mg	SEM 1 mg	Placebo
Screened, N	652			534		
Randomized	129	130	129	132	132	133
Premature treatment discontinuation, N (%)	17 (13.3)	16 (12.3)	14 (10.9)	14 (10.6)	16 (12.2)	13 (9.8)
Adverse events	8 (6.3)	7 (5.4)	3 (2.3)	6 (4.5)	10 (7.6)	1 (0.8)
Protocol violation	4 (3.1)	2 (1.5)	1 (0.8)	1 (0.8)	0	2 (1.5)
Pregnancy	0	0	1 (0.8)	1 (0.8)	0	0
Other	5 (3.9)	7 (5.4)	9 (7.0)	6 (4.5)	6 (4.6)	10 (7.5)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	0	0	0	0	0	0
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FAS, N (%)	128 (99.2)	130 (100)	129 (100)	132 (100)	131 (99.2)	133 (100)
SAS, N (%)	128 (99.2)	130 (100)	129 (100)	132 (100)	131 (99.2)	133 (100)

FAS = full analysis set; RCT = randomized controlled trial; SAS = safety analysis set; SEM = semaglutide.

Source: Clinical Study Reports of SUSTAIN-1[7] and SUSTAIN-5.[8]

Table 14: Glycemic Control Outcomes (SEM as Second-Line Therapy, Add-On to MET Only)

	SUSTAIN-2			SUSTAIN-3		SUSTAIN-4			SUSTAIN-7			
	SEM 0.5 mg	SEM 1 mg	SIT	SEM 1 mg	EXE	SEM 0.5 mg	SEM 1 mg	IG	SEM 0.5 mg N = 301	SEM 1 mg N = 300	DUL 0.75 mg N = 299	DUL 1.5 mg N = 299
A1C, %												
Patients contribute to the analysis, n (%)												
Baseline, mean (SD)									8.3 (0.96)	8.2 (0.92)	8.2 (0.91)	8.2 (0.89)
End of study, mean (SE)									6.72 (0.06)	6.45 (0.06)	7.12 (0.05)	6.86 (0.06)
Change from baseline at end of study, mean (SE)									–1.51 (0.06)	–1.78 (0.06)	–1.11 (0.05)	–1.37 (0.06)
Treatment group difference versus comparator (95% CI)									–0.40 (–0.55 to –0.25) *P* < 0.0001	–0.41 (–0.57 to –0.25) *P* < 0.0001	NA	NA

A1C = glycated hemoglobin; CI = confidence interval; DUL = dulaglutide; EXE = exenatide; IG = insulin glargine; MET = metformin; NA = not applicable; SD = standard deviation; SE = standard error; SEM = semaglutide; SIT = sitagliptin.

Note: for SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4, on-treatment without rescue medication data are presented. The post-baseline data are analyzed using the mixed model for repeated measurements with treatment and baseline OAD subgroup as fixed factors, interaction between treatment and OAD subgroup, and baseline A1C as covariate, all nested within visit. For SUSTAIN-7, on-treatment without rescue medication data are presented. The post-baseline responses are analyzed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

Source: Additional information of subgroup analyses in SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4 provided in Submission;[16] Clinical Study Report of SUSTAIN-7.[13]

Table 15: Patient Disposition (CV Outcome RCT)

Characteristics	SUSTAIN-6			
	SEM 0.5 mg	SEM 1 mg	Placebo 0.5 mg	Placebo 1 mg
Screened, N	4,346			
Randomized	826	822	824	825
Premature treatment discontinuation, N (%)	164 (19.9%)	186 (22.6%)	151 (18.3%)	159 (19.3%)
Adverse events	98 (11.9)	118 (14.4)	48 (5.8)	63 (7.7)
Withdrawal of informed consent	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Introduction of disallowed medication	3 (0.4%)	3 (0.4%)	8 (1.0%)	8 (1.0%)
Suspicion of placebo (without introduction of disallowed medication)	3 (0.4%)	3 (0.4%)	15 (1.8%)	10 (1.2%)
Randomized in error	12 (1.5%)	13 (1.6%)	16 (1.9%)	6 (0.7%)
Resistance to injections	2 (0.2%)	0	2 (0.2%)	0
Trial fatigue	5 (0.6%)	5 (0.6%)	15 (1.8%)	11 (1.3%)
Other	40 (4.8%)	43 (5.2%)	46 (5.6%)	60 (7.3%)
FAS, N	826 (100.0%)	822 (100.0%)	824 (100.0%)	825 (100.0%)
SAS, N	823 (99.6%)	819 (99.6%)	819 (99.4%)	825 (100.0%)

CV = cardiovascular; FAS = full analysis set; RCT = randomized controlled trial; SAS = safety analysis set; SEM = semaglutide.

Source: Clinical Study Report of SUSTAIN-6.[9]

Exposure to Study Treatments

The mean duration of study treatment ranged from 189 days to 208 days in trials with 30 weeks of treatment; from 249 days to 268 days in trials with 40 weeks of treatment; and from 335 days to 373 days in trials with 56 weeks of treatment. For the two-year CVOT SUSTAIN-6, the mean in-trial observation period was 2.1 years, while the on-treatment observation period was 1.8 years in all three treatment arms (Table 16 and Table 17).

Table 16: Exposure (Placebo-Controlled RCTs)

Exposure	SUSTAIN-1			SUSTAIN-5			SUSTAIN-6		
	SEM 0.5 mg	SEM 1 mg	Placebo	SEM 0.5 mg	SEM 1 mg	Placebo	SEM 0.5 mg	SEM 1 mg	Placebo
Duration of study treatment, days, mean (SD)	[redacted]						NR		
On-treatment without rescue medication observation period, days, mean (SD)	[redacted]						NA		
On-treatment observation period, days, mean (SD)	[redacted]						[redacted]		
In-trial observation period, days, mean (SD)	[redacted]						[redacted]		

NA = not applicable; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SEM = semaglutide.

Source: Clinical Study Reports of SUSTAIN-1, 5, and 6.[7-9]

Table 17: Exposure (Active-Controlled RCTs; SAS)

	SUSTAIN-2			SUSTAIN-3		SUSTAIN-4			SUSTAIN-7				Seino		
	SEM 0.5 mg	SEM 1 mg	SIT	SEM 1 mg	EXE	SEM 0.5 mg	SEM 1 mg	IG	SEM 0.5 mg	SEM 1 mg	DUL 0.75 mg	DUL 1.5 mg	SEM 0.5 mg	SEM 1 mg	SIT
Duration of study treatment, days, mean (SD)	[redacted]													NR	
On-treatment without rescue medication observation period, days, mean (SD)	[redacted]													NR	
On-treatment observation period, days, mean (SD)	[redacted]													NR	
In-trial observation period, days mean (SD)	[redacted]													NR	

DUL = dulaglutide; EXE = exenatide; FAS = full analysis set; IG = insulin glargine; NR = not reported; RCT = randomized controlled trial; SAS = safety analysis set; SD = standard deviation; SEM = semaglutide; SIT = sitagliptin.

Source: Clinical Study Reports of SUSTAIN-2, 3, 4, 7,[10-13] and Seino study.[14]

Critical Appraisal

Internal Validity

In the included studies, randomization was conducted using a validated system. In some trials differences in characteristics were noted which may have occurred by chance or may be reflective of issues with the randomization implementation itself. For example in SUSTAIN-1, patients treated with higher dose SEM had shorter duration of the disease (mean of 3.65 years in the SEM 1 mg group compared with 4.85 years in the SEM 0.5 mg group). This implies that patients in higher dose group were more likely to achieve treatment goals, because they did not have as long-standing diabetes as those in the lower dose group, therefore the treatment effect of SEM 1 mg could be overestimated.

For trials using a double-blind design, appropriate methods were used to ensure allocation concealment. However, it is possible that patients and investigators could review and discuss changes in the A1C levels, body weight, and AEs, particularly some specific drug effects which are known to be associated with the administration of GLP-1 receptor agonists, such as gastrointestinal AEs. This may have allowed certain patients and/or investigators to surmise the assigned treatment, and subsequently may have an impact on patient-reported outcomes or AEs. For trials with open-label design, patients were aware of the treatment allocation, therefore the evaluation of patient-reported outcomes or AEs may also be affected by unblinded treatment regimen. The primary outcome variable in the majority of the included trials was change in A1C, which is an objective outcome measure. Even though it is unlikely that this had an important impact on the study results for the primary analysis, the clinicians could easily determine the A1C levels and may have adjusted medications or initiated rescue medications accordingly, thus the secondary end points and sensitivity analyses could have been affected.

In terms of the methods of statistical analysis, efficacy analyses were performed in FAS. Although a true ITT population was not used (patients were required to receive at least one dose of the study drug) in all trials except for SUSTAIN-6, it is less likely that this would have an impact on the study results due to the small number of patients that were excluded from FAS. For NI trial, acceptable margins (0.5% change in A1C in placebo-controlled trial, or 0.3% change in A1C in active-controlled trial) were used.

A hierarchical testing procedure was used to account for multiple comparisons among primary end point and the key secondary end points. Various approaches (e.g., model-based imputation and LOCF) were used to handle missing data in the included studies. The hierarchical sequence in the included studies was pre-specified and included clinically outcomes that were commonly accepted in diabetes trials. Outcomes outside of the testing hierarchy, such as occurrence of diabetes-related morbidity (e.g., individual component of MACE or expanded composite CV outcome), change in blood pressure, and HRQoL, need to be interpreted with caution due to the possible inflated type I error. Moreover, it is unclear how to interpret the diabetes-related morbidity end points as determination of the NI margin for these individual component analyses were not specified in the study protocol. Some important outcomes in diabetes trials were not included in the testing hierarchy, such as hypoglycemia.

The proportion of missing data were substantial (greater than 20%) and differential between SEM and the controls in most of the trials. MMRM was used in primary efficacy analysis, and it assumes that data are MAR. However, missing data can be associated with treatment discontinuation due to lack of efficacy (e.g., poor glycemic control) or intolerable adverse

effects from the treatment, it would not be considered MAR, and may potentially impact the results of the trials in favour of SEM. In addition, due to the repeated measures design of MMRM, the potential impact of missing data during scheduled time points on the overall study results which were measured at the end of follow-up is uncertain and could have affected the study results. In the SUSTAIN trials, sensitivity analyses were conducted to assess the validity of MAR assumption and to evaluate the robustness of the conclusion of the primary analysis. Although these analyses showed similar results as the primary data analysis, these analyses cannot fully account for the impact of missing data. In a chronic progressive disease like diabetes where patients continue to lose glycemic control over time, the LOCF can introduce bias as it assumes patients remain stable for all subsequent time points which is rarely the case in the real world. Thus, although the trials outlined appropriately the various approaches of missing data handling, none are sufficient to overcome the missing data and may have introduced bias into the results.

The majority of the included trials evaluated the change from baseline in A1C as the primary outcome and were not designed to test for longer-term diabetes-related morbidity or mortality. There is one single cardiovascular safety trial (SUSTAIN-6) included in this review, and this two-year trial may address some of the questions of interest in clinical practice.

None of the included trials were powered to assess efficacy outcomes such as change in blood pressure or blood lipids, or for harm outcomes such as hypoglycemia.

In the SUSTAIN trials, a number of pre-defined subgroup analyses based on various patient's baseline characteristics were conducted to examine the consistency of the primary analysis results across subgroup levels; however most of these, such as the subgroups based on renal function in SUSTAIN-5 or subgroups based on A1C level at baseline in SUSTAIN-6, were not included as a stratification variable at randomization. Thus, balance of patient's baseline characteristics was unlikely to be maintained between such subgroups, and this could subsequently bias the results. In SUSTAIN-2, 3, and 4, subgroup analyses based on prior antidiabetic therapy were performed to explore treatment effect of the study drug in special subgroups. However, these were post hoc analyses and were exploratory in nature, therefore it is challenging in data interpretation due to insufficient power to detect a true difference between treatment groups, imbalance of patient's baseline characteristics across the subgroups, complexity of testing interaction effect (*P*-values less than 0.05 for some of the interaction tests), or the inconsistency between statistical significance and clinical importance. Wider 95% CIs for the point estimate of between-group differences in efficacy outcomes were observed in several of these subgroups, which may be expected given the lack of power within the subgroup analyses. In addition, multiplicity and potential inflated type I error are concerns within the subgroups. As a result, the interpretation of subgroup analyses with respect to various outcomes is difficult. Moreover, in these NI trials, it is unclear how the specific subgroups effects should have been interpreted with respect to the NI margins which were defined for the overall population, or whether subgroup-specific margins should have been employed. Similarly, in SUSTAIN-6, it is questionable to interpret the results of individual component based on the NI margin used for the composite outcome, as the margin for individual component may not be the same as the composite outcome. In this trial, the observed CV benefits appeared to be mainly driven by non-fatal MI and non-fatal stroke, while the rate of CV death was similar between SEM and placebo. There is also a concern with multiplicity of testing in SUSTAIN-6.

Patients in SUSTAIN-2, 3, and 4 had various background antidiabetic therapies before entering the trials. Therefore, SEM was used as second-line or third-line therapy. Given that patients who are controlled on two prior OADs represent a more advanced diabetes

population (longer history of disease, more comorbidities or diabetes-related complications, inadequate response to previous treatment, etc.) than those controlled on one OAD, it is questionable to mix these patients in one analysis. This also affects the generalizability of the study findings.

For most of the trials (e.g., SUSTAIN-2, 3, 4, and 6), safety outcomes were reported in the full population where semaglutide can be used as first-line, second-line or third-line therapy, and subgroup data were not available. It is difficult to examine the safety outcome according to patient's prior background antidiabetic therapy.

In general, diet and exercise are a part of the standard care of patients with T2DM. In SUSTAIN-2 to 7, it was unknown whether "diet and exercise" was background therapy. Therefore, there could be validity issues related to this and likely decreases generalizability of the study results.

External Validity

SEM was not used as a first-line therapy in the vast majority of the included trials. SUSTAIN-1 recruited patients who were drug naive, therefore did not provide evidence to support the manufacturer's requested reimbursement criteria of "for the treatment of adult patients with T2DM to improve glycemic control, in combination with MET (second-line treatment) and in combination with MET + SU (third-line treatment)". All included trials except for the Japanese study were multinational. Although few Canadian patients were enrolled, the consulted clinical expert indicates that the study results are generalizable to Canadian population, according to the selection criteria and the patient's baseline characteristics including diabetes-related characteristics.

The treatment duration of the included trials (ranging from 30 weeks to 56 weeks) was considered adequate in terms of assessing efficacy of semaglutide treatment versus comparators on change in A1C, the safety, tolerability, and patient satisfaction, but may not be sufficient for assessment of sustainability of A1C change or CV outcomes. The CVOT (SUSTAIN-6) had a treatment duration of 104 weeks; therefore, it would be able to provide some evidence on longer-term effect of the study drug.

The included trials provide direct evidence for the comparisons between semaglutide and other GLP-1 receptor agonists, DPP-4 inhibitors, or insulin glargine. There is a lack of direct evidence on the comparisons between semaglutide and other currently available active treatment, such as SGLT2 inhibitors.

Efficacy

Only those efficacy outcomes identified in the review protocol (Table 4) are reported below. Data are presented based on the lines of therapy (first-line, second-line and third-line) for SEM, refer to the table "Efficacy Outcomes Presented in the Current CDR Review" below. Additional efficacy data with respect to glycemic control and change in body weight and BMI in the overall population (lines of therapy were mixed in the study population) for SUSTAIN-2 to 4 are presented in Appendix 4. Limited data were available on HRQoL. None of the trials evaluated hospitalizations.

Results show that none of the hierarchy tests for NI hypothesis and superiority hypotheses failed.

Table 18: Efficacy Outcomes Presented in the Current CDR Review

Categories	RCTs	Number of Tables
SEM used as first-line	SUSTAIN-1	Table 18: glycemic control Table 24: mortality Table 30: BMI/body weight Table 36: blood pressure Table 42: lipid profile
SEM used as second-line	Subgroup of SUSTAIN-2 Subgroup of SUSTAIN-3 Subgroup of SUSTAIN-4 SUSTAIN-7	Table 19: glycemic control Table 25: mortality Table 31: BMI/body weight Table 37: blood pressure Table 43: lipid profile
SEM used as third-line	Subgroup of SUSTAIN-2 Subgroup of SUSTAIN-3 Subgroup of SUSTAIN-4	Table 20: glycemic control Table 32: BMI/body weight Table 38: blood pressure Table 44: lipid profile
CVOT	SUSTAIN-6	Table 21: glycemic control Table 26: mortality Table 29: diabetes-related morbidity Table 33: BMI/body weight Table 39: blood pressure Table 45: lipid profile
SEM used as second- or third-line, no separate results available for specific background therapy	SUSTAIN-5	Table 22: glycemic control Table 27: mortality Table 34: BMI/body weight Table 40: blood pressure Table 46: lipid profile
SEM used as first- or second-line, no separate results provided for specific background therapy	Seino 2018	Table 23: glycemic control Table 28: mortality Table 35: BMI/body weight Table 41: blood pressure Table 47: lipid profile

BMI = body mass index; CDR = CADTH Common Drug Review; CVOT = cardiovascular outcome trial; RCT = randomized control trial; SEM = semaglutide.

Glycemic Control

SEM Used as First-Line Therapy

SUSTAIN-1 reported change in A1C from baseline to week 30 in drug-naive patients. At week 30, the mean change in A1C was -1.45% (SE 0.10), -1.55% (SE 0.10) and -0.02% (SE 0.10) for patients who received SEM 0.5 mg, SEM 1 mg, and placebo, respectively. The mean differences were statistically significant for both SEM groups compared with placebo (SEM 0.5 mg: -1.43%; 95% CI -1.71% to -1.15%; SEM 1 mg: -1.53%, 95% CI -1.81% to -1.25 %) (Table 18). Because the upper limit of the 2-sided 95% CI for the estimated differences was below 0%, superiority of SEM 0.5 mg or SEM 1 mg versus placebo in glycemic control was demonstrated. The between-group differences were considered clinically important.

Table 19: Glycemic Control Outcomes (SEM as First-Line Therapy)

	SUSTAIN-1		
	SEM 0.5 mg N = 128	SEM 1.0 mg N = 130	Placebo N = 129
A1C, %			
Patients contribute to the analysis	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	8.09 (0.89)	8.12 (0.81)	7.95 (0.85)
Week 30, mean (SE)	6.60 (0.10)	6.50 (0.10)	8.03 (0.10)
Change from baseline at week 30, mean (SE)	–1.45 (0.10)	–1.55 (0.10)	–0.02 (0.10)
Treatment group difference versus placebo (95% CI)	–1.43 (–1.71 to –1.15) *P* < 0.0001	–1.53 (–1.81 to –1.25) *P* < 0.0001	NA

A1C = glycated hemoglobin; CI = confidence interval; NA = not applicable; SD = standard deviation; SE = standard error; SEM = semaglutide.

Source: Clinical Study Report of SUSTAIN-1.[7]

SEM Used As Second-Line Therapy (Add-On to MET)

Results of post hoc subgroup analyses on glycemic control in SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4 are presented. Patients in SUSTAIN-7 received treatment with SEM or DUL with background therapy of MET monotherapy.

In patients receiving SEM as the second-line therapy (add-on to MET), treatment with either dose of SEM for 30 to 56 weeks was associated with greater glycemic control, compared with SIT, EXE, or IG (Table 19). The mean change from baseline in A1C ranged from [redacted] for the SEM 0.5 mg group, and from [redacted] for the SEM 1 mg group. Compared with SIT, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group. Compared with EXE, the mean between-group difference was [redacted] for the SEM 1 mg group. Compared with IG, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group. Compared with DUL, the mean between-group differences were -0.40% (95% CI -0.55 to -0.25) for the SEM 0.5 mg group and -0.41% (95% CI -0.57 to -0.25) for the SEM 1 mg group. In SUSTAIN-7, superiority in reducing A1C was concluded for each dose of SEM compared with the respective dose level of DUL.

According to the clinical expert consulted for this review, the between-group differences in A1C were considered clinically relevant.

Table 20: Glycemic Control Outcomes (SEM as Second-Line Therapy, Add-On to MET Only)

	SUSTAIN-2			SUSTAIN-3		SUSTAIN-4			SUSTAIN-7			
	SEM 0.5 mg	SEM 1 mg	SIT	SEM 1 mg	EXE	SEM 0.5 mg	SEM 1 mg	IG	SEM 0.5 mg N = 301	SEM 1 mg N = 300	DUL 0.75 mg N = 299	DUL 1.5 mg N = 299
A1C, %												
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8.3 (0.96)	8.2 (0.92)	8.2 (0.91)	8.2 (0.89)
End of study, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6.72 (0.06)	6.45 (0.06)	7.12 (0.05)	6.86 (0.06)
Change from baseline at end of study, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–1.51 (0.06)	–1.78 (0.06)	–1.11 (0.05)	–1.37 (0.06)
Treatment group difference versus comparator (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–0.40 (–0.55 to –0.25) *P* < 0.0001	–0.41 (–0.57 to –0.25) *P* < 0.0001	NA	NA

A1C = glycated hemoglobin; CI = confidence interval; DUL = dulaglutide; EXE = exenatide; IG = insulin glargine; MET = metformin; NA = not applicable; SD = standard deviation; SE = standard error; SEM = semaglutide; SIT = sitagliptin.

Note: for SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4, on-treatment without rescue medication data are presented. The post-baseline data are analyzed using the mixed model for repeated measurements with treatment and baseline OAD subgroup as fixed factors, interaction between treatment and OAD subgroup, and baseline A1C as covariate, all nested within visit. For SUSTAIN-7, on-treatment without rescue medication data are presented. The post-baseline responses are analyzed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

Source: Additional information of subgroup analyses in SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4 provided in Submission;[16] Clinical Study Report of SUSTAIN-7.[13]

SEM Used as Third-Line Therapy (Add-On to MET + TZD or MET + SU)

Results of post hoc subgroup analyses on glycemic control in SUSTAIN-2 to SUSTAIN-4 are presented. Note that this analysis did not provide subgroup results based on background therapy of MET + SU only in accordance with the listing criteria.

In patients receiving SEM as the third-line therapy (add-on to MET + TZD or MET + SU), treatment with either dose of SEM for 30 weeks to 56 weeks was associated with greater glycemic control, compared with SIT, EXE, or IG (Table 20). The mean change from baseline in A1C ranged from [redacted] for the SEM 0.5 mg group, and from [redacted] for the SEM 1 mg group. Compared with SIT, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group. Compared with EXE, the mean between-group difference was [redacted] for the SEM 1 mg group. Compared with IG, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group.

According to the clinical expert consulted for this review, the between-group differences in A1C were considered clinically relevant.

Table 21: Glycemic Control Outcomes (SEM as Third-Line Therapy, Add-On to MET + TZD or MET + SU; FAS)

	SUSTAIN-2[a]			SUSTAIN-3[b]		SUSTAIN-4[b]		
	SEM 0.5 mg [redacted]	SEM 1 mg [redacted]	SIT [redacted]	SEM 1 mg [redacted]	EXE [redacted]	SEM 0.5 mg [redacted]	SEM 1 mg [redacted]	IG [redacted]
A1C, %								
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of study, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at end of study, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment group difference versus comparator (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; CI = confidence interval; EXE = exenatide; FAS = full analysis set; IG = insulin glargine; MET = metformin; NA = not applicable; OAD = oral antidiabetic drug; SD = standard deviation; SE = standard error; SEM = semaglutide; SIT = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

[a] Add-on to MET + TZD.

[b] Add-on to MET + SU.

Note: for SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4, on-treatment without rescue medication data are presented. The post-baseline data are analyzed using the mixed model for repeated measurements with treatment and baseline OAD subgroup as fixed factors, interaction between treatment and OAD subgroup, and baseline A1C as covariate, all nested within visit.

Source: Additional information of subgroup analyses in SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4 provided in Submission.[16]

SEM Used in Mixed Population (as Second- or Third-Line Therapy, Add-On to Standard of Care)

Efficacy of study medications on glycemic control in SUSTAIN-6 was presented in Table 21. In patients with clinical evidence or subclinical evidence of CV disease and who received standard of care for T2DM, treatment with either dose of SEM for 30 weeks was associated with greater glycemic control, compared with placebo. The mean change from baseline in

A1C was –1.09% (SE 0.05) for the SEM 0.5 mg group, and –1.41% (SE 0.05) for the SEM 1 mg group. Compared with placebo, the mean between-group differences were –0.66% (95% CI –0.80 to –0.52, *P* < 0.0001) for the SEM 0.5 mg group and –1.05% (95% CI –1.19 to –0.91, *P* < 0.0001) for the SEM 1 mg group.

According to the clinical expert consulted for this review, the between-group differences in A1C were considered clinically relevant.

Table 22: Glycemic Control Outcomes (Cardiovascular Outcome RCT; SEM as Second- or Third-Line Therapy, Add-On to Standard of Care; FAS)

	SUSTAIN-6			
	SEM 0.5 mg N = 826	**SEM 1 mg N = 822**	**Placebo 0.5 mg N = 824**	**Placebo 1 mg N = 825**
A1C, %				
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	8.67 (1.39)	8.73 (1.51)	8.70 (1.49)	8.70 (1.45)
Week 30, mean (SE)	7.61 (0.05)	7.29 (0.05)	8.26 (0.05)	8.34 (0.05)
Change from baseline at week 104, mean (SE)	–1.09 (0.05)	–1.41 (0.05)	–0.44 (0.05)	–0.36 (0.05)
Treatment group difference versus placebo (95% CI)	–0.66 (–0.80 to –0.52) *P* < 0.0001	–1.05 (–1.19 to –0.91) *P* < 0.0001	NA	NA

A1C = glycated hemoglobin; CI = confidence interval; CV = cardiovascular; FAS = full analysis set; NA = not applicable; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; SEM = semaglutide.

Note: "In-trial" data are presented. The post-baseline responses are analyzed using a mixed model for repeated measurements with treatment (four levels) and stratification (nine levels) as fixed factors and baseline value as covariate, all nested within visit.

Source: Clinical Study Report of SUSTAIN-6.[9]

SEM Used in Mixed Population (Second- or Third-Line Therapy; Add-On to Basal Insulin Alone or Basal Insulin + MET)

Efficacy of study medications on glycemic control in SUSTAIN-5 was presented in Table 22. This was a mixed population where subgroup results based on background therapy was not available. In patients who received background basal insulin or basal insulin plus MET, treatment with either dose of SEM for 30 weeks was associated with greater glycemic control, compared with placebo.

The mean change from baseline in A1C was –1.45% (SE 0.09) for the SEM 0.5 mg group, and –1.85% (SE 0.09) for the SEM 1 mg group. Compared with placebo, the mean between-group differences were –1.35% (95% CI –1.61 to –1.10, *P* < 0.0001) for the SEM 0.5 mg group and –1.75% (95% CI –2.01 to –1.50, *P* < 0.0001) for the SEM 1 mg group.

In SUSTAIN-5, the between-group differences were statistically significant. Superiority in reducing A1C was concluded for each dose of SEM compared with placebo, when the upper limit of the two-sided 95% CI for the estimated difference was below 0%.

According to the clinical expert consulted for this review, the between-group differences in A1C were considered clinically relevant.

Table 23: Glycemic Control Outcomes (SEM as Second- or Third-Line Therapy, Add-On to Basal Insulin Alone or Basal Insulin + MET; FAS)

	SUSTAIN-5		
	SEM 0.5 mg N = 132	**SEM 1 mg N = 131**	**Placebo N = 133**
A1C, %			
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	8.36 (0.83)	8.31 (0.82)	8.42 (0.88)
Week 30, mean (SE)	6.92 (0.09)	6.52 (0.09)	8.27 (0.09)
Change from baseline at Week 30, mean (SE)	–1.45 (0.09)	–1.85 (0.09)	–0.09 (0.09)
Treatment group difference versus placebo (95% CI)	–1.35 (–1.61 to –1.10) *P* < 0.0001	–1.75 (–2.01 to –1.50) *P* < 0.0001	NA

A1C = glycated hemoglobin; CI = confidence interval; FAS = full analysis set; MET = metformin; NA = not applicable; SD = standard deviation; SE = standard error; SEM = semaglutide.

Note: "On-treatment without rescue medication" data are presented. The post-baseline responses are analyzed using a mixed model for repeated measurements with treatment, country and stratification variable (A1C level at screening [less than and equal to 8.0% or greater than 8.0%] crossed with use of metformin [yes or no]; two by two levels) as fixed factors and baseline value as covariate, all nested within visit.

Source: Clinical Study Report of SUSTAIN-5.[8]

SEM Used in Mixed Population (First- or Second-Line Therapy; Add-On to Diet/Exercise Alone or Diet/Exercise + OAD)

Efficacy of study medications on glycemic control in the Seino study was presented in Table 23. This was a mixed population where subgroup results based on background therapy were not available. In patients receiving background therapy of diet and exercise alone or diet and exercise plus OAD, treatment with either dose of SEM for 30 weeks was associated with greater glycemic control, compared with SIT. The mean change from baseline in A1C was –1.9% (SE 0.1) for the SEM 0.5 mg group, and –2.2% (SE 0.1) for the SEM 1 mg group. Compared with SIT, the mean between-group differences were –1.13% (95% CI –1.32 to –0.94, *P* < 0.0001) for the SEM 0.5 mg group and –1.44% (95% CI –1.63 to –1.24, *P* < 0.0001) for the SEM 1 mg group.

The between-group differences were statistically significant. According to the clinical expert consulted for this review, the between-group differences in A1C were considered clinically relevant.

Table 24: Glycemic Control Outcomes (SEM as First- and Second-Line Therapy; FAS)

	Seino 2018		
	SEM 0.5 mg N = 103	**SEM 1 mg N = 102**	**SIT N = 103**
A1C, %			
Baseline value, mean (SD)	8.2 (1.0)	8.0 (0.9)	8.2 (0.9)
Week 30, mean (SE)	NR		
Change from baseline at week 30, mean (SE)	–1.9 (0.1)	–2.2 (0.1)	–0.7 (0.1)
Treatment group difference versus SIT (95% CI)	–1.13 (–1.32 to –0.94) *P* < 0.0001	–1.44 (–1.63 to –1.24) *P* < 0.0001	NA

A1C = glycated hemoglobin; CI = confidence interval; FAS = full analysis set; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error; SEM = semaglutide; SIT = sitagliptin.

Source: Seino 2018.[14]

Efficacy results of SUSTAIN-2, 3, and 4 in the overall population are presented in Appendix 4. The results were consistent with those reported in the subgroups based on background therapy (Table 19 and Table 20). Given that the upper limit of the two-sided 95% CI for the estimated difference in A1C between both doses of SEM and SIT was less than the pre-specified 0.3% margin, NI of both doses of SEM treatment to SIT at week 56 was concluded in SUSTAIN-2. In SUSTAIN-3, because the upper limit of the 95% CI for the estimated between-group difference was below the 0.3% margin, NI of SEM 1 mg versus EXE 2.0 mg was demonstrated for change from baseline in A1C at week 56. In SUSTAIN-4, NI of both doses of SEM to IG was demonstrated when the upper limit of the 95% CI for the estimated between-group difference was below the 0.3% margin. Following confirmation of NI, subsequent testing for superiority was performed, and for all three trials superiority was concluded for both doses of SEM versus SIT, EXE, and IG for change from baseline in A1C.

Mortality

There were no cases of death reported in SUSTAIN-1 (Table 24), SUSTAIN-5 (Table 27), and the Seino study (Table 28).

In SUSTAIN-2, there were six deaths reported during the trial, all of which occurred during the “on-treatment” observation period. Two deaths occurred with SEM 0.5 mg (“ischemic cardiomyopathy” and “cardiovascular disorder”), one with SEM 1.0 mg (“cardiorespiratory arrest”), and three with SIT (“ischemic stroke,” “road traffic accident,” and “death”). All deaths were assessed as unlikely related to study medication by the investigator.

In SUSTAIN-3, two deaths were reported in the SEM 1 mg group (one hepatocellular carcinoma and one invasive lobular breast carcinoma). Both deaths were adjudicated as malignant neoplasms and non-cardiovascular deaths by EAC. Both deaths were assessed as unlikely related to the study medication by the investigator.

In SUSTAIN-4, six deaths were reported during the trial: four with SEM 0.5 mg and two with IG. The four deaths reported in the SEM 0.5 mg group were due to myocarditis, cerebrovascular accident, ischemic stroke, and pancreatic carcinoma; while those reported for IG were caused by atherosclerosis coronary artery and an undetermined cause of death. Of the six fatal events, five were assessed as unlikely to be related to the study medication. The pancreatic carcinoma event was assessed as possibly related to the treatment.

Deaths were not reported in subgroups based on background therapy in SUSTAIN-2, 3, and 4 (Table 25).

The proportion of death and CV death were similar across treatment arms in SUSTAIN-6 (Table 26).

In SUSTAIN-7, six patients died during the trial: five during the “on-treatment” observation period (one with SEM 1.0 mg, two with DUL 0.75 mg, and two with DUL 1.5 mg) and one with SEM 0.5 mg during the “in-trial” period after prematurely discontinuing treatment. None of the deaths were considered to be related to the study medication (Table 25).

Table 25: Mortality (SEM as First-Line Therapy, SAS)

	SUSTAIN-1		
	SEM 0.5 mg N = 128	SEM 1.0 mg N = 130	Placebo N = 129
All-cause death, n	0		
CV-related death, n	0		

CV = cardiovascular; SAS = safety analysis set; SEM = semaglutide.

Source: Clinical Study Report of SUSTAIN-1.[7]

Table 26: Mortality (SEM as Second-Line Therapy, Add-On to MET, SAS)

	SUSTAIN-2			SUSTAIN-3		SUSTAIN-4			SUSTAIN-7			
	SEM 0.5 mg N = 409	SEM 1 mg N = 409	SIT N = 407	SEM 1 mg N = 404	EXE N = 405	SEM 0.5 mg N = 362	SEM 1 mg N = 362	IG N = 365	SEM 0.5 mg N = 301	SEM 1 mg N = 300	DUL 0.75 mg N = 299	DUL 1.5 mg N = 299
All-cause death, n	NR in subgroups			NR in subgroups		NR in subgroups			1	1	2	2
CV-related death, n	NR in subgroups			NR in subgroups		NR in subgroups			0	0	2	1

CV = cardiovascular; DUL = dulaglutide; EXE = exenatide; IG = insulin glargine; MET = metformin; NR = not reported; SAS = safety analysis set; SEM = semaglutide; SIT = sitagliptin.

Source: Clinical Study Reports of SUSTAIN-2, 3, 4, 7.[10-13]

Table 27: Mortality (Cardiovascular Outcome RCT; SEM as Second- or Third-Line Therapy, Add-On to Standard of Care, FAS)

	SUSTAIN-6		
	SEM 0.5 mg N = 826	SEM 1 mg N = 822	Placebo N = 1,649
All-cause death (investigator-reported), n (%)	31 (3.8)	31 (3.8)	61 (3.7)
EAC-categorization of all-cause death – FAS in-trial, n (%)	30 (3.6)	32 (3.9)	60 (3.6)
CV-related death, n (%)	21 (2.5)	23 (2.8)	46 (2.8)

CV = cardiovascular; EAC = Event Adjudication Committee; FAS = full analysis set.

Source: Clinical Study Report of SUSTAIN-6.[9]

Table 28: Mortality (SEM as Second- or Third-Line Therapy, Add-On to Basal Insulin or Basal Insulin + MET; SAS)

	SUSTAIN-5		
	SEM 0.5 mg N = 132	SEM 1 mg N = 132	Placebo N = 133
All-cause death, n	0		
CV-related death, n	0		

CV = cardiovascular; MET = metformin; SAS = safety analysis set; SEM = semaglutide.

Source: Clinical Study Report of SUSTAIN-5.[8]

Table 29: Mortality (SEM as First- and Second-Line Therapy; SAS)

	Seino 2018		
	SEM 0.5 mg N = 103	SEM 1 mg N = 102	SIT N = 103
All-cause death, n	0		
CV-related death, n	0		

CV = cardiovascular; SEM = semaglutide; SIT = sitagliptin.

Source: Seino 2018.[14]

Diabetes-Related Morbidity and Mortality

This outcome was not assessed in SUSTAIN-1 to 5, SUSTAIN-7, or the Seino study.

In SUSTAIN-6, the proportion of patients with first EAC-confirmed MACE (consisted of CV death, non-fatal MI, and non-fatal stroke) was lower with SEM therapy compared with placebo. A total of 108 patients (6.6%) treated with SEM experienced EAC-confirmed MACE versus 146 patients (8.9%) treated with placebo: [redacted] (Table 29). Treatment with either dose of SEM was also associated with numerically lower events of non-fatal MI and non-fatal stroke, while the number of deaths from CV causes was similar across treatment groups. The estimated HR for time to first MACE was 0.74 (95% CI 0.58 to 0.95, below the NI margin of 1.8), indicating that SEM statistically significantly reduced the risk of experiencing a MACE by 26% when compared with placebo, in patients with existing CV disease. *P* value was 0.0167 for the superiority test. The results of the sensitivity analyses were consistent with the results from the primary analysis. The results of the subgroup analyses (pre-planned, based on baseline A1C levels, heart failure class II-III, prior MI/stroke and renal impairment) were consistent with the results from the primary analysis.

For the composite outcome of all-cause death, non-fatal MI, or non-fatal stroke and its individual components, treatment with SEM was associated with numerically lower events in the study population, compared with placebo (Table 29).

For the expanded composite outcome of EAC-confirmed MACE, revascularization, unstable angina pectoris requiring hospitalization or hospitalization for heart failure, treatment with SEM was associated with numerically lower events in the study population, compared with placebo (Table 29).

Furthermore, proportions of new or worsening nephropathy were numerically lower in the SEM groups than in the placebo groups: [redacted]. However, proportions of diabetic retinopathy complications were numerically

higher in the SEM groups than in the placebo groups: [redacted].

Table 30: Diabetes-Related Morbidity and Mortality (CV Outcome Trial; SEM as Second- or Third-Line Therapy, Add-On to Standard of Care; FAS)

	SUSTAIN-6			
	SEM 0.5 mg N = 826	**SEM 1 mg N = 822**	**Placebo 0.5 mg N = 824**	**Placebo 1 mg N = 825**
Primary outcome				
EAC-confirmed first MACE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
MI, non-fatal	[redacted]	[redacted]	[redacted]	[redacted]
Stroke, non-fatal	[redacted]	[redacted]	[redacted]	[redacted]
CV death	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcome				
All EAC-confirmed first all-cause death, non-fatal MI, or non-fatal stroke, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
CV death	[redacted]	[redacted]	[redacted]	[redacted]
Non-CV death	[redacted]	[redacted]	[redacted]	[redacted]
MI, non-fatal	[redacted]	[redacted]	[redacted]	[redacted]
Stroke, non-fatal	[redacted]	[redacted]	[redacted]	[redacted]
Expanded composite outcome (EAC-confirmed MACE, revascularization, UAP requiring hospitalization, hospitalization for HF), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
CV death	[redacted]	[redacted]	[redacted]	[redacted]
MI, non-fatal	[redacted]	[redacted]	[redacted]	[redacted]
Stroke, non-fatal	[redacted]	[redacted]	[redacted]	[redacted]
Revascularization	[redacted]	[redacted]	[redacted]	[redacted]
UAP requiring hospitalization	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalization for HF	[redacted]	[redacted]	[redacted]	[redacted]
First EAC-confirmed composite microvascular outcome (retinopathy, nephropathy), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Diabetic retinopathy	[redacted]	[redacted]	[redacted]	[redacted]
New or worsening nephropathy	[redacted]	[redacted]	[redacted]	[redacted]

CV = cardiovascular; EAC = Event Adjudication Committee; FAS = full analysis set; HF = heart failure; MACE = major adverse cardiovascular event; MI = myocardial infarction; SEM = semaglutide; UAP = unstable angina pectoris.

Note: In-trial summary of MACEs comprises events with onset on or after the day of randomization and until end-of-trial, defined for trial completers as the subject's planned end-of-trial visit or death, whichever comes first, and defined as the last direct subject-site contact for withdrawals and for subjects lost to follow-up.

Source: Clinical Study Report of SUSTAIN-6.[9]

Hospitalization

This outcome was not assessed in the included clinical trials.

Health-Related Quality of Life

HRQoL was not evaluated in SUSTAIN-1 and the Seino study. Patient-reported HRQoL was not included in the hierarchical testing procedure to control the familywise type I error rate in any of the SUSTAIN trials.

In SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4, the change in DTSQ scores and SF-36 domain scores was evaluated in the overall population, but not in the subgroups based on the background antihyperglycemic therapy.

Results from these SUSTAIN trials showed numerically higher score at the end of study compared with baseline for the "treatment satisfaction" component in DTSQ, for all treatment groups, indicating more patient satisfaction associated with the study drug. For SF-36, all domains had improved with SEM and the comparators from baseline; however, the improvements were not considered clinically important. Details of patient-reported outcomes are presented in Appendix 4, Table 54.

Change in Body Weight and/or BMI

SEM Used as First-Line Therapy

SUSTAIN-1 reported change in body weight from baseline to week 30 in drug-naive patients with T2DM and had inadequate glycemic control after therapy with diet and exercise. At week 30, the mean change in body weight was –3.73 kg (SE 0.41), –4.53 kg (SE 0.41), and –0.98 kg (SE 0.43) for patients who received SEM 0.5 mg, SEM 1 mg, and placebo, respectively. The mean differences were statistically significant for both SEM groups compared with placebo (SEM 0.5 mg: –2.75 kg, 95% CI –3.92 to –1.58, $P < 0.0001$; SEM 1 mg: –3.56 kg, 95% CI –4.74 to –2.38) (Table 30). Because the upper limit of the two-sided 95% CI for the estimated differences was below 0 kg, superiority of SEM 0.5 mg or SEM 1 mg versus placebo in change in body weight was demonstrated. According to the clinical expert consulted for this review, the between-group differences were considered clinically important.

SUSTAIN-1 also reported change in BMI from baseline to week 30 in drug-naive patients. At week 30, the mean change in BMI was –1.36 kg/m^2 (SE 0.15), –1.61 kg/m^2 (SE 0.14) and –0.38 kg/m^2 (SE 0.15) for patients who received SEM 0.5 mg, SEM 1 mg, and placebo, respectively. The mean differences were statistically significant for both SEM groups compared with placebo (SEM 0.5 mg: –0.98 kg/m^2, 95% CI –1.40 to –0.56, $P < 0.0001$; SEM 1 mg: –1.23 kg/m^2, 95% CI –1.65 to –0.82) (Table 30).

Table 31: Body Weight/BMI (SEM as First-Line Therapy; FAS)

	SUSTAIN-1		
	SEM 0.5 mg N = 128	**SEM 1.0 mg N = 130**	**Placebo N = 129**
Body weight, kg			
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	89.81 (22.96)	96.87 (25.59)	89.05 (22.16)
End of study, mean (SE)	88.20 (0.41)	87.40 (0.41)	90.95 0.43
Change from baseline, mean (SE)	–3.73 (0.41)	–4.53 (0.41)	–0.98 (0.43)
Treatment group difference vs. placebo (95% CI)	–2.75 (–3.92 to –1.58) *P* < 0.0001	–3.56 (–4.74 to –2.38) *P* < 0.0001	NA
BMI, kg/m^2			
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	32.46 (7.62)	33.92 (8.43)	32.40 (6.86)
End of study, mean (SE)	30.94 (6.99)	31.95 (7.80)	30.86 (6.34)
Change from baseline, mean (SE)	– 1.36 (0.15)	– 1.61 (0.14)	– 0.38 (0.15)
Treatment group difference vs. placebo (95% CI)	– 0.98 (–1.40 to –0.56) *P* < 0.0001	– 1.23 (–1.65 to – 0.82) *P* < 0.0001	NA

BMI = body mass index; FAS = full analysis set; NA = not applicable; SD = standard deviation; SE = standard error; SEM = semaglutide.

Source: Clinical Study Report of SUSTAIN-1.[7]

SEM Used as Second-Line Therapy (Add-On to MET)

Results of post hoc subgroup analyses on body weight in SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4 are presented. Patients in SUSTAIN-7 received treatment with SEM or DUL with background therapy of MET monotherapy.

In patients with T2DM and received SEM as the second-line therapy (add-on to MET), treatment with either dose of SEM for 30 to 56 weeks was associated with greater reduction in body weight, compared with SIT, EXE, or IG (Table 31). The mean change from baseline in body weight ranged from [redacted] for the SEM 0.5 mg group, and from [redacted] for the SEM 1 mg group. Compared with SIT, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group. Compared with EXE, the mean between-group difference was [redacted] for the SEM 1 mg group. Compared with IG, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group. Compared with DUL, the mean between-group differences were –2.26 kg (95% CI –3.02 to –1.51, *P* < 0.0001) for the SEM 0.5 mg group and –3.55 kg (95% CI –4.32 to –2.78, *P* < 0.0001) for the SEM 1 mg group. According to the clinical expert consulted for this review, the between-group differences in body weight were considered clinically relevant. In SUSTAIN-7, superiority in reducing body weight was concluded for each dose of SEM compared with the respective dose level of DUL.

Results of post hoc subgroup analyses on BMI in SUSTAIN-2 to SUSTAIN-4 are presented. In the subgroups of patients with T2DM and received SEM as the second-line therapy (add-on to MET), treatment with either dose of SEM for 30 weeks to 56 weeks was associated with greater reduction in BMI, compared with SIT, EXE, or IG (Table 31). Patients in SUSTAIN-7 received treatment with SEM or DUL with background therapy of MET monotherapy. The mean change from baseline in BMI ranged from [redacted] for the SEM 0.5 mg group, and from [redacted] for the SEM 1 mg group. Compared with SIT, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group. Compared with EXE, the mean between-group difference was [redacted] for the SEM 1 mg group. Compared with IG, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group. Compared with DUL, the mean between-group differences were –0.81 kg/m^2 (95% CI –1.08 to –0.54) for the SEM 0.5 mg group and –1.25 kg/m^2 (95% CI –1.52 to –0.98) for the SEM 1 mg group.

Table 32: Body Weight/BMI (SEM as Second-Line Therapy, Add-On to MET; FAS)

	SUSTAIN-2			SUSTAIN-3		SUSTAIN-4			SUSTAIN-7			
	SEM 0.5 mg [redacted]	SEM 1 mg [redacted]	SIT [redacted]	SEM 1 mg [redacted]	EXE [redacted]	SEM 0.5 mg [redacted]	SEM 1 mg [redacted]	IG [redacted]	SEM 0.5 mg N = 301	SEM 1 mg N = 300	DUL N = 299	DUL N = 299
Body weight, kg												
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	96.4 (24.38)	95.5 (20.90)	95.6 (23.01)	93.4 (21.79)
End of study, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	90.67 (0.28)	88.70 (0.28)	92.94 (0.27)	92.25 (0.27)
Change from baseline, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–4.56 (0.28)	–6.53 (0.28)	–2.30 (0.27)	–2.98 (0.27)
Treatment group difference vs. comparator (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–2.26 (–3.02 to –1.51) P < 0.0001	–3.55 (–4.32 to –2.78) P < 0.0001	NA	NA
BMI, kg/m^2												
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33.7 (7.12)	33.6 (6.49)	33.6 (6.90)	33.1 (6.57)
End of study, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31.87 (0.10)	31.17 (0.10)	32.68 (0.10)	32.42 (0.10)
Change from baseline, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–1.63 (0.10)	–2.33 (0.10)	–0.82 (0.10)	–1.08 (0.10)

	SUSTAIN-2			SUSTAIN-3		SUSTAIN-4			SUSTAIN-7			
Treatment group difference vs. comparator (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–0.81 (–1.08 to –0.54) *P* < 0.0001	–1.25 (–1.52 to –0.98) *P* < 0.0001	NA	NA

BMI = body mass index; CI = confidence interval; DUL = dulaglutide; EXE = exenatide; FAS = full analysis set; IG = insulin glargine; NA = not applicable; SD = standard deviation; SE = standard error; SEM = semaglutide; SIT = sitagliptin.

Note: For SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4, on-treatment without rescue medication data are presented. The post-baseline data are analyzed using the mixed model for repeated measurements with treatment and baseline OAD subgroup as fixed factors, interaction between treatment and OAD subgroup, and baseline body weight or pulse (for BMI assessment) as covariate, all nested within visit. For SUSTAIN-7, on-treatment without rescue medication data are presented. The post-baseline responses are analyzed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

Source: Additional information of subgroup analyses in SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4 provided in Submission;[16] Clinical Study Report of SUSTAIN-7.[13]

SEM Used as Third-Line Therapy (Add-On to MET + TZD or MET + SU)

Results of post hoc subgroup analyses on body weight in SUSTAIN-2 to SUSTAIN-4 are presented.

In the patients receiving SEM as the third-line therapy (add-on to MET + TZD or MET + SU), treatment with either dose of SEM for 30 weeks to 56 weeks was associated with greater reduction in body weight, compared with SIT, EXE, or IG (Table 32). The mean change from baseline in A1C ranged from [redacted] for the SEM 0.5 mg group, and from [redacted] for the SEM 1 mg group. Compared with SIT, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group. Compared with EXE, the mean between-group difference was [redacted] for the SEM 1 mg group. Compared with IG, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group.

According to the clinical expert consulted for this review, the between-group differences in body weight were considered clinically relevant.

Results of post hoc subgroup analyses on BMI from SUSTAIN-2 to SUSTAIN-4 are presented. In the subgroups of patients with T2DM and received SEM as the third-line therapy (add-on to MET + TZD or MET + SU), treatment with either dose of SEM for 30 weeks to 56 weeks was associated with greater reduction in BMI, compared with SIT, EXE, or IG (Table 32). The mean change from baseline in BMI ranged from [redacted] for the SEM 0.5 mg group, and from [redacted] for the SEM 1 mg group. Compared with SIT, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group. Compared with EXE, the mean between-group difference was [redacted] for the SEM 1 mg group. Compared with IG, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group.

Table 33: Body Weight/BMI (SEM as Third-Line Therapy, Add-On to MET+TZD or MET+SU; FAS)

	SUSTAIN-2 [a]			SUSTAIN-3 [b]		SUSTAIN-4 [b]		
	SEM 0.5 mg [redacted]	SEM 1 mg [redacted]	SIT [redacted]	SEM 1 mg [redacted]	EXE [redacted]	SEM 0.5 mg [redacted]	SEM 1 mg [redacted]	IG [redacted]
Body weight, kg								
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of study, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment group difference vs. comparator (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2								

	SUSTAIN-2 [a]			SUSTAIN-3 [b]		SUSTAIN-4 [b]		
Patients contribute to the analysis, n (%)	[redacted]							
Baseline value, mean (SD)	[redacted]							
End of study, mean (SE)	[redacted]							
Change from baseline, mean (SE)	[redacted]							
Treatment group difference vs. comparator (95% CI)	[redacted]							

BMI = body mass index; CI = confidence interval; EXE = exenatide; FAS = full analysis set; IG = insulin glargine; NR = not reported; SD = standard deviation; SE = standard error; SEM = semaglutide; SIT = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

[a] Add-on to MET + TZD.

[b] Add-on to MET + SU.

Note: For SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4, on-treatment without rescue medication data are presented. The post-baseline data are analyzed using the mixed model for repeated measurements with treatment and baseline OAD subgroup as fixed factors, interaction between treatment and OAD subgroup, and baseline body weight or pulse (for BMI assessment) as covariate, all nested within visit.

Source: Additional information of subgroup analyses in SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4 provided in Submission.[16]

SEM Used in Mixed Population (as Second- or Third-Line Therapy, Add-On to Standard of Care)

Efficacy of study medications on body weight in SUSTAIN-6 was presented in Table 33. In patients with clinical evidence or subclinical evidence of CV disease and received standard of care for T2DM, treatment with either dose of SEM for 30 weeks was associated with greater reduction in body weight, compared with placebo. The mean change from baseline in body weight was
–3.57 kg (SE 0.21) for the SEM 0.5 mg group, and –4.88 kg (SE 0.22) for the SEM 1 mg group. Compared with placebo, the mean between-group differences were –2.95 kg (95% CI –3.47 to –2.44, $P < 0.0001$) for the SEM 0.5 mg group and –4.27 kg (95% CI –4.78 to –3.75, $P < 0.0001$) for the SEM 1 mg group.

According to the clinical expert consulted for this review, the between-group differences in A1C were considered clinically relevant.

Efficacy of study medications on BMI in SUSTAIN-6 was also presented in Table 33. In patients with clinical evidence or subclinical evidence of CV disease and received standard of care for T2DM, treatment with either dose of SEM for 30 weeks was associated with greater reduction in BMI, compared with placebo. The mean change from baseline in BMI was [redacted] for the SEM 0.5 mg group, and [redacted] for the SEM 1 mg group. Change from baseline in BMI was [redacted] in placebo 0.5 mg group and [redacted] in placebo 1 mg group. Between-group differences for SEM versus DUL were not reported.

Table 34: Body Weight/BMI (CV Outcome Trial; SEM as Second- or Third-Line Therapy, Add-On to Standard of Care; FAS)

	SUSTAIN-6		
	SEM 0.5 mg N = 826	**SEM 1 mg N = 822**	**Placebo N = 1,649**
Body weight, kg			
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	91.80 (20.25)	92.86 (21.05)	91.86 (20.55)
Week 104, mean (SE)	88.53 (0.21)	87.21 (0.22)	91.48 (0.15)
Change from baseline, mean (SE)	–3.57 (0.21)	–4.88 (0.22)	–0.62 (0.15)
Treatment group difference vs. placebo (95% CI)	–2.95 (–3.47 to –2.44) *P* < 0.0001	–4.27 (–4.78 to –3.75) *P* < 0.0001	NA
BMI, kg/m^2			
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	32.71 (6.29)	32.90 (6.18)	32.80 (6.16)
Week 104, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Treatment group difference vs. placebo	[redacted]	[redacted]	[redacted]

BMI = body mass index; CI = confidence interval; CV = cardiovascular; FAS = full analysis set; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error; SEM = semaglutide.

Note: for change in body weight, 'in-trial' data are presented. The post-baseline responses are analyzed using a mixed model for repeated measurements with treatment (4 levels) and stratification (nine levels) as fixed factors and baseline value as covariate, all nested within visit.

Source: Clinical Study Report of SUSTAIN-6.[9]

SEM Used in Mixed Population (as Second- or Third-Line Therapy; Add-On to Basal Insulin or Basal Insulin + MET)

Efficacy of study medications on body weight in SUSTAIN-5 was presented in Table 34. This was a mixed population where subgroup results based on background therapy were not available. In patients who received background basal insulin or basal insulin plus MET, treatment with either dose of SEM for 30 weeks was associated with greater reduction in body weight, compared with placebo: the mean between-group differences were –2.31 kg (95% CI, –3.33 to –1.29, *P* < 0.0001) for the SEM 0.5 mg group and –5.06 kg (95% CI –6.08 to –4.04, *P* < 0.0001) for the SEM 1 mg group.

In SUSTAIN-5, the between-group differences were statistically significant. Superiority in reducing body weight was concluded for each dose of SEM compared with placebo, because the upper limit of the two-sided 95% CI for the estimated difference was below 0 kg.

Efficacy of study medications on BMI in SUSTAIN-5 was also presented in Table 34. In patients who received background basal insulin or basal insulin plus MET, treatment with either dose of SEM for 30 weeks was associated with greater reduction in BMI, compared with placebo: the mean between-group differences were –0.84 kg/m^2 (95% CI, –1.20 to

–0.49, *P* < 0.0001) for the SEM 0.5 mg group and –1.82 kg/m^2 (95% CI, –2.18 to –1.47, *P* < 0.0001) for the SEM 1 mg group.

Table 35: Body Weight/BMI (SEM as Second- and Third-Line Therapy, Add-On to Basal Insulin or Basal Insulin + MET; FAS)

	SUSTAIN-5		
	SEM 0.5 mg N = 132	**SEM 1 mg N = 131**	**Placebo N = 133**
Body weight, kg			
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	92.74 (19.57)	92.49 (22.23)	89.88 (21.06)
End of study, mean (SE)	88.02 (0.36)	85.27 (0.36)	90.33 (0.37)
Change from baseline, mean (SE)	–3.67 (0.36)	–6.42 (0.36)	–1.36 (0.37)
Treatment group difference vs. placebo (95% CI)	–2.31 (–3.33 to –1.29) P < 0.0001	–5.06 (–6.08 to –4.04) P < 0.0001	NA
BMI, kg/m^2			
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	32.77 (6.01)	32.00 (6.41)	31.77 (6.05)
End of study, mean (SE)	30.87 (0.12)	29.89 (0.13)	31.71 (0.13)
Change from baseline, mean (SE)	–1.31 (0.12)	–2.29 (0.13)	–0.47 (0.13)
Treatment group difference vs. placebo (95% CI)	–0.84 (–1.20 to –0.49) *P* < 0.0001	–1.82 (–2.18 to –1.47) *P* < 0.0001	NA

BMI = body mass index; CI = confidence interval; FAS = full analysis set; MET = metformin; NA = not applicable; SD = standard deviation; SE = standard deviation; SEM = semaglutide.

Note: "On-treatment without rescue medication" data. The post-baseline responses are analyzed using a mixed model for repeated measurements with treatment, country and stratification variable (A1C level at screening [less than and equal to 8.0% or greater than 8.0%] crossed with use of metformin [yes or no]; two by two levels) as fixed factors and baseline value as covariate, all nested within visit.

Source: Clinical Study Report of SUSTAIN-5.[8]

SEM Used in Mixed Population (as First- or Second-Line Therapy; Add-On to Diet/Exercise Alone or Diet/Exercise + OAD)

Efficacy of study medications on body weight in the Seino study is presented in Table 35. This was a mixed population where subgroup results based on background therapy were not available. In patients who received background therapy of diet and exercise alone or diet and exercise plus OAD, treatment with either dose of SEM for 30 weeks was associated with greater reduction in body weight, compared with SIT: the mean between-group differences were –2.22 kg (95% CI –3.02 to –1.42, *P* < 0.0001) for the SEM 0.5 mg group and –3.88 kg (95% CI –4.70 to –3.07, *P* < 0.0001) for the SEM 1 mg group.

The between-group differences were statistically significant. According to the clinical expert consulted for this review, the between-group differences in A1C were considered clinically relevant.

Efficacy of study medications on BMI in SUSTAIN-5 was also presented in Table 35. In patients who received background basal insulin or basal insulin plus MET, treatment with either dose of SEM for 30 weeks was associated with greater reduction in BMI, compared with placebo: the mean between-group differences were –0.84 kg/m^2 (95% CI –1.13 to –0.54, *P* < 0.0001) for the SEM 0.5 mg group and –1.44 kg/m^2 (95% CI –1.74 to –1.14, *P* < 0.0001) for the SEM 1 mg group.

Table 36: Body Weight/BMI (SEM as First- and Second-Line Therapy; FAS)

	Seino 2017		
	SEM 0.5 mg N = 103	**SEM 1 mg N = 102**	**Placebo N = 103**
Body weight, kg			
Baseline value, mean (SD)	67.8 (11.7)	70.8 (16.4)	69.4 (12.9)
End of study, mean (SE)	NR		
Change from baseline, mean (SE)	–2.2 (0.3)	–3.9 (0.3)	0 (0.3)
Treatment group difference vs. placebo, mean (95% CI)	–2.22 (–3.02 to –1.42) *P* < 0.0001	–3.88 (–4.70 to –3.07) *P* < 0.0001	NA
BMI, kg/m^2			
Baseline value, mean (SD)	25.1 (3.8)	26.1 (5.2)	25.1 (3.6)
End of study, mean (SE)	NR		
Change from baseline, mean (SE)	–0.8 (0.1)	–1.4 (0.1)	0 (0.1)
Treatment group difference vs. placebo, mean (95% CI)	–0.84 (–1.13 to –0.54) *P* < 0.0001	–1.44 (–1.74 to –1.14) *P* < 0.0001	NA

BMI = body mass index; CI = confidence interval; FAS = full analysis set; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error; SEM = semaglutide.

Source: Seino 2017.[14]

Change in Blood Pressure

Change in blood pressure was not included in the hierarchical testing procedure to control the familywise type I error rate.

SEM Used as First-Line Therapy

SUSTAIN-1 reported change in blood pressure from baseline to week 30 in drug-naive patients with T2DM and had inadequate glycemic control after therapy with diet and exercise. At week 30, all three treatment groups showed reduced SBP from baseline. The mean differences were not statistically significant for either SEM groups compared with placebo (SEM 0.5 mg: –0.86 mm Hg, 95% CI –4.15 to 2.43, *P* = 0.60; SEM 1 mg: –1.03, 95% CI –4.29 to –2.24). At week 30, change in DBP was inconsistent across the treatment groups, and the between-group differences in change in DBP were not statistically significant (Table 36).

Table 37: Blood Pressure (SEM as First-Line Therapy; FAS)

	SUSTAIN-1		
	SEM 0.5 mg N = 128	**SEM 1.0 mg N = 130**	**Placebo N = 129**
Systolic pressure, mm Hg			
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	127.87 (13.15)	128.89 (12.92)	129.57 (13.50)
End of study, mean (SE)	125.68 (14.05)	125.82 (14.55)	127.07 (12.09)
Change from baseline, mean (SE)	–2.58 (1.13)	–2.74 (1.12)	–1.72 (1.23)
Treatment group difference vs. placebo (95% CI)	–0.86 (–4.15 to 2.43) *P* = 0.6059	–1.03 (–4.29 to 2.24) *P* = 0.5369	NA
Diastolic pressure, mm Hg			
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]

	SUSTAIN-1		
Baseline value, mean (SD)	79.52 (9.06)	79.25 (8.52)	79.14 (8.39)
End of study, mean (SD)	78.40 (7.76)	79.46 (8.07)	79.64 (9.10)
Change from baseline, mean (SE)	–0.50 (0.66)	0.18 (0.65)	0.40 (0.71)
Treatment group difference vs. placebo (95% CI)	–0.89 (–2.81 to 1.02) *P* = 0.3586	–0.21 (–2.12 to 1.69) *P* = 0.8245	NA

CI = confidence interval; FAS = full analysis set; NA = not applicable; SD = standard deviation; SE = standard error; SEM = semaglutide.

Source: Clinical Study Report of SUSTAIN-1.[7]

SEM Used as Second-Line Therapy (Add-On to MET)

Results of post hoc subgroup analyses on blood pressure in SUSTAIN-2 to SUSTAIN-4 are presented. Patients in SUSTAIN-7 received treatment with SEM or DUL with background therapy of MET monotherapy.

In the subgroups of patients with T2DM and who received SEM as the second-line therapy (add-on to MET), treatment with either dose of SEM for 30 weeks to 56 weeks was associated with greater reduction in SBP and DBP, compared with SIT, EXE, or IG. In SUSTAIN-7, patients in the SEM 1 mg group had greater reduction in SBP and DBP than those with SEM 0.5 mg and DUL (Table 37).

For change in SBP compared with SIT, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group. Compared with EXE, the mean between-group difference was [redacted] for the SEM 1 mg group. Compared with IG, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group. In SUSTAIN-7, SBP levels at week 40 were reduced in all groups but no statistically significant differences between SEM and DUL were observed: the mean differences were –0.28 mm Hg (95% CI –2.37 to 1.81, *P* = 0.79) for SEM 0.5 mg versus DUL 0.75 mg and –2.02 mm Hg (95% CI –4.14 to 0.09, *P* = 0.06) for SEM 1 mg versus DUL 1.5 mg.

For change in DBP, compared with SIT, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group. Compared with EXE, the mean between-group difference was [redacted] for the SEM 1 mg group. Compared with IG, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group. In SUSTAIN-7, the reductions in DBP at week 40 were significantly greater with SEM 1 mg as compared with DUL 1.5 mg (mean between-group difference: –2.02 mm Hg; 95% CI –3.35 to –0.68), while no treatment difference was observed between SEM 0.5 mg and DUL 0.75 mg.

According to the clinical expert consulted for this review, the between-group differences in blood pressure were not considered clinically relevant.

Table 38: Blood Pressure (SEM as Second-Line Therapy, Add-On to MET; FAS)

	SUSTAIN-2			SUSTAIN-3		SUSTAIN-4			SUSTAIN-7			
	SEM 0.5 mg [redacted]	SEM 1 mg [redacted]	SIT [redacted]	SEM 1 mg [redacted]	EXE [redacted]	SEM 0.5 mg [redacted]	SEM 1 mg [redacted]	IG [redacted]	SEM 0.5 mg N = 301	SEM 1 mg N = 300	DUL 0.75 mg N = 299	DUL 1.5 mg N = 299
Systolic pressure, mm Hg												
Patients contribute to the analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	134.08 (14.82)	133.31 (14.50)	132.53 (14.01)	131.92 (13.65)
End of study, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	130.52 (0.76)	128.08 (0.77)	130.80 (0.75)	130.11 (0.75)
Change from baseline, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–2.44 (0.76)	–4.88 (0.77)	–2.16 (0.75)	–2.86 (0.75)
Treatment group difference vs. comparator (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–0.28 (–2.37 to 1.81) *P* = 0.79	–2.02 (–4.14 to 0.09) *P* = 0.06	NA	NA
Diastolic pressure, mm Hg												
Patients contribute to the analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	81.00 (9.05)	81.50 (9.13)	80.79 (8.90)	80.12 (8.66)
End of study, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	80.28 (0.48)	78.80 (0.49)	80.50 (0.47)	80.82 (0.47)
Change from baseline, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–0.57 (0.48)	–2.05 (0.49)	–0.35 (0.47)	–0.03 (0.47)
Treatment group difference vs. comparator (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–0.22 (–1.54 to 1.10)	–2.02 (–3.35 to –0.68)	NA	NA

CI = confidence interval; DUL = dulaglutide; EXE = exenatide; IG = insulin glargine; MET = metformin; NA = not applicable; SD = standard deviation; SE = standard error; SEM = semaglutide; SIT = sitagliptin.

Note: for SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4, on-treatment without rescue medication data are presented. The post-baseline data are analyzed using the mixed model for repeated measurements with treatment and baseline OAD subgroup as fixed factors, interaction between treatment and OAD subgroup, and baseline SBP or DBP (mm Hg) as covariate, all nested within visit. For SUSTAIN-7, on-treatment without rescue medication data are presented. The post-baseline responses are analyzed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

Source: additional information of subgroup analyses in SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4 provided in Submission;[16] Clinical Study Report of SUSTAIN-7.[13]

SEM Used as Third-Line Therapy (Add-On to MET + TZD or MET + SU)

Results of post hoc subgroup analyses on blood pressure in SUSTAIN-2 to SUSTAIN-4 are presented. In the subgroups of patients receiving SEM as third-line therapy (add-on to MET + TZD or MET + SU), reduction in SBP was observed in all treatment groups (Table 38). Compared with SIT, the mean between-group differences in change in SBP were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group. Compared with EXE, the mean between-group difference was [redacted] for the SEM 1 mg group. Compared with IG, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group.

Reduction in DBP was reported in some trials after 40 weeks treatment with study medications. Compared with SIT, the mean between-group differences in change in DBP were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group. Compared with EXE, the mean between-group difference was [redacted] for the SEM 1 mg group. Compared with IG, the mean between-group differences were [redacted] for the SEM 0.5 mg group and [redacted] for the SEM 1 mg group.

According to the clinical expert consulted for this review, the between-group differences in blood pressure were not considered clinically relevant.

Table 39: Blood Pressure (SEM as Third-Line Therapy, Add-On to MET + TZD or MET + SU; FAS)

	SUSTAIN-2[a]			SUSTAIN-3[b]		SUSTAIN-4[b]		
	SEM 0.5 mg [redacted]	SEM 1 mg [redacted]	SIT [redacted]	SEM 1 mg [redacted]	EXE [redacted]	SEM 0.5 mg [redacted]	SEM 1 mg [redacted]	IG [redacted]
Systolic pressure, mm Hg								
Patients contribute to the analysis	[redacted]							
Baseline value, mean (SD)	[redacted]							
End of study, mean (SE)	[redacted]							
Change from baseline, mm Hg, mean (SE)	[redacted]							
Treatment group difference vs. comparator (95% CI)	[redacted]							
Diastolic pressure, mm Hg								
Patients contribute to the analysis	[redacted]							
Baseline value, mean (SD)	[redacted]							
End of study, mean (SE)	[redacted]							
Change from baseline, mean (SE)	[redacted]							
Treatment group difference vs. comparator (95% CI)	[redacted]							

	SUSTAIN-2[a]			SUSTAIN-3[b]		SUSTAIN-4[b]		
	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	

CI = confidence interval; EXE = exenatide; FAS = full analysis set; IG = insulin glargine; MET = metformin; NA = not applicable; SD = standard deviation; SE = standard error; SEM = semaglutide; SIT = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

[a] Add-on to MET + TZD.

[b] Add-on to MET + SU.

Note: for SUSTAIN-2/3/4, on-treatment without rescue medication data are presented. The post-baseline data are analyzed using the mixed model for repeated measurements with treatment and baseline OAD subgroup as fixed factors, interaction between treatment and OAD subgroup, and baseline SBP or DBP (mm Hg) as covariate, all nested within visit.

Source: Additional information of subgroup analyses in SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4 provided in Submission.[16]

SEM Used in Mixed Population (as Second- or Third-Line Therapy; Add-On to Standard of Care)

Efficacy of study medications on blood pressure in SUSTAIN-6 is presented in Table 39. In patients with clinical evidence or subclinical evidence of CV disease and who received standard of care for T2DM, reduction in SBP and DBP was observed in all treatment groups. Compared with placebo, the mean between-group differences in SBP were –1.27 mm Hg (95% CI –2.77 to –0.23, *P* =0.10) for the SEM 0.5 mg group and –2.59 mm Hg (95% CI –4.09 to –1.08, *P* = 0.0008) for the SEM 1 mg group; the mean between-group differences in DBP were 0.04 mm Hg (95% CI –0.83 to 0.92, *P* = 0.92) for the SEM 0.5 mg group and 0.14 mm Hg (95% CI –0.74 to 1.03, *P* = 0.75).

According to the clinical expert consulted for this review, the between-group differences in SBP and DBP were not considered clinically relevant.

Table 40: Blood Pressure (CV Outcome RCT; Used as Second- or Third-Line Therapy, Add-On to Standard of Care; FAS)

	SUSTAIN-6			
	SEM 0.5 mg N = 826	**SEM 1 mg N = 822**	**Placebo 0.5 mg N = 824**	**Placebo 1 mg N = 825**
Systolic blood pressure, mm Hg				
Patients contribute to the analysis	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	136.1 (17.97)	135.8 (16.96)	135.8 (16.16)	134.8 (17.45)
End of study, mean (SE)	132.19 (0.54)	130.25 (0.54)	133.46 (0.54)	132.84 (0.54)
Change from baseline, mean (SE)	–3.44 (0.54)	–5.37 (0.54)	–2.17 (0.54)	–2.78 (0.54)
Treatment group difference vs. placebo	–1.27 (–2.77 to 0.23) *P* = 0.0976	–2.59 (–4.09 to –1.08) *P* = 0.0008	NA	NA
Diastolic blood pressure, mm Hg				
Patients contribute to the analysis	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	77.10 (9.78)	76.88 (10.21)	77.54 (9.85)	76.66 (10.21)
End of study, mean (SE)	75.67 (0.32)	75.48 (0.32)	75.63 (0.32)	75.33 (0.32)
Change from baseline, mean (SE)	–1.37 (0.32)	–1.57 (0.32)	–1.42 (0.32)	–1.71 (0.32)
Treatment group difference vs. placebo	0.04 (–0.83 to 0.92) *P* = 0.9205	0.14 (–0.74 to 1.03) *P* = 0.7477	NA	NA

CV = cardiovascular; FAS = full analysis set; NA = not applicable; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; SEM = semaglutide.

Note: 'In-trial' data. The post-baseline responses are analyzed using a mixed model for repeated measurements with treatment (four levels) and stratification (nine levels) as fixed factors and baseline value as covariate, all nested within visit.

Source: Clinical Study Report of SUSTAIN-6.[9]

SEM Used in Mixed Population (as Second- or Third-Line Therapy; Add-On to Basal Insulin or Basal Insulin + MET)

Efficacy of study medications on blood pressure in SUSTAIN-5 was presented in Table 40. This was a mixed population where subgroup results based on background therapy was not available. In patients who received background basal insulin or basal insulin plus MET, reduction in SBP and DBP was observed in all treatment groups. Compared with placebo, the mean between-group differences in SBP were –3.31 mm Hg (95% CI –6.92 to 0.31, *P* = 0.07) for the SEM 0.5 mg group and –6.29 mm Hg (95% CI –9.91 to –2.66, *P* =0.0007) for the SEM 1 mg group; the mean between-group differences in DBP were 0.33 mm Hg (95% CI –1.80 to 2.45, *P* = 0.76) for the SEM 0.5 mg group and 0.66 mm Hg (95% CI –1.47 to 2.80, *P* = 0.54).

Table 41: Blood Pressure (SEM as Second- and Third-Line Therapy, Add-On to Basal Insulin or Basal Insulin + MET; FAS)

	SUSTAIN-5		
	SEM 0.5 mg N = 132	**SEM 1 mg N = 131**	**Placebo N = 133**
Systolic blood pressure, mm Hg			
Patients contribute to the analysis	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	134.87 (15.00)	134.40 (16.32)	134.99 (16.68)
End of study, mean (SE)	130.46 (1.26)	127.49 (1.27)	133.77 (1.34)
Change from baseline, mean (SE)	–4.29 (1.26)	–7.27 (1.27)	–0.99 (1.34)
Treatment group difference vs. placebo	–3.31 (–6.92 to 0.31) *P* = 0.0728	–6.29 (–9.91 to –2.66) *P* = 0.0007	NA
Diastolic blood pressure, mm Hg			
Patients contribute to the analysis	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	78.89 (9.72)	78.73 (9.98)	79.35 (9.71)
End of study, mean (SE)	77.16 (0.73)	77.49 (0.74)	76.83 (0.79)
Change from baseline, mean (SE)	–1.84 (0.73)	–1.50 (0.74)	–2.17 (0.79)
Treatment group difference vs. placebo	0.33 (–1.80 to 2.45) *P* = 0.7606	0.66 (–1.47 to 2.80) *P* = 0.5412	NA

FAS = full analysis set; NA = not applicable; SD = standard deviation; SE = standard deviation; SEM = semaglutide.

Note: "On-treatment without rescue medication" data are presented. The post-baseline responses are analyzed using a mixed model for repeated measurements with treatment, country and stratification variable (A1C level at screening [less than and equal to 8.0% or greater than 8.0%] crossed with use of metformin [yes or no]; two by two levels) as fixed factors and baseline value as covariate, all nested within visit.

Source: Clinical Study Report of SUSTAIN-5.[8]

SEM Used in Mixed Population (as First- or Second-Line Therapy; Add-On to Diet/Exercise or Diet/Exercise + OAD)

Efficacy of study medications on blood pressure in the Seino study is presented in Table 41. This was a mixed population where subgroup results based on background therapy were not available. In patients who received background therapy of diet and exercise alone or diet and exercise plus OAD, treatment with either dose of SEM for 30 weeks was associated with greater reduction in SBP. Compared with SIT, the mean between-group differences were –2.54 mm Hg (95% CI –5.64 to 0.55, *P* = 0.11) for the SEM 0.5 mg group and –6.01 mm Hg (95% CI –9.16 to –2.85, *P* = 0.0002) for the SEM 1 mg group.

The mean between-group differences in DBP were 0.12 mm Hg (95% CI –1.97 to 2.21, *P* = 0.91) for SEM 0.5 mg versus SIT, and -1.99 mm Hg (95% CI –4.13 to 0.16, *P* = 0.07) for SEM 1 mg versus SIT.

Table 42: Blood Pressure (SEM as First- and Second-Line Therapy; FAS)

	Seino 2017		
	SEM 0.5 mg N = 103	**SEM 1 mg N = 102**	**Placebo N = 103**
Systolic blood pressure, mm Hg			
Baseline value, mean (SD)	NR		
End of study, mean (SE)			
Change from baseline, mean (SE)	–5.3 (1.1)	–8.8 (1.2)	–2.8 (1.1)
Treatment group difference vs. placebo (95% CI)	–2.54 (–5.64 to 0.55) *P* = 0.1067	–6.01 (–9.16 to –2.85) *P* = 0.0002	NA
Diastolic blood pressure, mm Hg			
Baseline value, mean (SD)	NR		
End of study, mean (SE)			
Change from baseline, mean (SE)	–1.5 (0.7)	–3.6 (0.8)	–1.6 (0.8)
Treatment group difference vs. placebo (95% CI)	0.12 (–1.97 to 2.21) *P* = 0.9072	–1.99 (–4.13 to 0.16) *P* = 0.0690	NA

CI = confidence interval; FAS = full analysis set; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error; SEM = semaglutide.

Source: Seino 2017.[14]

Change in Blood Lipid

Change in blood lipid was not included in the hierarchical testing procedure to control the familywise type I error rate.

SEM Used as First-Line Therapy

SUSTAIN-1 reported change in blood lipid from baseline to week 30 in drug-naive patients. At week 30, total cholesterol level and LDL cholesterol level were statistically significantly reduced in the SEM 1 mg group, compared with placebo. There were no statistically significant changes in lipid profile observed for SEM 0.5 mg versus placebo (Table 42).

Table 43: Lipid Profile (SEM as First-Line Therapy; FAS)

	SUSTAIN-1		
	SEM 0.5 mg N = 128	**SEM 1.0 mg N = 130**	**Placebo N = 129**
Total cholesterol (mmol/L)			
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]
Baseline value, geometric mean (CoV)	4.85 (22.56)	4.92 (23.43)	5.02 (23.07)
End of study, geometric mean (CoV)	4.84 (23.59)	4.64 (20.54)	5.09 (26.47)
Ratio to baseline, mean (SE)	0.98 (0.02)	0.93 (0.02)	1.01 (0.02)
Treatment group difference vs. placebo (95% CI)	0.97 (0.92 to 1.02) *P* = 0.1984	0.92 (0.87 to 0.96) *P* = 0.0006	NA
HDL cholesterol (mmol/L)			
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]
Baseline value, geometric mean (CoV)	1.21 (30.05)	1.17 (28.50)	1.26 (29.97)

	SUSTAIN-1		
End of study, geometric mean (CoV)	1.26 (29.54)	1.16 (30.90)	1.33 (29.46)
Ratio to baseline, mean (SE)	1.02 (0.01)	0.99 (0.01)	1.02 (0.02)
Treatment group difference vs. placebo (95% CI)	1.01 (0.96 to 1.05) *P* = 0.7993	0.97 (0.93 to 1.01) *P* = 0.2016	NA
LDL cholesterol (mmol/L)			
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]
Baseline value, geometric mean (CoV)	2.56 (45.88)	2.65 (38.79)	2.80 (38.27)
End of study, geometric mean (CoV)	2.66 (38.04)	2.47 (34.29)	2.75 (40.69)
Ratio to baseline, mean (SE)	1.00 (0.03)	0.92 (0.02)	1.00 (0.03)
Treatment group difference vs. placebo (95% CI)	0.99 (0.92 to 1.07) *P* = 0.8361	0.92 (0.85 to 0.99) *P* = 0.0290	NA

CI = confidence interval; CoV = coefficient of variation; FAS = full analysis set; HDL = high-density lipoproteins; LDL = low-density lipoproteins; NA = not applicable; SE = standard error; SEM = semaglutide.

Source: Clinical Study Report of SUSTAIN-1.[7]

SEM Used as Second-Line Therapy (Add-On to MET Alone)

Results of post hoc subgroup analyses on blood lipid levels in SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4 are presented. Patients in SUSTAIN-7 received treatment with SEM or DUL with background therapy of MET monotherapy.

In patients with T2DM who received SEM as second-line therapy (add-on to MET), treatment with SEM was associated with numerically greater reduction in total cholesterol when compared with SIT, IG, and DUL. In addition, SEM was associated with a numerically greater increase in HDL cholesterol versus SIT, EXE, IG, and DUL (except for the comparison between SEM 0.5 mg and DUL 0.75 mg in SUSTAIN-7). SEM was also associated with numerically greater reduction in LDL cholesterol versus SIT, IG, and DUL (except for the comparison between SEM 0.5 mg and DUL 0.75 mg in SUSTAIN-7).

Table 44: Lipid Profile (SEM as Second-Line Therapy, Add-On to MET)

	SUSTAIN-2			SUSTAIN-3		SUSTAIN-4			SUSTAIN-7[a]			
	SEM 0.5 mg [redacted]	SEM 1 mg [redacted]	SIT [redacted]	SEM 1 mg [redacted]	EXE [redacted]	SEM 0.5 mg [redacted]	SEM 1 mg [redacted]	IG [redacted]	SEM 0.5 mg N = 301	SEM 1 mg N = 300	DUL 0.75 mg N = 299	DUL 1.5 mg N = 299
Total cholesterol, mmol/L												
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.57 (23.76)	4.66 (24.48)	4.47 (24.44)	4.55 (26.23)
End of study, mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.38 (0.04)	4.42 (0.05)	4.41 (0.05)	4.49 0.05)
Ratio to baseline (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96 (0.01)	0.97 (0.01)	0.97 (0.01)	0.99 (0.01)
Treatment ratio (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.99 (0.97 to 1.02)	0.98 (0.96 to 1.01)	NA	NA
HDL cholesterol, mmol/L												
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.15 (24.48)	1.14 (23.76)	1.11 (22.06)	1.13 (24.69)
End of study, mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.12 (0.01)	1.15 (0.01)	1.13 (0.01)	1.15 (0.01)
Ratio to baseline (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.99 (0.01)	1.01 (0.01)	1.00 (0.01)	1.02 (0.01)
Treatment ratio (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.99 (0.97 to 1.01)	1.00 (0.98 to 1.02)	NA	NA

	SUSTAIN-2			SUSTAIN-3		SUSTAIN-4			SUSTAIN-7[a]			
LDL cholesterol, mmol/L												
Patients contribute to the analysis, n (%)												
Baseline value, mean (SD)									2.49 (37.40)	2.54 (41.17)	2.40 (39.55)	2.46 (43.35)
End of study, mean (95% CI)									2.39 (0.04)	2.47 (0.04)	2.39 (0.04)	2.49 (0.04)
Ratio to baseline (95% CI)									0.97 (0.02)	1.00 (0.02)	0.97 (0.02)	1.01 (0.02)
Treatment ratio (95% CI)									1.00 (0.96 to 1.05)	0.99 (0.95 to 1.04)	NA	NA

CI = confidence interval; DUL = dulaglutide; EXE = exenatide; HDL = high-density lipoprotein; IG = insulin glargine; LDL = low-density lipoprotein; MET = metformin; NA = not applicable; SD = standard deviation; SEM = semaglutide; SIT = sitagliptin.

Note: For SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4, on-treatment without rescue medication data are presented. The log-transformed post-baseline data are analyzed using the mixed model for repeated measurements with treatment and baseline OAD subgroup as fixed factors, interaction between treatment and baseline OAD subgroup, and baseline total cholesterol (or HDL or LDL) as covariate, all nested within visit. For SUSTAIN-7, on-treatment without rescue medication data are presented. The post-baseline responses are analyzed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

[a] The baseline value in SUSTAIN-7 was expressed as geometric mean (coefficient of variation).

Source: Additional information of subgroup analyses in SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4 provided in Submission;[16] Clinical Study Report of SUSTAIN-7.[13]

SEM Used as Third-Line Therapy (Add-On to MET + TZD or MET + SU)

Results of post hoc subgroup analyses on changes in lipid levels in SUSTAIN-2 to SUSTAIN-4 are presented.

In patients with T2DM and received SEM as the third-line therapy (add-on to MET + TZD or MET + SU), treatment with SEM was associated with numerically greater reduction in total cholesterol when compared with SIT (except for the comparison between SEM 0.5 mg and SIT in SUSTAIN-2), EXE, and IG. In addition, SEM was associated with numerically greater increase in HDL cholesterol versus SIT (except for the comparison between SEM 1 mg and SIT in SUSTAIN-2), EXE, and IG. SEM was also associated with numerically greater reduction in LDL cholesterol versus EXE and IG, but less reduction in LDL cholesterol versus SIT.

1 mg was associated with statistically significantly greater reduction in total cholesterol versus EXE ( ), (Table 44). There were no other significant changes in lipid levels observed between SEM and active comparators.

Table 45: Lipid Profile (SEM as Third-Line Therapy, Add-On to MET + TZD or MET + SU; FAS)

	SUSTAIN -2[a]			SUSTAIN-3[b]		SUSTAIN-4[b]		
	SEM 0.5 mg [redacted]	SEM 1 mg [redacted]	SIT [redacted]	SEM 1 mg [redacted]	EXE [redacted]	SEM 0.5 mg [redacted]	SEM 1 mg [redacted]	IG [redacted]
Total cholesterol, mmol/L								
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of study, mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ratio to baseline (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment ratio (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HDL cholesterol, mmol/L								
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of study, mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ratio to baseline (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment ratio (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDL cholesterol, mmol/L								
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of study, mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	SUSTAIN -2[a]			SUSTAIN-3[b]		SUSTAIN-4[b]		
Ratio to baseline (95% CI)	[redacted]							
Treatment ratio (95% CI)	[redacted]							

CI = confidence interval; EXE = exenatide; FAS = full analysis set; HDL = high-density lipoprotein; IG = insulin glargine; LDL = low-density lipoprotein; MET = metformin; NA = not applicable; SD = standard deviation; SEM = semaglutide; SIT = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

[a] Add-on to MET + TZD.

[b] Add-on to MET + SU.

Note: For SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4, on-treatment without rescue medication data are presented. The log-transformed post-baseline data are analyzed using the mixed model for repeated measurements with treatment and baseline OAD subgroup as fixed factors, interaction between treatment and baseline OAD subgroup, and baseline total cholesterol (or HDL or LDL) as covariate, all nested within visit.

Source: Additional information of subgroup analyses in SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4 provided in Submission[16]

SEM Used in Mixed Population (as Second- or Third-Line Therapy; Add-On to Standard of Care)

Efficacy of study medications on blood lipid levels in SUSTAIN-6 is presented in Table 45. In patients with clinical evidence or subclinical evidence of CV disease who received standard of care for T2DM, treatment with SEM 0.5 mg was associated with statistically significantly greater reduction in total cholesterol (treatment ratio 0.97, 95% CI 0.95 to 1.00) and greater reduction in LDL cholesterol (treatment ratio), compared with placebo; treatment with SEM 1 mg was associated with statistically significantly increase in HDL cholesterol (treatment ratio 1.04, 95% CI 1.02 to 1.06). There were no other significant changes in lipid levels observed between SEM and active comparators.

Table 46: Lipid Profile (CV Outcome RCT; as Second- or Third-Line Therapy, Add-On to Standard of Care; FAS)

	SUSTAIN-6			
	SEM 0.5 mg N = 826	**SEM 1 mg N = 822**	**Placebo 0.5 mg N = 824**	**Placebo 1 mg N = 825**
Total cholesterol, mmol/L				
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, geom. mean (CoV)	4.28 (27.05)	4.27 (25.29)	4.26 (27.26)	4.30 (26.97)
End of study, mean (SE)	4.16 (0.03)	4.17 (0.03)	4.27 (0.03)	4.22 (0.03)
Ratio to baseline (SE)	0.97 (0.01)	0.97 (0.01)	1.00 (0.01)	0.99 (0.01)
Treatment ratio (95% CI)	0.97 (0.95 to 1.00) *P* = 0.0149	0.99 (0.97 to 1.01) *P* = 0.2580	NA	NA
HDL cholesterol, mmol/L				
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

	SUSTAIN-6			
Baseline value, mean (SD)	1.19 (0.34)	1.16 (0.32)	1.19 (0.33)	1.16 (0.32)
End of study, mean (SE)	1.13 (0.01)	1.14 (0.01)	1.12 (0.01)	1.10 (0.01)
Ratio to baseline (SE)	0.99 (0.01)	1.01 (0.01)	0.99 (0.01)	0.97 (0.01)
Treatment ratio (95% CI)	1.00 (0.99 to 1.02) *P* = 0.8106	1.04 (1.02 to 1.06) *P* < 0.0001	NA	NA
LDL cholesterol, mmol/L				
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	2.32 (1.01)	2.32 (0.89)	2.31 (0.99)	2.36 (0.98)
End of study, mean (SE)	2.07 (0.03)	2.09 (0.03)	2.16 (0.03)	2.11 (0.03)
Ratio to baseline (SE)	0.97 (0.01)	0.98 (0.01)	1.01 (0.01)	0.99 (0.01)
Treatment ratio (95% CI)	0.96 (0.93 to 0.99) *P* = 0.0185	0.99 (0.96 to 1.03) *P* = 0.5997	NA	NA

CI = confidence interval; CoV = coefficient of variation; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable; SD = standard deviation; SE = standard error; SEM = semaglutide.

Note: 'In-trial' data are presented. The log-transformed post-baseline responses are analyzed using a mixed model for repeated measurements with treatment (4 levels) and stratification (9 levels) as fixed factors and baseline value as covariate, all nested within visit.

Source: Clinical Study Report of SUSTAIN-6.[9]

SEM Used in Mixed Population (As Second- or Third-Line Therapy; Add-On to Basal Insulin Alone or Basal Insulin + MET)

Efficacy of study medications on blood lipid levels in SUSTAIN-5 was presented in Table 46. This was a mixed population where subgroup results based on background therapy were not available. In patients who received background basal insulin or basal insulin plus MET, treatment with SEM 0.5 mg was associated with a statistically significant reduction in total cholesterol (treatment ratio 0.95, 95% CI 0.91 to 0.99), compared with placebo.

Table 47: Lipid Profile (SEM as Second- and Third-Line Therapy, Add-On to Basal Insulin or Basal Insulin + MET; FAS)

	SUSTAIN-5		
	SEM 0.5 mg N = 132	**SEM 1 mg N = 131**	**Placebo N = 133**
Total cholesterol, mmol/L			
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]
Baseline value, geometric mean (CoV)	4.62 (25.59)	4.61 (23.82)	4.53 (24.12)
End of study, mean (SE)	4.21 (0.06)	4.32 (0.07)	4.44 (0.07)
Ratio to baseline (SE)	0.92 (0.01)	0.94 (0.01)	0.97 (0.02)
Treatment ratio (95% CI)	0.95 (0.91 to 0.99) P = 0.0146	0.97 (0.93 to 1.02) P = 0.2174	NA
HDL cholesterol, mmol/L			
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]
Baseline value, geometric mean (CoV)	1.18 (27.13)	1.23 (31.47)	1.21 (32.31)
End of study, mean (SE)	1.15 (0.02)	1.17 (0.02)	1.16 (0.02)
Ratio to baseline (SE)	0.95 (0.01)	0.97 (0.01)	0.96 (0.01)
Treatment ratio (95% CI)	0.99 (0.95 to 1.03) P = 0.7298	1.01 (0.97 to 1.05) P = 0.7268	NA
LDL cholesterol, mmol/L			
Patients contribute to the analysis, n (%)	[redacted]	[redacted]	[redacted]
Baseline value, geometric mean (CoV)	2.42 (44.24)	2.49 (39.85)	2.41 (38.67)
End of study, mean (SE)	2.13 (0.07)	2.25 (0.08)	2.29 (0.08)
Ratio to baseline (SE)	0.88 (0.03)	0.92 (0.03)	0.94 (0.03)
Treatment ratio (95% CI)	0.93 (0.84 to 1.03) *P* = 0.1444	0.98 (0.89 to 1.08) *P* = 0.7173	NA

CI = confidence interval; CoV = coefficient of variation; FAS = full analysis set; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable; SE = standard error; SEM = semaglutide.

Note: "On-treatment without rescue medication" data are presented. The post-baseline responses are analyzed using a mixed model for repeated measurements with treatment, country and stratification variable (A1C level at screening [less than and equal to 8.0% or greater than 8.0%] crossed with use of metformin [yes or no]; two by two levels) as fixed factors and baseline value as covariate, all nested within visit.

Source: Clinical Study Report of SUSTAIN-5.[8]

SEM Used in Mixed Population (as First- or Second-Line Therapy; Add-On to Diet/Exercise Alone or Diet)

Efficacy of study medications on blood lipids in the Seino study is presented in Table 47. This was a mixed population where subgroup results based on background therapy were not available. In patients who received background therapy of diet and exercise alone or diet and exercise plus OAD, treatment with either dose of SEM for 30 weeks was associated with greater reduction total cholesterol and LDL cholesterol, compared with SIT. Results were presented graphically. No other details are available.

Table 48: Lipid Profile (SEM as First- and Second-Line Therapy; FAS)

	Seino 2017		
	SEM 0.5 mg N = 103	**SEM 1 mg N = 102**	**SIT N = 103**
Total cholesterol	Results presented graphically. The authors stated that total cholesterol and LDL cholesterol were significantly reduced with both SEM doses; there was no significant difference in change in HDL cholesterol between SEM and SIT.		
HDL cholesterol			
LDL cholesterol			

FAS = full analysis set; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SEM = semaglutide; SIT = sitagliptin.

Source: Seino 2017.[14]

Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol).

Adverse Events

The overall frequency of AEs was similar between treatment groups within trials. In the placebo-controlled trials (except for SUSTAIN-6), AEs were reported by 56% to 69% of patients treated with SEM, and by 54% to 58% of patients treated with placebo (Table 48). In the active-controlled trials, AEs were reported by 68% to 75% of patients with SEM, 66% to 72% of patients with SIT, 76% of patients with EXE, 62% to 74% of patients with DUL, and 65% of patients with IG (Table 49). In the CVOT trial (SUSTAIN-6), incidence of AEs were higher (88% to 89%) compared with other included trials.

Among patients who received SEM, GI disorders were the most commonly reported AEs (27% to 39% in the placebo-controlled trials; 34% to 44% in the active-controlled trials). Among the active-controlled trials, patients received SEM were more likely to report GI disorders compared with those received SIT, EXE, or IG. In SUSTAIN-7, SEM was compared with another GLP-1 receptor agonist (DUL). The rates of GI disorders were similar between the SEM treatment groups (43% to 44%) and the DUL groups (33% to 48%).

Serious Adverse Events

SAEs were reported by 4% to 7% of patients received placebo, 5% to 9% of patients received SEM (2% to 3% of these SAEs were GI disorders), 2% to 7% of patient received SIT, 6% of patients received EXE, 7% to 8% of patients received DUL and 5% of patients received IG (Table 48 and Table 49).

In SUSTAIN-6, the rates of SAEs were 32.1%, 29.3%, and 34.9% in patients who received SEM 0.5 mg, SEM 1 mg, and placebo, respectively (Table 50). The most commonly reported SAEs in this trial were cardiac disorders, e.g., angina unstable, acute MI, coronary artery disease or cardiac failure, 9.8%, 9.2%, and 12.0%, respectively.

AEs Leading to Treatment Discontinuation

The rates of AEs leading to treatment discontinuation were 3.9% to 6.8% in the placebo group, 2.9% to 9.7% in the SEM group, 1.9% to 2.9% in the SIT group, 7.2% in the EXE group, 4.7% to 6.7% in the DUL groups, and 1.1% in the IG group. The differences between SEM and other treatment groups was mainly due to a greater proportion of patients with GI disorders that led to premature treatment discontinuation with SEM.

In SUSTAIN-6, the rates of AEs leading to premature treatment discontinuation were 11.5% to 14.5% in the SEM groups and 6.7% in the placebo group.

Mortality

There were no deaths reported in SUSTAIN-1, SUSTAIN-5, and Seino study. Details with respect to mortality are provided in the “Efficacy” section.

Notable Harms

The frequency of GI disorders was higher in the SEM group, compared with placebo, or active comparator which was not a GLP-1 receptor agonist, such as SIT or insulin (Table 48, Table 49 and Table 50).

The frequency of hypoglycemia was highest in the insulin glargine group in SUSTAIN-4 (39.4%). The risk of hypoglycemia for SEM was comparable to the other GLP-1 receptor agonists such as EXE and DUL, and was lower than SIT and IG. Severe hypoglycemia was reported infrequently in the included trials.

In general, injection site reaction was rare in the majority of the trials, while in SUSTAIN-3, the proportion of patients with injection site reaction was 22% in the EXE group compared with 1.2% in the SEM group.

The occurrence of other harms of special interest to this review was infrequent. Isolated cases of pancreatitis were reported. No cases of medullary thyroid carcinoma were identified. One EAC-confirmed thyroid malignant neoplasm was recorded in SUSTAIN-7.

Table 49: Harms (Placebo-Controlled RCTs; SAS)

Characteristics	SUSTAIN-1			SUSTAIN-5		
	SEM 0.5 mg N = 128	SEM 1 mg N = 130	Placebo N = 129	SEM 0.5 mg N = 132	SEM 1 mg N = 131	Placebo N = 133
AEs, n (%)						
Patients with > 0 AEs	82 (64.1)	73 (56.2)	69 (53.5)	91 (68.9)	84 (64.1)	77 (57.9)
Most common AEs (≥ 5%)						
GI disorders	49 (38.3)	50 (38.5)	19 (14.7)	36 (27.3)	45 (34.4)	21 (15.8)
Infections and infestations	31 (24.2)	21 (16.2)	31 (24.0)	37 (28.0)	29 (22.1)	41 (30.8)
Investigations	20 (15.6)	17 (13.1)	18 (14.0)	20 (15.2)	13 (9.9)	9 (6.8)
Metabolism and nutrition disorders	7 (5.5)	12 (9.2)	14 (10.9)	9 (6.8)	20 (15.3)	8 (6.0)
Musculoskeletal and connective tissue disorders	8 (6.3)	8 (6.2)	12 (9.3)	13 (9.8)	16 (12.2)	16 (12.0)
Nervous system disorders	21 (16.4)	14 (10.8)	10 (7.8)	13 (9.8)	8 (6.1)	11 (8.3)
General disorders and administration site conditions	7 (5.5)	10 (7.7)	11 (8.5)	7 (5.3)	7 (5.3)	5 (3.8)
Injury, poisoning, and procedural complications	4 (3.1)	4 (3.1)	2 (1.6)	11 (8.3)	3 (2.3)	4 (3.0)
Respiratory, thoracic, and mediastinal disorders	10 (7.8)	5 (3.8)	11 (8.5)	5 (3.8)	5 (3.8)	3 (2.3)
Skin and subcutaneous tissue disorders	7 (5.5)	3 (2.3)	3 (2.3)	8 (6.1)	7 (5.3)	5 (3.8)
Renal and urinary disorders	3 (2.3)	2 (1.5)	4 (3.1)	3 (2.3)	5 (3.8)	5 (3.8)
Vascular disorders	3 (2.3)	1 (0.8)	4 (3.1)	3 (2.3)	4 (3.1)	4 (3.0)
Cardiac disorders	2 (1.6)	3 (2.3)	3 (2.3)	5 (3.8)	1 (0.8)	3 (2.3)
SAEs, n (%)						
Patients with > 0 SAEs	7 (5.5)	7 (5.4)	5 (3.9)	8 (6.1)	12 (9.2)	9 (6.8)
GI disorders	1 (0.8)	0	1 (0.8)	0	1 (0.8)	0
Infections and infestations	2 (1.6)	0	1 (0.8)	1 (0.8)	3 (2.3)	4 (3.0)
Surgical and medical procedures	0	3 (2.3)	0	2 (1.5)	3 (2.3)	1 (0.8)
Cardiac disorders	0	2 (1.5)	0	2 (1.5)	0	1 (0.8)
Hepatobiliary disorders	1 (0.8)	0	0	0	1 (0.8)	0
Neoplasms benign, malignant, and unspecified	1 (0.8)	1 (0.8)	0	NR		
AEs leading to premature treatment discontinuation, n (%)						
Patients with > 0 AEs leading to premature treatment discontinuation	8 (6.3)	7 (5.4)	3 (2.3)	6 (4.5)	8 (6.1)	1 (0.8)
GI disorders	5 (3.9)	4 (3.1)	1 (0.8)	3 (2.3)	6 (4.6)	0
Deaths, n						
All-cause deaths	0			0		
CV death	0			0		
Notable harms, n (%)						
GI AEs	49 (38.3)	50 (38.5)	19 (14.7)	36 (27.3)	45 (34.4)	21 (15.8)
Hypoglycemia	0	0	2 (1.5)	48 (36.4)	63 (48.1)	39 (29.3)
Severe hypoglycemia	0			0	2 (1.5)	1 (0.8)
Injection site reaction	1 (0.8)	0	1 (0.8)	0	0	1 (0.8)
Anaphylaxis	NR			NR		
Pancreatitis	0			0		
Medullary thyroid carcinoma	0			0		

AE = adverse event; CV = cardiovascular; GI = gastrointestinal; NR = not reported; RCT = randomized controlled trial; SAE = serious adverse event; SAS = safety analysis set; SEM = semaglutide.

Note: "On-treatment" observation data are presented.

Source: Clinical Study Reports of SUSTAIN-1[7] and SUSTAIN-5.[8]

Table 50: Harms (Active-Controlled RCTs; SAS)

	SUSTAIN-2			SUSTAIN-3		SUSTAIN-4			SUSTAIN-7				Seino 2017		
	SEM 0.5 mg N = 409	SEM 1 mg N = 409	SIT N = 407	SEM 1 mg N = 404	EXE N = 405	SEM 0.5 mg N = 362	SEM 1 mg N = 360	IG N = 360	SEM 0.5 mg N = 301	SEM 1 mg N = 300	DUL 0.75 mg N = 299	DUL 1.5 mg N = 299	SEM 0.5 mg N = 103	SEM 1 mg N = 102	SIT N = 103
AEs, n (%)															
Patients with > 0 AEs	306 (74.8)	292 (71.4)	292 (71.7)	303 (75.0)	309 (76.3)	253 (69.9)	264 (73.3)	235 (65.3)	204 (67.8)	207 (69.0)	186 (62.2)	221 (73.9)	77 (74.8)	73 (71.6)	68 (66.0)
Most common AEs (> 5%)															
GI disorders	178 (43.5)	163 (39.9)	96 (23.6)	169 (41.8)	135 (33.3)	149 (41.2)	156 (43.3)	54 (15.0)	129 (42.9)	133 (44.3)	100 (33.4)	143 (47.8)	37 (35.9)	41 (34.2)	6 (5.8)
Infections and infestations	142 (34.7)	118 (28.9)	140 (34.4)	141 (34.9)	129 (311.9)	108 (29.8)	103 (28.6)	123 (34.2)	74 (24.6)	68 (22.7)	76 (25.4)	86 (28.8)	17 (16.5)	18 (17.6)	30 (29.1)
Investigations	78 (19.1)	72 (17.6)	73 (17.9)	76 (18.8)	83 (20.5)	57 (15.7)	59 (16.4)	47 (13.1)	39 (13.0)	37 (12.3)	38 (12.7)	37 (12.4)	16 (15.5)	9 (8.8)	6 (5.8)
Metabolism and nutrition disorders	66 (16.1)	53 (13.0)	63 (15.5)	55 (13.6)	42 (10.4)	45 (12.4)	46 (12.8)	21 (5.8)	37 (12.3)	40 (13.3)	27 (9.0)	41 (13.7)	9 (8.7)	8 (7.8)	0
Musculoskeletal and connective tissue disorders	61 (14.9)	49 (12.0)	61 (15.0)	58 (14.4)	67 (16.5)	35 (9.7)	42 (11.7)	48 (13.3)	37 (12.3)	33 (11.0)	50 (16.7)	30 (10.0)	NR		
Nervous system disorders	43 (10.5)	50 (12.2)	47 (11.5)	74 (18.3)	68 (16.8)	49 (13.5)	57 (15.8)	45 (12.5)	43 (14.3)	47 (15.7)	32 (10.7)	35 (11.7)	12 (11.7)	0	5 (4.9)
General disorders and administration site conditions	33 (8.1)	36 (8.8)	31 (7.6)	41 (10.1)	121 (29.9)	31 (8.6)	20 (5.6)	19 (5.3)	40 (13.3)	32 (10.7)	32 (10.7)	41 (13.7)	NR		
Injury, poisoning, and procedural complications	20 (4.9)	30 (7.3)	24 (5.9)	38 (9.4)	22 (5.4)	25 (6.9)	19 (5.3)	18 (5.0)	24 (8.0)	21 (7.0)	17 (5.7)	18 (6.0)	NR		
Respiratory, thoracic, and mediastinal disorders	31 (7.6)	19 (4.6)	24 (5.9)	31 (7.7)	35 (8.6)	32 (8.8)	19 (5.3)	30 (8.3)	14 (4.7)	16 (5.3)	22 (7.4)	19 (6.4)	NR		
Skin and subcutaneous tissue disorders	20 (4.9)	23 (5.6)	30 (7.4)	18 (4.5)	34 (8.4)	19 (5.2)	20 (5.6)	23 (6.4)	25 (8.3)	17 (5.7)	19 (6.4)	14 (4.7)	NR		
Renal and urinary disorders	23 (5.6)	20 (4.9)	29 (7.1)	23 (5.7)	23 (5.7)	12 (3.3)	12 (3.3)	10 (2.8)	9 (3.0)	10 (3.3)	6 (2.0)	9 (3.0)	NR		

	SUSTAIN-2			SUSTAIN-3		SUSTAIN-4			SUSTAIN-7				Seino 2017		
	SEM 0.5 mg N = 409	SEM 1 mg N = 409	SIT N = 407	SEM 1 mg N = 404	EXE N = 405	SEM 0.5 mg N = 362	SEM 1 mg N = 360	IG N = 360	SEM 0.5 mg N = 301	SEM 1 mg N = 300	DUL 0.75 mg N = 299	DUL 1.5 mg N = 299	SEM 0.5 mg N = 103	SEM 1 mg N = 102	SIT N = 103
Vascular disorders	28 (6.8)	22 (5.4)	18 (4.4)	17 (4.2)	20 (4.9)	9 (2.5)	13 (3.6)	15 (4.2)	8 (2.7)	10 (3.3)	12 (4.0)	6 (2.0)	NR		
Cardiac disorders	17 (4.2)	24 (5.9)	16 (3.9)	15 (3.7)	14 (3.5)	7 (1.9)	13 (3.6)	8 (2.2)	10 (3.3)	10 (3.3)	11 (3.7)	14 (4.7)	NR		
SAEs, n (%)															
Patients with > 0 SAEs	30 (7.3)	30 (7.3)	29 (7.1)	38 (9.4)	24 (5.9)	22 (6.1)	17 (4.7)	18 (5.0)	17 (5.6)	23 (7.7)	24 (8.0)	22 (7.4)	6 (5.8)	2 (2.0)	2 (1.9)
GI disorders	11 (2.7)	4 (1.0)	3 (0.7)	6 (1.5)	3 (0.7)	3 (0.8)	0	2 (0.6)	3 (1.0)	6 (2.0)	1 (0.3)	2 (0.7)	NR		
Infections and infestations	5 (1.2)	3 (0.7)	6 (1.5)	6 (1.5)	5 (1.2)	5 (1.4)	5 (1.4)	2 (0.6)	4 (1.3)	2 (0.7)	4 (1.3)	3 (1.0)	2 (1.9)	0	0
Cardiac disorders	4 (1.0)	4 (1.0)	4 (1.0)	3 (0.7)	4 (1.0)	2 (0.6)	2 (0.6)	4 (1.1)	0	4 (1.3)	5 (1.7)	7 (2.3)	1 (1.0)	0	0
Hepatobiliary disorders	2 (0.5)	4 (1.0)	1 (0.2)	1 (0.2)	1 (0.2)	NR			0	1 (0.3)	1 (0.3)	4 (1.3)	0	1 (1.0)	1 (1.0)
Neoplasms benign, malignant, and unspecified	1 (0.2)	3 (0.7)	3 (0.7)	8 (2.0)	2 (0.5)	3 (0.8)	0	1 (0.3)	2 (0.7)	1 (0.3)	2 (0.7)	2 (0.7)	2 (1.9)	2 (2.0)	4 (3.9)
Surgical and medical procedures	1 (0.2)	1 (0.2)	0	5 (1.2)	1 (0.2)	1 (0.3)	1 (0.3)	1 (0.3)	4 (1.3)	0	1 (0.3)	1 (0.3)	1 (1.0)	0	0
AEs leading to premature treatment discontinuation, n (%)															
Patients with AEs leading to premature treatment discontinuation	33 (8.1)	39 (9.5)	12 (2.9)	38 (9.4)	29 (7.2)	20 (5.5)	27 (7.5)	4 (1.1)	24 (8.0)	29 (9.7)	14 (4.7)	20 (6.7)	3 (2.9)	11 (10.8)	2 (1.9)
GI disorders	27 (6.6)	31 (7.6)	3 (0.7)	23 (5.7)	11 (2.7)	11 (3.0)	19 (5.3)	0	16 (5.3)	18 (6.0)	6 (2.0)	14 (4.7)	NR		
Deaths															
All-cause death, n	2 (0.5)	1 (0.2)	3 (0.7)	2 (0.5)	0	4	0	2	1 (0.3)	1 (0.3)	2 (0.7)	2 (0.7)	0		
CV death, n	2 (0.5)	1	2 (0.5)	0	0	3	0	2	0	0	2	1	0		
Notable harms, n (%)															
GI AEs	178 (43.5)	163 (39.9)	96 (23.6)	169 (41.8)	135 (33.3)	149 (41.2)	156 (43.3)	54 (15.0)	129 (42.9)	133 (44.3)	100 (33.4)	143 (47.8)	37 (35.9)	41 (34.2)	6 (5.8)
Hypoglycemia	34 (8.3)	38 (9.3)	46 (11.3)	94 (23.3)	98 (24.2)	82 (22.7)	90 (25.0)	142 (39.4)	36 (12.0)	32 (10.7)	36 (12.0)	37 (12.4)	NR		

	SUSTAIN-2			SUSTAIN-3		SUSTAIN-4			SUSTAIN-7				Seino 2017		
	SEM 0.5 mg N = 409	SEM 1 mg N = 409	SIT N = 407	SEM 1 mg N = 404	EXE N = 405	SEM 0.5 mg N = 362	SEM 1 mg N = 360	IG N = 360	SEM 0.5 mg N = 301	SEM 1 mg N = 300	DUL 0.75 mg N = 299	DUL 1.5 mg N = 299	SEM 0.5 mg N = 103	SEM 1 mg N = 102	SIT N = 103
Severe hypoglycemia	0	0	2 (0.5)	1 (0.2)	0	2 (0.6)	5 (1.4)	5 (1.4)	0	1 (0.3)	1 (0.3)	2 (0.7)	0 [a]	1 (1.0) [a]	0 [a]
Injection site reaction	2 (0.5)	1 (0.2)	2 (0.2)	5 (1.2)	89 (22.0)	3 (0.8)	2 (0.6)	6 (1.7)	4 (1.3)	6 (2.0)	4 (1.3)	8 (2.7)	NR		
Anaphylaxis	NR			NR		NR			NR				NR		
Pancreatitis	3 (0.7)	1 (0.2)	0	2 (0.5)	3 (0.7)	1 (0.3)	1 (0.3)	0	0	1 (0.3)	1 (0.3)	0	0		
Medullary thyroid carcinoma	NR			NR		0			0	0	0	1 thyroid malignant neoplasm	0		

AE = adverse event; CV = cardiovascular; DUL = dulaglutide; EXE = exenatide; GI = gastrointestinal; IG = insulin glargine; NR = not reported; RCT = randomized controlled trial; SAE = serious adverse event; SAS = safety analysis set; SEM = semaglutide; SIT = sitagliptin.

[a] An episode that is severe according to the ADA classification or BG-confirmed by a plasma glucose value less than 3.1 mmol/L, with symptoms consistent with hypoglycemia.

Note: "On-treatment" observation data are presented.

Source: Clinical Study Reports of SUSTAIN-2, 3, 4, 7,[8-13] and Seino 2018.[14]

In SUSTAIN-6, AEs were reported in a higher proportion of subjects or with a higher rate with SEM than with placebo within the GI disorders System Organ Class and for Preferred Terms of lipase increased, amylase increased, decreased appetite, diabetic retinopathy, cataracts, and dizziness. Back pain, urinary tract infection and influenza were reported in a similar proportion of subjects with SEM (0.5 mg and 1.0 mg) and placebo. Headache, nasopharyngitis, upper respiratory tract infection, bronchitis, and joint pain (arthralgia) were reported in a lower proportion of subjects with SEM (0.5 mg and 1.0 mg) than with placebo. In addition, less frequent AEs related to glucose control (BG increased), and lipids (hypercholesterolemia) were reported in a lower proportion of subjects with SEM than with placebo.

Table 51: Harms (CV Outcome Trial; SEM as Second- or Third-Line Therapy, Add-On to Standard of Care; SAS)

	SUSTAIN-6		
	SEM 0.5 mg N = 823	**SEM 1 mg N = 819**	**Placebo N = 1,644**
Patients with > 0 AEs, n (%)	732 (88.9)	722 (88.2)	1,453 (88.4)
Most common AEs (> 5%), %			
GI disorders	67.1	80.4	31.4
nausea	17.3	21.7	7.7
diarrhea	17.6	17.7	10.8
vomiting	10.2	14.5	4.7
constipation	5.6	9.5	4.2
decreased appetite	10.2	9.3	1.7
dyspepsia	6.2	7.7	2.3
Lipase increased	10.6	9.9	7.3
Urinary tract infection	9.1	7.7	7.7
Headache	6.6	6.7	8.4
Nasopharyngitis	7.2	6.3	8.5
Back pain	5.6	5.9	5.6
Diabetic retinopathy	5.1	5.9	4.6
Upper respiratory tract infection	6.1	5.5	7.2
Amylase increased	3.3	5.4	2.9
Dizziness	5.8	5.3	4.7
Influenza	5.8	5.3	5.7
Abdominal pain upper	4.0	5.1	2.3
Cataract	6.2	5.0	4.8
Bronchitis	4.9	4.3	6.0
Abdominal pain	5.5	4.2	3.9
Arthralgia	4.7	3.7	6.5
Patients with > 0 SAEs, n (%)	264 (32.1)	240 (29.3)	574 (34.9)
Cardiac disorders	81 (9.8)	74 (9.0)	197 (12.0)
Infections and infestations	23 (2.8)	13 (1.5)	43 (2.6)
Surgical and medical procedures	29 (3.5)	18 (2.3)	75 (4.6)
Nervous system disorders	8 (1.0)	6 (0.7)	18 (1.1)
Renal and urinary disorders	18 (2.2)	9 (1.1)	46 (2.8)
Injury, poisoning, and procedural complications	9 (1.1)	4 (0.5)	14 (0.9)

	SUSTAIN-6		
	SEM 0.5 mg N = 823	**SEM 1 mg N = 819**	**Placebo N = 1,644**
Musculoskeletal and connective tissue disorders	5 (0.6)	6 (0.7)	18 (1.1)
AEs leading to premature treatment discontinuation, n (%)	95 (11.5)	119 (14.5)	110 (6.7)
Deaths, n (%)			
All-cause deaths	30 (3.6)	32 (3.9)	60 (3.6)
CV-deaths	21 (2.5)	23 (2.8)	46 (2.8)
Notable harms, n (%)			
GI AEs	67.1%	80.4%	31.4%
Hypoglycemia	386 (46.9)	403 (49.2)	744 (45.3)
Severe hypoglycemia	14 (1.7)	9 (1.1)	26 (1.6)
Injection site reaction	6 (0.7)	9 (1.1)	20 (1.2)
Pancreatitis	5 (0.6)	3 (0.4)	10 (0.6)
Medullary thyroid carcinoma	0		

AE = adverse event; CV = cardiovascular; GI = gastrointestinal; SAE = serious adverse event; SAS = safety analysis set; SEM = semaglutide.

Note: "On-treatment" observation data are presented.

Source: Clinical Study Report of SUSTAIN-6.[9]

Discussion

Summary of Available Evidence

A total of eight phase III RCTs (SUSTAIN-1 to SUSTAIN-7, and the Seino study; four placebo-controlled and four active-controlled trials) provided evidence on the efficacy and safety of SEM in adults with T2DM and inadequate glycemic controlled with various background antidiabetic therapy, such as diet and exercise, metformin monotherapy, metformin plus an OAD, insulin alone, or insulin combined with OAD. These trials examined shorter-term (30 weeks to 56 weeks) surrogate outcomes including A1C, body weight, BMI, and blood pressure for SEM 0.5 mg and 1 mg once weekly versus placebo or active comparators. Change from baseline in level of A1C was the primary outcome in most of the trials. One of the placebo-controlled trials was a longer-term cardiovascular safety trial (SUSTAIN-6), where time from randomization to first occurrence of MACE was the primary outcome measure, and the study participants received treatment with study medications for up to 104 weeks. This is the only trial that assessed diabetes-related morbidity and mortality. Number of TEAEs was the primary outcome in a Japanese trial. In all trials, key secondary outcomes included the change in body weight from baseline to end of study. Other efficacy outcomes included the change in blood pressure from baseline and HRQoL.

A hierarchical testing procedure was adopted in all trials in order to control the overall type I error. Results of the outcomes measures outside of the testing hierarchy, such as change in blood pressure and patient-reported outcome, should be interpreted with consideration of potentially inflated type I error.

Interpretation of Results

Efficacy

SEM used as first-line, second-line, or third-line therapy was associated with statistically significant reductions in A1C after 30 weeks to 56 weeks compared with placebo or active treatment. SEM 1 mg was more likely to be related to greater glycemic control compared with SEM 0.5 mg. Somewhat larger mean differences were noted between SEM and SIT.

First-line therapy (add-on to diet and exercise):

- When compared with placebo, the between-group difference in A1C reduction was –1.43% to –1.53% (SUSTAIN-1).

Second-line therapy (add-on to MET):

- When compared with SIT, the between-group difference in A1C reduction was [redacted] (subgroup data from SUSTAIN-2).
- When compared with EXE, the between-group difference in A1C reduction was [redacted] (subgroup data from SUSTAIN-3).
- When compared with insulin glargine, the between-group difference in A1C reduction was [redacted] (subgroup data from SUSTAIN-4).
- When compared with DUL, the between-group difference in A1C reduction was –0.40% to –0.41% (SUSTAIN-7).

Third-line therapy (add-on to MET + SU or MET + TZD):

- When compared with SIT, the between-group difference in A1C reduction was [redacted] (subgroup data from SUSTAIN-2).
- When compared with EXE, the between-group difference in A1C reduction was [redacted] (subgroup data from SUSTAIN-3).
- When compared with insulin glargine, the between-group difference in A1C reduction was [redacted] (subgroup data from SUSTAIN-4).

In addition, results for glycemic control were also reported for patients received SEM as add-on to one or two OADs background antidiabetic therapy. The difference between SEM (add-on to standard of care, or basal insulin alone, or basal insulin plus MET) and placebo in A1C reduction was –0.66% to –1.75%; the difference between SEM (add-on to diet and exercise or diet and exercise plus one OAD) and SIT in A1C reduction was –1.13% to –1.14%. The change in A1C versus placebo or an active control was considered clinically relevant by the clinical expert consulted for this review. SUSTAIN-2, 3, 4, and 7 were NI trials, and the results suggested that SEM was noninferior and superior to the active control for the change from baseline in A1C based on a pre-defined 0.3% NI margin.

SEM used as first-line, second-line, or third-line therapy was also associated with statistically significant reductions in weight after 30 weeks to 56 weeks compared with placebo or active treatment. SEM 1 mg was more likely to be related to greater reduction in weight compared with SEM 0.5 mg. Somewhat larger mean differences were noted between SEM and insulin glargine.

First-line therapy (add-on to diet and exercise):

- When compared with placebo, the between-group difference in weight reduction was –2.75 kg to 3.56 kg (SUSTAIN-1).

Second-line therapy (add-on to MET):

- When compared with SIT, the between-group difference in weight reduction was [redacted] (subgroup data from SUSTAIN-2).
- When compared with EXE, the between-group difference in weight reduction was [redacted] (subgroup data from SUSTAIN-3).
- When compared with insulin glargine, the between-group difference in weight reduction was [redacted] (subgroup data from SUSTAIN-4).
- When compared with DUL, the between-group difference in weight reduction was –2.26 kg to –3.55 kg (SUSTAIN-7).

Third-line therapy (add-on to MET + SU or MET + TZD):

- When compared with SIT, the between-group difference in weight reduction was [redacted] (subgroup data from SUSTAIN-2).
- When compared with EXE, the between-group difference in weight reduction was [redacted] (subgroup data from SUSTAIN-3).
- When compared with insulin glargine, the between-group difference in weight reduction was [redacted] (subgroup data from SUSTAIN-4).

In addition, results for weight reduction were also reported for patients received SEM as add-on to one or two OADs background antidiabetic therapy: the difference between SEM (add-on to standard of care, or basal insulin alone, or basal insulin plus MET) and placebo in weight reduction was –2.31 kg to –5.06 kg; the difference between SEM (add-on to diet and exercise or diet and exercise plus one OAD) and SIT in weight reduction was –2.22 kg to –3.88 kg. The change in weight versus placebo or an active control was considered clinically relevant by the clinical expert consulted for this review.

Note that some results for A1C reduction and weight reduction were extracted from post hoc subgroup analyses. Due to the limitations existing in this statistical method, such as insufficient power to detect between-group differences, multiplicity not adjusted for, potential interactions between treatment and background therapy, data should be interpreted with caution.

SEM used as first-line, second-line, or third-line therapy was also associated with some improvements in blood pressure (SBP and DBP) and blood lipids. However, the differences between SEM and placebo or between SEM and active control were either not statistically significant, or statistical significance cannot be concluded in subgroup analyses.

Risk of cardiovascular events was examined in patients with existing CV disease in the two-year safety trial, SUSTAIN-6. The results showed that the proportion of patients with first MACE (defined as CV death, non-fatal MI, or non-fatal stroke) was lower with SEM (6.6%) therapy compared with placebo (8.9%). Treatment with either dose of SEM was also associated with numerically lower non-fatal MI and non-fatal stroke events, while the number of deaths from CV causes was similar across treatment groups. The estimated HR was 0.74 (95% CI, 0.58 to 0.95, $P < 0.0001$ for NI test, $P = 0.0167$ for superiority test), indicating that SEM statistically significantly reduced the risk of experiencing a MACE by 26% when compared with placebo in patients with existing CV disease. Non-inferiority of SEM versus placebo was confirmed according to the pre-defined NI margin. Treatment with SEM was also associated with fewer revascularizations, unstable angina pectoris requiring hospitalization, or hospitalization for heart failure. Furthermore, the proportion of new or worsening nephropathy was numerically lower in the SEM groups than in the placebo groups, while the proportion of diabetic retinopathy complications was numerically higher in the SEM groups than in the placebo groups: [redacted] with SEM 0.5 mg, [redacted] with SEM 1 mg, [redacted] with placebo 0.5 mg, and [redacted] with placebo 1 mg.

Results from SUSTAIN-6 show that patients with existing CV disease may benefit from treatment with SEM as add-on to standard of care. The risk of future CV events could be lower with SEM compared with placebo. This beneficial effect may be explained by the improved glycemic control, weight loss, lower blood pressure, and improved lipid profile. In the United Kingdom Prospective Diabetes Study (UKPDS), the authors indicated that each 1.0% (absolute) reduction in mean A1C associated with a 37% decline in the risk of microvascular complications, a 14% lower rate of myocardial infarction and a 21% reduction in deaths from diabetes.[43] The UKPDS also showed that for every 10 mm Hg decrease in SBP, there was a 15% decrease in diabetes-related deaths. Results from our review imply that SEM is able to provide additional glycemic control and weight benefit when added to a background of MET monotherapy or combination therapy of MET plus another OAD, in patients with T2DM. However, the change in blood pressure and lipid profile did not appear to be improved with SEM versus comparators in the SUSTAIN trials. It is uncertain if trials with longer treatment duration can provide more evidence to support the role of lowered blood pressure and improved lipid profile in reducing CV events in the study population. At the time of drafting this review report, only one GLP-1 receptor agonist (liraglutide) and

two SGLT2 inhibitors (canagliflozin and empagliflozin) have indications for add-on use in the T2DM population at high risk of cardiovascular events. Although SUSTAIN-6 results suggest that SEM does not increase the risk of certain cardiovascular events (MACE) and may reduce the risk of cardiovascular events as compared with placebo, the drug does not have the indication in this specific population.

SEM was compared with GLP-1 receptor agonist and DPP-4 inhibitors in the SUSTAIN trials. However, direct evidence is lacking for other comparisons. The manufacturer submitted three separate indirect treatment comparisons (ITCs) in patients inadequately controlled on one OAD that compared SEM to other GLP-1 agonists, SGLT2 inhibitors, and SU. Results of these ITCs suggested a reduction in A1C and weight with SEM versus the comparators; however, the data should be interpreted with caution, due to the use of separate networks for each drug class rather than one connected network that included all drugs relevant to the decision-making comparator set, and the low methodological quality of the ITCs. Details of critical appraisal and summaries of these ITCs are presented in Appendix 5 to Appendix 7.

The patient groups expressed that patients with T2DM hope to have a new drug that can help with glycemic control, weight loss, as well as avoidance of polypharmacy and eliminating or reducing the need for injections (Patient Input, Appendix 1). SEM may enhance patient adherence as it is administered once a week.

Harms

The AE profile of SEM appears to be similar to other drugs in the class and no new safety signals were identified based on the included trials. The overall frequency of AEs was similar between treatment groups within trials. In the placebo-controlled trials (except for SUSTAIN-6), AEs were reported by 56% to 69% of patients treated with SEM, and by 54% to 58% of patients treated with placebo. In the active-controlled trials, AEs were reported by 68% to 75% of patients with SEM, and 62% to 76% of patients with other active treatments. SAEs were reported by 4% to 7% of patients who received placebo, 5% to 9% of patients who received SEM (2% to 3% of these SAEs were GI disorders), and 2% to 8% of patient received other active treatments. The rates of AEs leading to treatment discontinuation were 4% to 7% in the placebo group, 3% to 10% in the SEM group, and 1% to 7% in other active treatment groups. The frequency of GI disorders was higher in the SEM group, compared with placebo, or active comparator which was not a GLP-1 receptor agonist, such as SIT or insulin. The frequency of hypoglycemia was highest in the insulin glargine group in SUSTAIN-4 (39.4%). The risk of hypoglycemia for SEM was comparable to the other GLP-1 receptor agonists such as EXE and DUL, and was lower than SIT and insulin glargine. Severe hypoglycemia was reported infrequently in the included trials.

Patients in the CVOT (SUSTAIN-6) reported higher AE rates compared with the other SUSTAIN trials. The incidence of TEAEs was 88% to 89%. The rates of SAEs were 32.1%, 29.3%, and 34.9% in patients who received SEM 0.5 mg, SEM 1 mg, and placebo, respectively. The rates of AEs leading to premature treatment discontinuation were 11.5% to 14.5% in the SEM groups and 6.7% in the placebo group.

The ITC that examined all-cause mortality among patients with T2DM treated with GLP-1 agonists, DPP-4 inhibitors, or SGLT2 inhibitors suggested that the risk of death among those who received SEM was similar to other therapies with the exception of empagliflozin. These data should be interpreted with caution due to potential heterogeneity in-trial and patient characteristics of the included studies that was not adequately explored in the ITC.

Potential Place in Therapy[2]

The first-line therapy for most patients with T2DM remains MET. The place for SEM is as second- or third-line therapy for patients not achieving their glycemic target.

The DCCPG recommend that, for patients with clinical CV disease, the preferred choice for second-line therapy is an agent with demonstrated CV benefit. The DCCPG list empagliflozin (Grade A, Level 1A), liraglutide (Grade A, Level 1A) or canagliflozin (Grade C, Level 2) as agents meeting this criterion. SEM would be an additional agent that could be included in this category, and it would be the only once-weekly medication in this group. For patients without clinical CV disease, the DCCPG recommend choosing the second-line therapy best suited to the individual. In particular, avoidance of hypoglycemia or weight gain is a priority for many patients, so DPP-4 inhibitors, GLP-1 receptors agonists, or SGLT2 inhibitors can be considered as potential agents. SEM would be one more within this already extensive category. For all patients, continuing escalation of therapy by the addition of third- or fourth-line agents may be needed to achieve glycemic targets.

Only about 50% of T2DM patients in Canada achieve glycemic targets,[15] which represents the primary unmet medical need for this population. Continuing escalation of therapy with more and more add-on agents is burdensome for patients, increases their exposure to potential adverse effects, and may impair their adherence with therapy. Although insulin is particularly effective at improving glycemia, treatment intensification in the real world is often limited by hypoglycemia, as well as patient reluctance to take multiple daily injections. SEM may in part fulfill this unmet need, as the data suggest that it is particularly efficacious at lowering A1C, it does not lead to hypoglycemia or weight gain, and although it is an injectable, it is only administered once per week (rather than at least once per day for insulin). Thus, patients taking SEM may be able to achieve lower A1C levels without hypoglycemia than those on other agents, reducing the need for intensification with further add-on therapy.

The patients who will receive this drug in practice are patients with type 2 diabetes who require intensification of therapy to meet glycemic targets and who are willing to take a once-weekly injectable medication. These will include patients with clinical cardiovascular disease, but also a substantial proportion of the much larger population of patients without clinical cardiovascular disease. There will be no barriers to identifying such patients.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Conclusions

In patients with type 2 diabetes and inadequate glycemic control on previous antidiabetic treatment, SEM 0.5 mg or 1 mg as monotherapy, or as add-on therapy to MET, or MET plus another antidiabetic agent, was associated with statistically significant reductions in A1C and body weight as compared with placebo plus add-on therapies. SEM 0.5 mg or 1 mg was superior to active treatments, such as DPP-4 inhibitors, other GLP-1 receptor agonists, or IG, in reduction in A1C and body weight.

In patients who have T2DM and existing CV disease, SEM 0.5 mg or 1 mg, as add-on to standard of care, does not increase the risk of certain CV events (measured with MACE) and may reduce the risk of CV events as compared with placebo.

HRQoL was improved for all treatment groups within trials, but statistically significant differences between treatment groups were not always observed. In addition, treatment with SEM was associated with lowered SBP and DBP, and improved blood lipid profile, compared with placebo or other active treatments. However, statistically significant differences were not always observed.

The results of the manufacturer-provided ITCs suggested a reduction in A1C and weight with SEM versus other GLP-1 agonists, SGLT2 inhibitors, and SU in patients inadequately control on one OAD drug. However, the data were analyzed as separate networks for each drug class, rather than one connected network that included all drugs relevant to the decision-making comparator set. The restricted scope of the comparisons limited the evidence included in each analysis, excluded comparisons with the DPP-4 inhibitor class, and limited the applicability of the findings. No conclusions could be drawn from the indirect comparisons of SEM versus other GLP-1 agonists or SGLT2 inhibitors as add-on to one or two OAD drug due to fundamental limitations of these analyses.

The AE profile of SEM appears to be similar to other drugs in the class and no new safety signals were identified based on the included trials.

It is unclear whether SEM fills a specific unmet clinical need for patients with T2DM. It is the fifth GLP-1 receptor agonist approved for the management of T2DM in Canada, and given the availability of a number of antihyperglycemics from other drug classes, SEM represents an additional treatment option.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Two patient groups, Diabetes Canada and Patient Commando, provided patient input for this submission. Diabetes Canada is a national health charity representing 11 million Canadians living with diabetes or prediabetes. The priorities of Diabetes Canada's mission are diabetes prevention, care, and cure. Diabetes Canada focuses on research and policy initiatives for better prevention and treatment strategies. The organization received funding from multiple pharmaceutical companies and organizations, including Novo Nordisk Canada Inc., who was one of five companies that provided more than $350,000 over the past two years. They reported that they had no help from outside their organization to collect and analyze data, or to complete the submission.

Patient Commando is a group that supports and enables its community by sharing stories of patient experience, and facilitation of meaningful, relevant conversations. It aims to amplify the patient experience as a guide to improve health care practice using online patient stories, training health care professionals in narrative competency, and fostering collaborations between patients and health care professionals focused on improving disease-specific therapeutic relationships. They reported that they have not received funding from any companies or organizations with interest in this review over the past two years, nor had they had help from outside their organization to collect and analyze data, or to complete the submission.

2. Condition-Related Information

Diabetes Canada collected patient input through online surveys conducted in October 2016 and from November to December 2018, using a self-administered questionnaire targeting people living with type 2 diabetes and their caregivers across Canada. The 2018 survey asked questions specific to semaglutide. A total of 847 people responded to the 2016 survey, including 790 patients and 57 caregivers. Of those who responded to questions about age and time since diagnosis (n = 379), 70% were older than the age of 55 years and 60% having lived with diabetes for more than 10 years. A total of 15 people participated in the 2018 survey, including 13 patients and two caregivers. Among them, all were older than the age of 40 years and four reported having lived with diabetes for at least six years.

Patient Commando reported the following sources of data for their submission: personal interviews and facilitated group discussions; conversation threads in social media platforms; their website story collection; and community responses to their Experience Exchange program. They also noted that they used an inductive qualitative approach that focused on the narratives, which linked identified themes with the data set, rather than to theoretical perspectives. It is unclear how many patients from Patient Commando shared their stories.

Diabetes Canada highlighted that diabetes is a chronic, progressive disease without a cure. The two patient groups described common symptoms of diabetes such as extreme fatigue, unusual thirst, frequent urination, and weight change (gain or loss). They also noted that diabetes requires considerable self-management: eating well, engaging in regular physical activity, maintaining a healthy body weight, taking medications (oral and/or injectable) as prescribed, monitoring blood glucose, and managing stress. Poor glucose control is serious and problematic, and requires attention at both extremes: low blood glucose can precipitate an acute crisis, such as confusion, coma, or seizure, while high blood glucose over time can

irreversibly damage blood vessels and nerves, resulting in blindness, heart disease, kidney problems, foot damage, and lower limb amputations, among other issues. Patients also reported feeling anxious and fearful of complications and long-term effects of the disease. Respondents of Diabetes Canada stated that diabetes affects everything from eating and exercising, to working and socializing. Besides the physical impact of T2DM, Patient Commando indicated that T2DM has a striking burden on the patients' emotional, social, and economic status. The patient group described a stigma associated with diabetes as a result of linking the disease to patient's perception of self and self-care efforts, as well as perception of others that diabetes is the fault of the individual. Some of the social issues described were restrictions on social engagement due to the cost of T2DM, preparation for travel, and the restriction on social interaction, which are often based around food and drink. As for the economic aspect, the patient group noted that poorly managed health and the complications of diabetes can affect work opportunities, which presents a significant challenge for lower income populations. Further, costly diabetes management may force patients to trade off optimal therapy for basic needs.

Some quotes from the two patient groups:

"[I am] exhausted all of the time." (from Diabetes Canada)

"There is no vacation from diabetes" (from Patient Commando)"I have neuropathy in my legs and hands. I have diabetic neuropathy in my eyes. I can't drive any more and have to rely on help from family and [an accessible transit service]. I was off for a year with Charcots[sic] foot. I walk with a cane now. Before this happened I was walking 5 kms[sic] a day. Im[sic] lucky if I get to the end of my driveway. Diabetes has taken away all my independance[sic]." (from Diabetes Canada)

"The two diabetes specialists heading the class used shaming as a tool to let me know what a terrible diabetic I was. The shaming didn't make me straighten up...it made me shut down and try even less." (from Patient Commando)

"My doctor asked me 'What plan are you on?' It only occurred to me afterwards what a difference that question makes to the treatment chosen or available to a patient" (from Patient Commando)

Living with T2DM also has a significant impact on the families and caregivers of patients, as described by both of the patient input summaries. Those who care for patients suffer anxiety, stress, and worry, and also tend to serve as life-saving interventionists, and a source of support. The submission from Patient Commando included reports from patients and their caregivers that described the burden T2DM puts on the caregivers, with one individual having reported that her husband wakes them up at 3:00 a.m. every night to check blood sugar levels. Another individual said they feel like a nurse, ensuring their partner takes their medication, checks their blood glucose, and is eating well, on top of working a full-time job, taking care of children, and continuing their daily responsibilities, which was very overwhelming, as highlighted in the quote below.

"I am trying to hold it together for him and be everything that everyone needs. But I have so much on my plate that I find myself not eating any more and I have really forgotten what sleep is. It seems like all I do is think about what his last number was."

3. Current Therapy-Related Information

The goal of diabetes management is to keep glucose levels within a target range to minimize symptoms and avoid or delay complications. Both patient groups indicated the complexity of treatment modalities for diabetes. Individualization of therapy, based on a patient's degree of glycemic control and various other considerations, is essential. Patients who responded to the surveys conducted by Diabetes Canada (n = 667 for 2016 survey and n = 6 for 2018 survey) reported they have used (in the past or currently) the following antihyperglycemic agents: metformin, glucagon-like peptide 1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 (SGLT2) inhibitors, combination of SGLT2 inhibitors and metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, combination of DPP-4 inhibitors and metformin, sulfonylureas, thiazolidinediones (TZDs), combination of TZDs and metformin, combination of TZDs and glimepiride, meglitinides, acarbose, and insulin. These factors were considered "quite important" or "very important" in choosing diabetes medications among respondents: keeping blood glucose at a satisfactory level, avoiding low blood sugar, avoiding weight gain or facilitating weight loss, reducing risk of heart problems, and avoiding gastrointestinal (GI) issues (nausea, vomiting, diarrhea, pain), urinary tract and/or yeast infections, and fluid retention.

More than 60% of respondents (from the 2016 survey) noted improvements in meeting target blood glucose levels (fasting, postprandial, upon waking) and glycated hemoglobin (A1C) levels after initiation on their current medication regimen, compared with when they were not on treatment. About 46% patients reported they were "better" or "much better" able to avoid hypoglycemia, and 39% said their current regimen helped them maintain or lose weight more effectively than in the past. Gastrointestinal side effects were "neither better nor worse" than with previous treatments in 39% of respondents. Further, nearly two-thirds indicated they were either "satisfied" or "very satisfied" with the medication or combination of medications they are currently taking for their diabetes management. The Patient Commando submission relayed a different patient experience, as it highlighted widespread frustration among patients with the available options, how to assess, and how to understand the disease. It also reported that the number of patients with T2DM that escalate to insulin therapy was increasing. This patient input response also noted geographical access inequalities, institutional protocols, and access to specialized diabetes care teams, as components of treatment that further complicate the process.

4. Expectations About the Drug Being Reviewed

The two surveys conducted by Diabetes Canada reported that respondents expressed a strong desire for medications that can normalize or stabilize blood glucose levels and improve A1C without causing weight gain or hypoglycemia. They would also like new treatments that are proven to be safe, enhance weight loss, and improve health outcomes. Affordability of new drugs was also highlighted, ideally with medications and diabetes-related devices covered by public and private plans. Patients also want new treatments to be easily administered, with minimal disruption to lifestyle, allowing for flexibility with food intake and choices. They want medications that minimize the risk of diabetes-related complications, avoid polypharmacy, and eliminate the need for injections. Several respondents hope future treatments will reverse or cure diabetes. One respondent from this patient group said *"Expectations are that eventually there will be a medication that can be taken once a day that will help my pancreas produce the right amount of insulin to keep up with me (or possibly even cure the disease). I would hope that medications are made available to anyone living with diabetes and covered under by our government benefits*."

Among the six patients who responded to Diabetes Canada's 2018 survey, three reported taking semaglutide, two had no experience with it, and one did not know whether they were, or had ever been, on it. Two out of three people reported having switched to semaglutide from another medication. One person was paying out-of-pocket for the medication, one had coverage through a private insurance plan, and one received samples from their physician. Two patients reported that semaglutide helped them achieve their target A1C better than previous therapies, while one said it was worse. Two respondents reported semaglutide was "better" or "much better" at helping them avoid low blood sugar, while one said it was the same as previous treatments. All three respondents said semaglutide was the same or worse in terms of weight management properties and GI side effects. The patient input from the Patient Commando group provided general feedback about semaglutide, as well as a list of quotes from patients who had experience with the drug, both of which were aligned with the survey results from Diabetes Canada. In summary, the respondents described the ability to control blood sugar and reduced fear of hypoglycemia, by reducing or eliminating the use of insulin. Improved dosage management was also described, which they noted is important for patients with concomitant conditions who have difficulty monitoring various symptoms. In addition, the patients reported various GI symptoms such as nausea, constipation, and a loss of appetite.

5. Additional Information

Semaglutide is not associated with any companion diagnostic testing.

The Patient Commando submission elaborated on the number of tools and instruments associated with monitoring and treatment of diabetes, including lancets, monitors, blood glucose test strips, ketone strips, needles, pumps, and associated supplies. They highlighted the high cost and consequent distress associated with management of T2DM, which complicates treatment. The response also noted the issue around "treating the whole patient" and not just gaining control of blood sugar levels, as many experience other comorbidities and symptoms of T2DM that are also a concern to the patient.

The patient group from Diabetes Canada also stated that diabetes is a disease that requires intensive self-management. Diabetes Canada's 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada highlight the importance of personalized care when it comes to the pharmacologic management of the condition, which the patient group expressed was reinforced by the results of their survey. They noted that while current therapies have generally led to improvement for many people with diabetes in blood glucose and A1C control, respondents hope for even better, more affordable antihyperglycemic agents that they can access equitably, in a timely manner, and with good result to help them lead a normal life. They would like semaglutide to be an option for people with diabetes, "as it may help them to achieve better glycemic control and, in so doing, improve lives and save millions of dollars in direct health care costs."

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	December 20, 2018
Alerts:	Bi-weekly search updates until project completion, April 2019
Study Types:	No filters were applied to limit retrieval by study type
Limits:	Publication date limit: no date limit Humans-only Language limit: no language limit Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.dq	Candidate Term Word
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(Ozempic* or semaglutide* or NN 9535 or NN9535 or "NNC 0113 0217" or NNC01130217 or "NNC 01130217" or "NNC0113 0217").ti,ab,kf,ot,nm,rn,hw.
2	53AXN4NNHX.rn,nm.
3	1 or 2
4	3 use medall
5	exp *semaglutide/
6	(Ozempic* or semaglutide* or NN 9535 or NN9535 or "NNC 0113 0217" or NNC01130217 or "NNC 01130217" or "NNC0113 0217").ti,ab,kw,dq.

MULTI-DATABASE STRATEGY	
7	5 or 6
8	7 use oemezd
9	4 or 8
10	9 not conference abstract.pt.
11	exp animals/
12	exp animal experimentation/ or exp animal experiment/
13	exp models animal/
14	nonhuman/
15	exp vertebrate/ or exp vertebrates/
16	or/11-15
17	exp humans/
18	exp human experimentation/ or exp human experiment/
19	or/17-18
20	16 not 19
21	10 not 20
22	remove duplicates from 21

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.

Grey Literature

Dates for Search:	December 12-18, 2018
Keywords:	Ozempic, semaglutide, NN 9535, NN9535, type 2 diabetes, T2DM
Limits:	No date limits

Relevant websites from the following sections of the CADTH grey literature checklist, Grey matters: a practical tool for evidence-based searching (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Internet Search
- Open Access Journals.

Appendix 3: Excluded Studies

Table 52: Excluded Studies

Studies	Reasons
Kaku K, Yamada Y, Watada H, et al. Safety and efficacy of once-weekly semaglutide vs additional oral antidiabetic drugs in Japanese people with inadequately controlled type 2 diabetes: A randomized trial. *Diabetes Obes Metab*. 2018 05;20(5):1202-1212.	Comparator was "additional OAD added to background therapy" which included DPP-4 inhibitor, biguanide, SU, glinide, alpha-glucosidase inhibitor or TZD, and no separate results presented for each of them.

DPP-4 = dipeptidyl peptidase-4; OAD = oral antidiabetic drug; SU = sulfonylurea; TZD = thiazolidinedione.

Appendix 4: Detailed Outcome Data

Efficacy results of SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4 in the overall population are presented in this section.

Table 53: Glycemic Control Outcomes (SEM as Second- or Third-Line Therapy, Add-On to MET + TZD or MET + SU; FAS and PP)

		SUSTAIN-2			SUSTAIN-3		SUSTAIN-4		
		SEM 0.5 mg N = 409	SEM 1 mg N = 409	SIT N = 407	SEM 1 mg N = 404	EXE N = 405	SEM 0.5 mg N = 362	SEM 1 mg N = 360	IG N = 360
A1C, %									
Patients contribute to the analysis		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)		8.01 (0.92)	8.04 (0.93)	8.17 (0.92)	8.36 (0.95)	8.33 (0.96)	8.13 (0.85)	8.25 (0.94)	8.13 (0.88)
FAS	End of study, mean (SE)	6.76 (0.05)	6.46 (0.05)	7.53 (0.05)	6.81 (0.06)	7.43 (0.06)	6.96 (0.05)	6.53 (0.05)	7.34 (0.05)
FAS	Change from baseline at end of study, mean (SE)	–1.32 (0.05)	–1.61 (0.05)	–0.55 (0.05)	–1.54 (0.06)	–0.92 (0.06)	–1.21 (0.05)	–1.64 (0.05)	–0.83 (0.05)
FAS	Treatment group difference versus comparator (95% CI)	–0.77 (–0.92 to –0.62) P < 0.0001	–1.06 (–1.21 to –0.91) P < 0.0001	NA	–0.62 (–0.80 to –0.44) *P* < 0.0001	NA	–0.38 (–0.52 to –0.24) *P* < 0.0001	–0.81 (–0.96 to –0.67) *P* < 0.0001	NA
PP	End of study, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP	Change from baseline at end of study, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP	Treatment group difference versus comparator (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; CI = confidence interval; EXE = exenatide; FAS = full analysis set; IG = insulin glargine; NA = not applicable; PP = per-protocol; SD = standard deviation; SE = standard error; SEM = semaglutide; SIT = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

Note: For SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4, "on-treatment without rescue medication" data are presented. The post-baseline responses are analyzed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

Source: Clinical Study Reports of SUSTAIN-2,[10] SUSTAIN-3,[11] and SUSTAIN-4.[12]

Table 54: Body Weight/BMI (SEM as Second- or Third-Line Therapy, Add-On to MET + TZD or MET + SU; FAS)

	SUSTAIN-2			SUSTAIN-3		SUSTAIN-4		
	SEM 0.5 mg N = 409	SEM 1 mg N = 409	SIT N = 407	SEM 1 mg N = 404	EXE N = 405	SEM 0.5 mg N = 362	SEM 1 mg N = 360	IG N = 360
Body weight, kg								
Patients contribute to the analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	89.93 (20.39)	89.21 (20.74)	89.29 (19.67)	96.21 (22.50)	95.37 (20.46)	93.73 (21.39)	94.00 (22.48)	92.61 (21.52)
End of study, mean (SE)	85.20 (0.25)	83.34 (0.25)	87.54 (0.26)	90.16 (0.29)	93.94 (0.29)	89.98 (0.24)	88.27 (0.24)	94.60 (0.23)
Change from baseline, mean (SE)	–4.28 (0.25)	–6.13 (0.25)	–1.93 (0.26)	–5.63 (0.29)	–1.85 (0.29)	–3.47 (0.24)	–5.17 (0.24)	1.15 (0.23)
Treatment group difference vs. comparator (95% CI)	–2.35 (–3.06 to –1.63) *P* < 0.0001	–4.20 (–4.91 to –3.49) *P* < 0.0001	NA	–3.78 (–4.58 to –2.98) *P* < 0.0001	NA	–4.62 (–5.27 to –3.96) *P* < 0.0001	–6.33 (–6.99 to –5.67) *P* < 0.0001	NA
BMI, kg/m^2								
Patients contribute to the analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline value, mean (SD)	32.43 (6.22)	32.50 (6.61)	32.45 (5.81)	33.97 (7.23)	33.57 (6.23)	33.11 (6.45)	32.96 (6.51)	32.95 (6.51)
End of study, mean (SE)	30.89 (0.09)	30.20 (0.09)	31.78 (0.09)	31.76 (0.10)	33.12 (0.10)	31.78 (0.08)	31.16 (0.09)	33.43 (0.08)
Change from baseline, mean (SE)	–1.58 (0.09)	–2.26 (0.09)	–0.68 (0.09)	–2.01 (0.10)	–0.65 (0.10)	–1.23 (0.08)	–1.85 (0.09)	0.42 (0.08)
Treatment group difference vs. comparator (95% CI)	–0.90 (–1.16 to –0.64) *P* < 0.0001	–1.58 (–1.84 to –1.32) *P* < 0.0001	NA	–1.36 (–1.64 to –1.07) *P* < 0.0001	NA	–1.66 (–1.89 to –1.43) *P* < 0.0001	–2.27 (–2.51 to –2.04) *P* < 0.0001	NA

BMI = body mass index; CI = confidence interval; EXE = exenatide; FAS = full analysis set; IG = insulin glargine; NA = not available; SD = standard deviation; SE = standard error; SEM = semaglutide; SIT = sitagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

Note: For SUSTAIN-2, SUSTAIN-3, and SUSTAIN-4, "on-treatment without rescue medication" data are presented. The post-baseline responses are analyzed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

Source: Clinical Study Reports of SUSTAIN-2,[10] SUSTAIN-3,[11] and SUSTAIN-4.[12]

Patient-reported HRQoL results are presented in Table 55.

Table 55: Health-Related Quality of Life (SUSTAIN-2 to SUSTAIN-7; FAS)

Study		DTSQ		SF-36			
		Baseline, Mean (SD)	End of Study, Mean (SD)	PCS Baseline, Mean (SD)	PCS End of Study, Mean (SD)	MCS Baseline, Mean (SD)	MCS End of Study, Mean (SD)
SUSTAIN-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUSTAIN-3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUSTAIN-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUSTAIN-5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUSTAIN-6	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
SUSTAIN-7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DTSQ = Diabetes Treatment Satisfaction Questionnaire; DUL = dulaglutide; EXE = exenatide; FAS = full analysis set; IG = insulin glargine; MCS = Mental Component Summary; NA = not applicable; PCS = Physical Component Summary; SD = standard deviation; SE = standard error; SEM = semaglutide; SF-36 = Short Form (36) Health Survey; SIT = sitagliptin.

Note: "On-treatment without rescue medication" data for SUSTAIN-2, 3, 4, 5, and 7; "in-trial" data for SUSTAIN-6.

Sources: Clinical Study Reports of SUSTAIN-2 to SUSTAIN-7.[8-13]

Appendix 5: Summary of Indirect Comparisons of Second-Line Therapy

Introduction

There is direct evidence comparing semaglutide to sitagliptin and dulaglutide in patients inadequately controlled on one oral antidiabetic drug (OAD), and to exenatide or insulin glargine in patients with inadequate glycemic control with one or two OADs, however data are lacking for other comparators. Furthermore, direct comparative data are lacking in patients with high cardiovascular risk.

The objective of this section was to summarize and appraise indirect comparisons that evaluated the efficacy and safety of semaglutide in patients who had inadequate control with metformin (second-line therapy), metformin plus sulfonylurea (third-line therapy), or those with cardiovascular disease or cardiovascular risk factors.

Methods

The manufacturer provided five indirect comparisons and one feasibility assessment as part of the CADTH Common Drug Review (CDR) submission.[44-49] A literature search was conducted to identify other relevant published network meta-analyses (NMAs). Potentially relevant indirect comparisons were screened by one researcher for inclusion based on the criteria in Table 55. A total of 16 potentially relevant indirect comparisons (described in 20 reports) were screened and six met the inclusion criteria (total of ten reports).[44-48,50-54]

Reasons for exclusion were as follows: population;[55,56] report does not include indirect comparison;[49] report did not provide outcome data specific to semaglutide;[57,58] report did not include semaglutide;[59-62] or did not include outcomes of interest.[63]

Three indirect comparisons of second-line therapy that were provided by the manufacturer will be summarized and appraised in this appendix.[44-46] The two NMA in patients inadequately controlled on one or two OADs[47,48] will be appraised in Appendix 6, and the published NMA by Zheng et al.[52] will be summarized in Appendix 7.

Table 56: Inclusion Criteria for Review of Indirect Comparisons

Patient Population	Adult patients with T2DM who have inadequate glycemic control with diet or exercise alone, or on therapy with metformin alone, sulfonylurea in combination with metformin, or basal insulin in combination with metformin, as adjunct to diet and exercise.
Intervention	Semaglutide SC injection 0.5 mg or 1 mg once weekly, as monotherapy or add-on therapy with one or more antidiabetic drugs
Comparators	One or more of the following: • Metformin • Sulfonylureas • SGLT2 inhibitors (i.e., canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) • Other GLP-1 analogues (i.e., dulaglutide, liraglutide, lixisenatide, exenatide) • DPP-4 inhibitors (i.e., alogliptin, linagliptin, sitagliptin, saxagliptin) • Thiazolidinediones (i.e., pioglitazone, rosiglitazone) • Meglitinides (i.e., repaglinide) • Alpha-glucosidase inhibitors (i.e., acarbose) • Insulin/insulin analogues (including basal and prandial regimens)

Outcomes	**Efficacy outcomes:** • Glycemic control (e.g., A1C) • Mortality (all-cause, cardiovascular related) • Diabetes-related macrovascular or microvascular morbidity • Hospitalization (all-cause, cardiovascular related) • HRQoL • Blood pressure • BMI and/or body weight • Lipid profile **Harms outcomes:** • AEs • SAEs • WDAEs • Mortality • Notable harms: gastrointestinal AEs, hypoglycemia (including severe hypoglycemia), injection site reactions, anaphylaxis, pancreatitis, MTC
Study Design	Published and unpublished ITC

A1C = glycated hemoglobin; AE = adverse event; BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide 1; HRQoL = health-related quality of life; ITC = indirect treatment comparison; MTC = medullary thyroid carcinoma; SAE = serious adverse event; SC = subcutaneous; SGTL-2 = sodium-glucose transport protein 2; T2DM = type 2 diabetes mellitus; WDAE = withdrawals due to adverse event.

Description of Manufacturer-Submitted ITCs in Second-Line Therapy

[redacted]

[redacted]

Table 57: Inclusion Criteria for Systematic Reviews of Second-Line Therapy

Criteria	SEM vs. GLP-1 Analogues as Add-On to 1 OAD	SEM vs. SGLT2 Inhibitors as Add-On to MET	SEM vs. SU as Add-On to MET
Population	[redacted]	Adult patients with diagnosed T2DM and inadequately controlled with MET (defined as ≥ 90% of the study patients on MET monotherapy)	[redacted]
Intervention	[redacted]	Once-weekly SEM 0.5 mg Once-weekly SEM 1.0 mg	[redacted]
Comparator	[redacted]	SGLT2 inhibitors: • Empagliflozin 10 mg and 25 mg once daily • Canagliflozin 100 mg and 300 mg once daily • Dapagliflozin 5 mg and 10 mg once daily Other treatments that are connected with once-weekly semaglutide and/or a SGLT2	[redacted]
Outcome	[redacted]	Change from baseline in: • A1C • fasting plasma glucose • postprandial glucose • body weight • BMI • SBP Proportion of patients achieving: • < 7% or ≤ 6.5% A1C • ≥ 5% or ≥ 10% weight loss • composite end point (< 7% A1C, no weight gain, and no hypoglycemia) Incidence of: • discontinuations due to adverse events • nausea, vomiting, diarrhea, or pancreatitis • hypoglycemia (overall, severe, non-severe, nocturnal)	[redacted]
Study design	[redacted]	RCTs with at least a 20-week duration[c]	[redacted]
Publication characteristics	[redacted]	English language From 1994 to August 16, 2017	[redacted]
Exclusions	[redacted]	Trials in 100% Asian population	[redacted]

Criteria	SEM vs. GLP-1 Analogues as Add-On to 1 OAD	SEM vs. SGLT2 Inhibitors as Add-On to MET	SEM vs. SU as Add-On to MET
	[redacted]		[redacted]

A1C = glycated hemoglobin; BMI = body mass index; CV = cardiovascular; DBP = diastolic blood pressure; GLP-1 = glucagon-like peptide -1; MET = metformin; OAD = oral antidiabetic drug; RCT = randomized controlled trial; SBP = systolic blood pressure; SEM = semaglutide; SGLT2 = sodium-glucose cotransporter-2; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.

[redacted]

[c] Crossover studies were included if data were reported prior to crossover and after at least 20 weeks of therapy.

Source: Manufacturer supplied NMAs.[44-46,50]

[redacted]

[redacted]

Table 58: Summary of Network Meta-Analysis Methods

Criteria	SEM vs. GLP-1 Add-On to 1 OAD (> 90% MET)	SEM vs. SGLT2 Inhibitors as Add-On to MET	SEM vs. SU as Add-On to MET
NMA methods	[redacted]	Bayesian NMA using FE and RE models. Continuous outcomes: normal likelihood with identity link (mean difference). Dichotomous outcomes: binomial likelihood with logit link (OR and RR) based on NICE DSU document. MCMC method (JAGS software and R version 3.3.3) with 40,000 iteration burn-in and 80,000 for parameter estimations using two chains. Convergence confirmed by the Gelman-Rubin statistic. Non-informative priors; model accounted for correlation in multi-arm trials. Model selection based on DIC (> 3 important differences); or those with statistically significant regression coefficient selected over unadjusted model if difference in DIC > 3. Consistency assessed by splitting model into direct and indirect information for each node and comparing the posterior distribution based on direct and indirect evidence for each comparison.	[redacted]

Criteria	SEM vs. GLP-1 Add-On to 1 OAD (> 90% MET)	SEM vs. SGLT2 Inhibitors as Add-On to MET	SEM vs. SU as Add-On to MET
			[redacted]
Sensitivity analyses	[redacted]	Sensitivity analysis that excluded trials with > 40% Asian population Meta-regression by gender, disease duration, weight, A1C at baseline	[redacted]
Outcomes	[redacted]	Change from baseline in • A1C • weight • FPG • SBP Proportion of patients with: • A1C < 7% • discontinued due to adverse events • diarrhea Eight trials reported data at week 26 ± 4 weeks and seven reported at week 52 ± 4 weeks.	[redacted]
Doses	[redacted]	Drug dosages analyzed as separate nodes	[redacted]

A1C = glycated hemoglobin; DIC = deviance information criterion; FE = fixed effect; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide -1; MCMC = Markov chain Monte Carlo; MET = metformin; NMA = network meta-analysis; NICE DSU = National Institute for Health and Care Excellence Decision Support Unit; OAD = oral antidiabetic drug; OR = odds ratio; RE = random effects; RR = relative risk; SBP = systolic blood pressure; SD = standard deviation; SEM = semaglutide; SGLT2 = sodium-glucose cotransporter-2; SU = sulfonylurea.

Source: Manufacturer-submitted NMAs.[44-46,50]

[redacted]

[redacted]

[redacted]

Figure 2: Evidence Network for Change in A1C and Weight at 24 Weeks for NMA of Semaglutide Versus Other GLP-1 Agonists

FIGURE CONTAINED CONFIDENTIAL INFORMATION AND WAS REDACTED AT THE REQUEST OF THE MANUFACTURER

[redacted]

Figure 3: Evidence Network for Change in A1C and Weight at 52 Weeks for NMA of Semaglutide Versus Other GLP-1 Agonists

FIGURE CONTAINED CONFIDENTIAL INFORMATION AND WAS REDACTED AT THE REQUEST OF THE MANUFACTURER

[redacted]

Table 59: NMA Results for Change From Baseline in A1C for GLP-1 Agonists

Comparator	Mean Difference in CFB in A1C (95% CrI) at 24 Weeks (FE)		Mean Difference in CFB in A1C (95% CrI) at 52 Weeks (FE)	
	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator
[redacted]				

[redacted]

Table 60: NMA Results for Change from Baseline in Weight (kg) for GLP-1 Agonists

Comparator	Mean Difference in CFB in Weight (95% CrI) at 24 Weeks (FE)		Mean Difference in CFB in Weight (95% CrI) at 52 Weeks (FE)	
	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator
[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	

[redacted]

[redacted]

[redacted]

[redacted]

Results of Indirect Treatment Comparison for Semaglutide Versus SGLT2 Inhibitors as Add-On to Metformin

Objective

The objective of this indirect treatment comparison (ITC) was to assess the relative efficacy and safety of once-weekly semaglutide compared with sodium-glucose cotransporter-2 (SGLT2) inhibitors for the treatment of adults with type 2 diabetes who were inadequately controlled with metformin.

Summary of Included Studies

A total of 23 trials were identified from the systematic review and of these, 15 were excluded for populations inadequately controlled on basal insulin or on OADs other than metformin monotherapy. Thus, eight randomized controlled trials (RCTs) were included in the NMA, including SUSTAIN-2 and SUSTAIN-7. Seven RCTs were double-blind and one was open label. The duration of follow-up ranged from 24 weeks to 104 weeks.

The patients enrolled in the included studies had a mean age ranging from 53.6 years to 60.7 years. The proportion of females ranged from 43% to 53% and most were white (53% to 100%). The mean disease duration was 5.8 years to 7.5 years, baseline A1C was 7.2% to 8.3%, and BMI was 28.7 kg/m^2 to 33.7 kg/m^2.

Six trials were rated as low risk of bias. One trial (SUSTAIN-7) was rated as high risk of bias for allocation concealment and blinding (open-label study) and other sources of bias (Critical Appraisal section of main report). One empagliflozin study was rated as high risk of bias due to selective outcome reporting and one other had unclear allocation concealment.

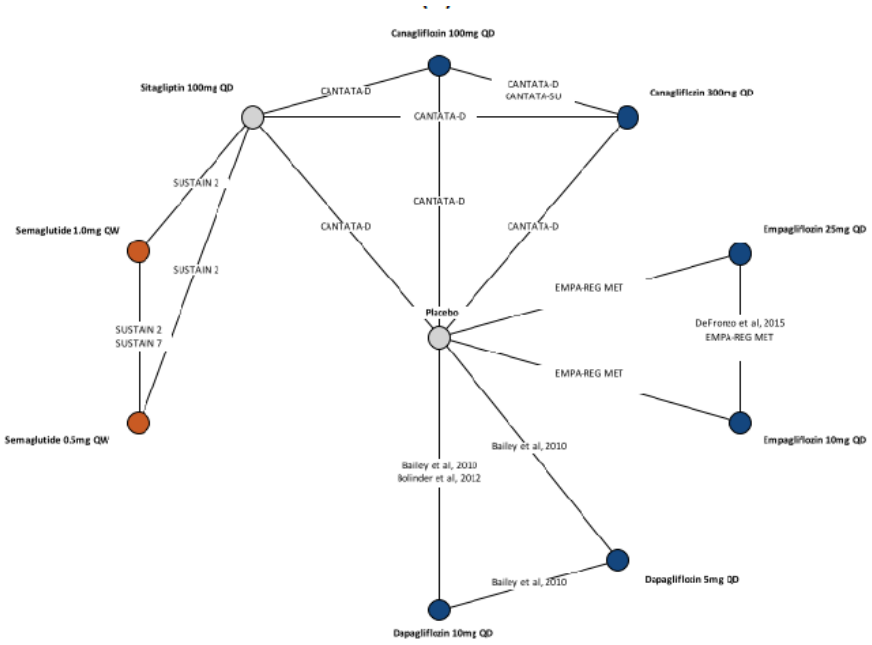
Placebo and sitagliptin were used as secondary comparators to connect the network. Based on the feasibility assessment, the time points for analysis selected were 26 weeks and 52 weeks plus or minus 4 weeks. The efficacy outcomes analyzed included the change from baseline in A1C, weight, fasting plasma glucose, and systolic blood pressure (SBP) (26 weeks and 52 weeks), as well as the proportion of patients with A1C less than 7% (26 weeks). Analysis of the proportion of patients with A1C less than 7% (52 weeks) or less than 6.5%, weight loss greater than 5% or greater than 10% was not possible due to disconnected network or the lack of data from semaglutide trials. Discontinuation due to adverse events (AEs) and diarrhea were the only safety outcomes that could be analyzed. Other safety outcome could not be analyzed due to disconnected network, or no data from semaglutide or any trial.

Evidence Network

Figure 4 and Figure 5 show the evidence network for the change from baseline in A1C at 26 weeks and 52 weeks for semaglutide versus SGLT2 inhibitors. Eight trials were included in the NMA of A1C at 26 weeks and three trials were included at 52 weeks.

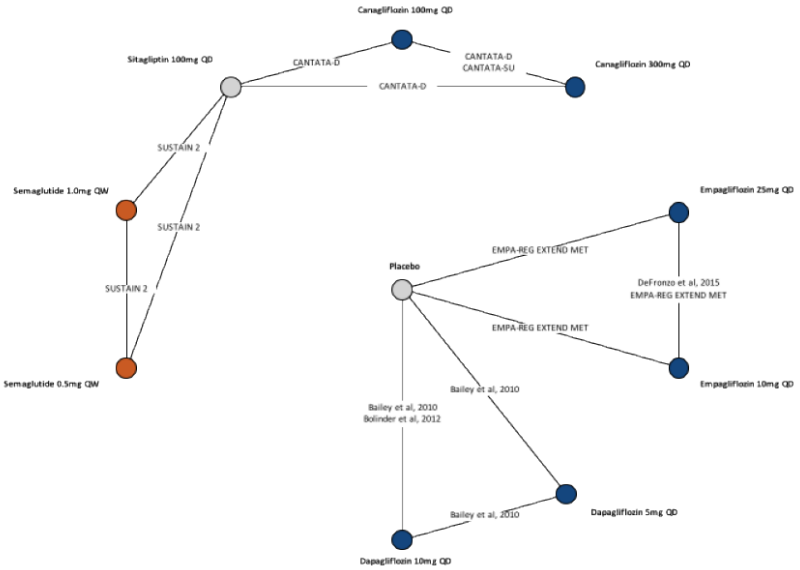
Of note: the control group from SUSTAIN-7 was excluded from the analysis at 26 weeks, thus data from the two semaglutide groups in this study were linked to the network via SUSTAIN-2. No explanation was provided for the exclusion of the dulaglutide groups in SUSTAIN-7, although it may be due to the narrow scope of the NMA.

Figure 4: Evidence Network for Change in A1C at 26 Weeks for NMA of Semaglutide Versus SGLT2 Inhibitors



A1C = glycated hemoglobin; NMA = network meta-analysis; QD = once daily; QW = once weekly; SEM = semaglutide; SGLT2 = sodium-glucose cotransporter-2.
Source: Manufacturer-submitted NMA of SEM versus SGLT2 inhibitors as second-line therapy.[45]

Figure 5: Evidence Network for Change in A1C at 52 Weeks for NMA of Semaglutide Versus SGLT2 Inhibitors



A1C = glycated hemoglobin; NMA = network meta-analysis; QD = once daily; QW = once weekly; SEM = semaglutide; SGLT2 = sodium-glucose cotransporter-2.
Source: Manufacturer-submitted NMA of SEM versus SGLT2 inhibitors as second-line therapy.[45]

Change From Baseline in A1C

Semaglutide 0.5 mg and 1 mg were associated with statistically significant reductions in A1C compared with placebo, canagliflozin, dapagliflozin, and empagliflozin at 26 weeks, and compared with canagliflozin at 52 weeks. The mean difference estimates ranged from –0.5% to –1.1% versus active comparators and –1.2% to –1.4% versus placebo (Table 61). Both networks were sparse.

Table 61: NMA Results for Change from Baseline in A1C for SGLT2 Inhibitors

Comparator	Mean Difference in CFB in A1C (95% CrI) at 26 Weeks (FE)		Mean Difference in CFB in A1C (95% CrI) at 52 Weeks (FE)	
	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator
Number of studies (patients)	8 (5,546)		[redacted]	
Semaglutide 0.5 mg q.w.	NA	**–0.20 (–0.30, –0.10)**	[redacted]	[redacted]
Semaglutide 1.0 mg q.w.	**0.20 (0.10, 0.30)**	NA	[redacted]	[redacted]
Canagliflozin 100 mg q.d.	**–0.60 (–0.77, –0.44)**	**–0.80 (–0.96, –0.64)**	[redacted]	[redacted]
Canagliflozin 300 mg q.d.	**–0.46 (–0.63, –0.30)**	**–0.66 (–0.82, –0.50)**	[redacted]	[redacted]
Dapagliflozin 5mg q.d.	**–0.91 (–1.17, –0.65)**	**–1.11 (–1.37, –0.85)**	–	–
Dapagliflozin 10 mg q.d.	**–0.86 (–1.08, –0.63)**	**–1.05 (–1.27, –0.84)**	–	–
Empagliflozin 10 mg q.d.	**–0.63 (–0.86, –0.40)**	**–0.83 (–1.06, –0.60)**	–	–
Empagliflozin 25 mg q.d.	**–0.61 (–0.84, –0.37)**	**–0.80 (–1.04, –0.58)**	–	–
Placebo	**–1.23 (–1.42, –1.03)**	**–1.42 (–1.61, –1.24)**	–	–
Comments	Model fit for FE and RE models was similar (DIC difference < 3). FE selected due to sparse networks. No evidence of inconsistency. Adjusting for covariates (sex, A1C, prior OADs) via meta-regression was reported to have minimal effects on results at 26 weeks and 52 weeks, however the results were not provided but model fit parameters appear to be similar. Results of sensitivity analyses excluding trials with ≥ 40% Asian population showed similar results to the .			

A1C = glycated hemoglobin; CFB = change from baseline; CrI = credible interval; DIC = deviance information criterion; FE = fixed effects; NA = not applicable; NMA = network meta-analysis; OAD = oral antidiabetic drug; q.d. = once daily; q.w. = once weekly; RE = random effects; SEM = semaglutide; SGLT2 = sodium-glucose cotransporter-2.

Note: Comparisons where the 95% CrI excludes the null are shown in bold.

Source: Manufacturer-submitted NMA of SEM versus SGLT2 inhibitors as second-line therapy.[45,50]

Change from Baseline in Weight

Semaglutide 1 mg was associated with statistically significant reductions in weight compared with placebo, canagliflozin, dapagliflozin, and empagliflozin at 26 weeks and compared with canagliflozin at 52 weeks. Mean differences (MDs) ranged from –1.6 kg to –2.5 kg versus active comparators and –4.1 kg versus placebo. Semaglutide 0.5 mg showed a greater reduction in weight than low dose empagliflozin at 26 weeks (MD –1.2 kg) and placebo (MD –2.8 kg) only. Both networks were sparse and included data from seven trials for the 26-week analysis, and three trials in the 52-week NMA.

Table 62: NMA Results for Change from Baseline in Weight (kg) for SGLT2 Inhibitors

Comparator	Mean Difference in CFB in Weight (95% CrI) at 26 Weeks (FE)		Mean Difference in CFB in Weight (95% CrI) at 52 Weeks (FE)	
	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator
Number of studies (patients)	7 (4,587)		[redacted]	
Semaglutide 0.5 mg q.w.	NA	**–1.34 (–1.77, –0.90)**	[redacted]	[redacted]
Semaglutide 1.0 mg q.w.	**1.34 (0.90, 1.77)**	NA	[redacted]	[redacted]
Canagliflozin 100 mg q.d.	–0.55 (–1.31, 0.20)	**–1.89 (–2.67, –1.13)**	[redacted]	[redacted]
Canagliflozin 300 mg q.d.	–0.25 (–0.99, 0.51)	**–1.59 (–2.35, –0.84)**	[redacted]	[redacted]
Dapagliflozin 5mg q.d.	–0.62 (–1.62, 0.35)	**–1.97 (–2.96, –0.98)**	--	--
Dapagliflozin 10 mg q.d.	–0.71 (–1.62, 0.19)	**–2.05 (–2.97, –1.13)**	--	--
Empagliflozin 10 mg q.d.	**–1.15 (–2.04, –0.26)**	**–2.49 (–3.39, –1.59)**	--	--
Empagliflozin 25 mg q.d.	–0.71 (–1.59, 0.18)	**–2.05 (–2.94, –1.15)**	--	--
Placebo	**–2.75 (–3.52, –2.00)**	**–4.09 (–4.85, –3.34)**	--	--
	Model fit for FE and RE models was similar (DIC difference < 3). FE selected due to sparse networks. No evidence of inconsistency. Adjusting for covariates (sex, A1C, weight, disease duration) via meta-regression, and sensitivity analysis based on ethnicity showed similar model fit. Results of sensitivity analyses excluding trials with ≥ 40% Asian population showed similar results to the base-case analysis.			

A1C = glycated hemoglobin; CFB = change from baseline; CrI = credible interval; DIC = deviance information criterion; FE = fixed effects; NA = not applicable; NMA = network meta-analysis; q.d. = once daily; q.w. = once weekly; RE = random effect; SEM = semaglutide; SGLT2 = sodium-glucose cotransporter-2.

Note: Comparisons where the 95% CrI excludes the null are shown in bold.

Source: Manufacturer-submitted NMA of SEM versus SGLT2 inhibitors as second-line therapy.[45,50]

Safety Outcomes

At 52 weeks, semaglutide was associated with increased odds of discontinuation due to AEs relative to canagliflozin and placebo, however the 95% credible interval (CrI) was wide, suggesting there is uncertainty in the results. Regarding the occurrence of diarrhea, the 95% CrI included the null for semaglutide versus canagliflozin and placebo (Table 63). The analyses were based on data from three trials.

Table 63: NMA Results for Adverse Events for Semaglutide Versus SGLT2 Inhibitors

	Discontinuation Due to Adverse Events OR (95% CrI) at 52 Weeks		Diarrhea OR (95% CrI) at 52 Weeks	
	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator
Number of trials (patients)	3 (3,296)		[redacted]	
Once-weekly semaglutide 0.5 mg	NA	1.20 (0.73, 1.96)	[redacted]	[redacted]
Once-weekly semaglutide 1.0 mg	0.83 (0.51, 1.36)	NA	[redacted]	[redacted]
Canagliflozin 100 mg once daily	**3.07 (1.19, 8.05)**	**3.68 (1.43, 9.53)**	[redacted]	[redacted]
Canagliflozin 300 mg once daily	**3.09 (1.20, 8.08)**	**3.72 (1.46, 9.71)**	[redacted]	[redacted]
Placebo	2.98 (0.98, 9.81)	**3.59 (1.21, 11.81)**	[redacted]	[redacted]
Comments	Model fit for FE and RE models was similar (DIC difference < 3); FE selected due to sparse networks; No evidence of inconsistency; Adjusting for covariates (sex, A1C, weight, disease duration) via meta-regression, and sensitivity analysis based on ethnicity and longest follow-up showed similar model fit. No results were reported for the sensitivity analyses that used the longest follow-up data available, or for meta-regression analyses.			

A1C = glycated hemoglobin; CrI = credible interval; DIC = deviance information criterion; FE = fixed effects; NA = not applicable; NMA = network meta-analysis; OR = odds ratio; RE = random effect; SEM = semaglutide; SGLT2 = sodium-glucose cotransporter-2.

Note: Comparisons where the 95% CrI excludes the null are shown in bold.

Source: Manufacturer-submitted NMA of SEM versus SGLT2 inhibitors as second-line therapy.[45,50]

[redacted]

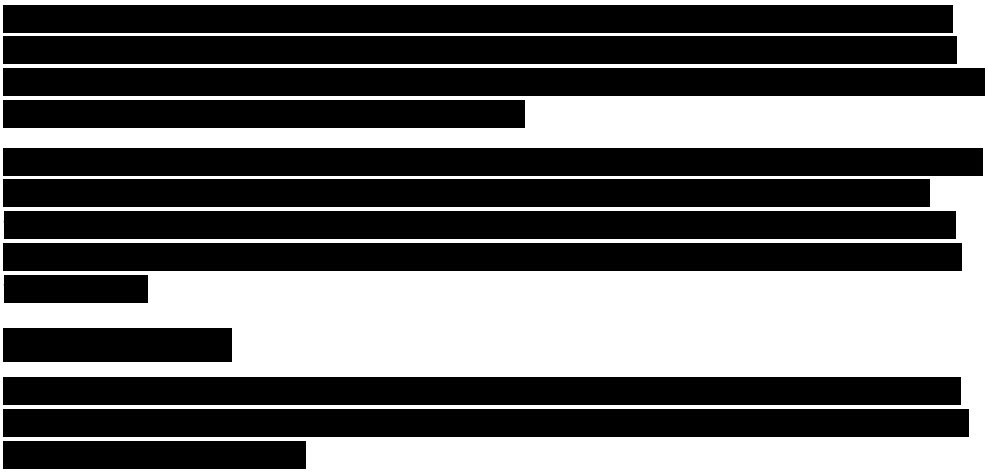


Figure 6: Evidence Network Change in A1C at 26 Weeks for NMA of Semaglutide Versus Sulfonylureas

FIGURE CONTAINED CONFIDENTIAL INFORMATION AND WAS REDACTED AT THE REQUEST OF THE MANUFACTURER

Figure 7: Evidence Network for Change in A1C at 52 Weeks for NMA of Semaglutide Versus Sulfonylureas

FIGURE CONTAINED CONFIDENTIAL INFORMATION AND WAS REDACTED AT THE REQUEST OF THE MANUFACTURER

Table 64: NMA Results for Change in A1C for SEM Versus Sulfonylureas

	Mean Difference in CFB in A1C (95% CrI) at 26 Weeks (FE)		Mean Difference in CFB in A1C (95% CrI) at 52 Weeks (FE)	
	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator
[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Mean Difference in CFB in A1C (95% CrI) at 26 Weeks (FE)		Mean Difference in CFB in A1C (95% CrI) at 52 Weeks (FE)	
	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	
	[redacted]			

[redacted]

Table 65: NMA Results for Change from Baseline in Weight (kg) for Sulfonylureas

	Mean Difference in CFB in Weight (95% CrI) at 26 Weeks (FE)		Mean Difference in CFB in Weight (95% CrI) at 52 Weeks (FE)	
	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator	SEM 0.5 mg vs. Comparator	SEM 1 mg vs. Comparator
[redacted]				

[redacted]

Critical Appraisal

The manufacturer submitted three NMAs that evaluated semaglutide as add-on therapy to metformin, with comparisons made to different drug classes: other glucagon-like peptide -1 (GLP-1) agonists,[44] SGLT2 inhibitors,[45] and sulfonylureas.[46] These data were used to inform the pharmacoeconomic model which assessed the cost-effectiveness of semaglutide relative to drugs from each of these drug classes. The manufacturer stated that the separate

drug class approach was taken to limit the introduction of inconsistency to the network, as larger networks may introduce further heterogeneity and potentially bias estimates.[64] They also stated that the National Institute for Health and Care Excellence (NICE) Decision Support Unit Guidelines caution researchers against extending the network beyond the decision-making comparator set, as there is the potential to introduce treatment-effect modifiers by including additional trials.[64] While this caution is warranted, it does not provide adequate justification for the fragmented approach taken in this case. First, the GLP-1 agonists, SGLT2 inhibitors, and sulfonylurea class of drugs were all part of the decision-making comparator set, as comparative data for all these drugs was needed to inform the pharmacoeconomic model. Secondly, the manufacturer's rationale that separate networks were necessary to avoid heterogeneity is not adequately supported. Each ITC was designed to identify trials that enrolled patients who were similar to those enrolled in the SUSTAIN studies, and for each ITC the authors concluded that the included studies were sufficiently homogeneous to allow for NMA. Thus it is logical that the three NMAs could have been combined into one comprehensive network that included all comparators of interest. This is the approach that is endorsed by NICE[65] and the International Society for Pharmacoeconomics and Outcomes Research, Inc. (ISPOR),[66] and numerous ITCs that include data from different drug classes have been published for patients with type 2 diabetes.

There could be a rationale for limiting the NMA to a within class comparison of GLP-1 agonists if the manufacturer was advocating for semaglutide as the best-in-class agent. However the manufacturer has chosen to designate semaglutide as a preferred drug over other classes of drugs, thus a comprehensive assessment of comparative efficacy and safety was warranted. The drug class approach restricted the evidence for each ITC, thereby excluding potentially relevant studies or treatment groups. For example the comparison of GLP-1 agonists excluded five exenatide trials and some treatment groups from multi-arm trials as they did not provide a secondary connection to other GLP-1 agonists within the model. The NMA of sulfonylureas excluded nine trials that were not bridging studies, and the NMA of SGLT2 inhibitors excluded the control group of the SUSTAIN-7 study. The decisions regarding which secondary comparators to include varied across networks and appear to have been made post hoc. Most of the evidence networks were sparse with some treatment effects informed by few studies, thus the parameter estimates may be more sensitive to the inclusion or exclusion of individual trials. In contrast, a comprehensive network that included additional evidence might potentially generate more robust estimates.[67]

Although all three ITCs were based on a systematic review of the literature, the study selection process had some potential limitations. After trials were identified as meeting the systemic review inclusion criteria, they underwent another round of screening that was specific to each ITC. As mentioned above, the limited scope of the ITC restricted the evidence base. After the feasibility assessment, additional trials were excluded for other reasons, such as patient populations that may have characteristics that differ from other trials. This included trials in Asian patients, the elderly, postmenopausal women, those with cardiovascular disease, or young obese patients. Two of the NMAs conducted sensitivity analyses that included or excluded these studies,[44,45] whereas the NMA of sulfonylureas[46] excluded these trials with no exploration of the potential impact of these decisions. Although the ITCs reported some information on the patient characteristics of the included studies, none conducted standard pairwise meta-analysis to explore possible statistical heterogeneity. Two of the NMAs tested for inconsistency of direct and indirect evidence;[44,45] however networks were sparse and many of the closed loops were from multi-arm studies,

where inconsistency is not possible. In addition, many of trials included in the three separate NMA's, there was overall moderate to high risk of bias, particularly on key trial aspects around randomization, allocation concealment, and blinding.

All three NMAs used similar Bayesian models that appear to follow acceptable methods (although reporting of number of iterations for burn-in and parameter estimates was unclear for two NMAs).[44,46] Both fixed and random effect models were analyzed and it appears that fixed effects models were selected appropriately, based on deviance information criterion (DIC) values and considering the sparse networks. Two of the NMAs conducted meta-regression analyses to explore potential effect modifiers; however the modifiers adjusted for were limited, only model fit parameters were reported, and given the sparse networks it is unclear if these analyses were appropriate.[44,45]

Within each class, the drugs and dosages included were relevant to the Canadian context. Decisions on which outcomes would be analyzed and at which time points were made after examining the trials and the reasons for excluding some outcomes was not reported in two of the studies.[44,46] Although 52-week data were reported, these networks were sparse, thus there may be greater uncertainty in the findings. The NMA of the SGLT2 inhibitors was the only ITC to report safety outcomes. Although A1C and weight are relevant outcomes, these are surrogates, and the manufacturer did not submit an ITC of cardiovascular safety studies. Different doses of drugs were analyzed as separate nodes in two of the NMAs,[44,45] and in the NMA of GLP-1 agonists the lixisenatide 20 mcg dosage was split into four nodes based on the titration schedule and timing of administration (a.m. or p.m. dosing). The rationale for splitting the lixisenatide nodes was not clear and it is not known what impact this may have had on the results. In addition, the manufacturer did not evaluate the comparative efficacy of semaglutide versus the dipeptidyl pepidase-4 (DPP-4) inhibitor class, which holds a significant market share in Canada and are more relevant alternatives to the GLP-1 agonists, as the DPP-4 inhibitors are second-line for many patients outside of the SGLT2 inhibitors.

Conclusion

The manufacturer submitted three NMAs that evaluated semaglutide as add-on therapy to metformin, with comparisons made to different drug classes: other GLP-1 agonists,[44] SGLT2 inhibitors,[45] and sulfonylureas.[46] Bayesian MCMC methods were used to analyze the change from baseline in glycated hemoglobin (A1C) and weight at 24 weeks or 26 weeks, and 52 weeks (plus or minus four weeks) for all three NMAs. Discontinuations due to AEs and diarrhea were also analyzed in the NMA comparing semaglutide to the SGLT2 inhibitors. Although the NMAs suggest a reduction in A1C and weight with semaglutide versus the comparators, these data should be interpreted with caution. The use of separate networks for each drug class, rather than one connected network that included all drugs relevant to the decision-making comparator set, was not consistent with guidance on the conduct of NMAs.[67] The justification provided by the manufacturer for this fragmented approach, namely to minimize heterogeneity, was not adequately supported by the data provided. The restricted scope of the ITCs limited the evidence included in each analysis, thus the networks were generally sparse, with most treatment comparisons informed by one or two trials. Moreover, the ITC did not evaluate the comparative efficacy of semaglutide versus the DPP-4 inhibitor class, which is a commonly used second-line agent. It is unclear what impact there would have been on the findings had a comprehensive evidence base been included in the ITC. No conclusions can be drawn with regards to comparative safety based on the data available, and the applicability of the efficacy findings is limited.

Appendix 6: Summary of Indirect Comparisons of Second- or Third-Line Therapy

Introduction

The manufacturer submitted two network meta-analyses (NMAs) that compared semaglutide to other glucagon-like peptide-1 (GLP-1) agonists or to sodium-glucose cotransporter-2 (SGLT2) inhibitors in patients inadequately controlled on one or two oral antidiabetic drugs (OAD).[47,48] Data from these NMAs were used to inform the pharmacoeconomic analysis. A brief summary of the methods used and a critical appraisal of these NMAs is provided in this appendix; however due to fundamental limitations of the NMAs, the results of these analyses have not been reported in this appendix.

Table 66: Inclusion Criteria for Manufacturer-Submitted NMA of Second- or Third-Line Therapy

Criteria	SEM Versus GLP-1 Analogues as Add-On to 1 to 2 OADs	SEM Versus SGLT2 Inhibitors as Add-On to 1 to 2 OADs
Population	Adult patients with diagnosed T2DM either: • Inadequately controlled with metformin (≥ 90% of study population) • Inadequately controlled with 1 to 2 OADs (< 100% of study population uncontrolled on 2 OADs)	[redacted]
Intervention	Once-weekly semaglutide 0.5 mg Once-weekly semaglutide 1.0 mg	[redacted]
Comparator	All EU and US licensed GLP-1 analogues: • Exenatide ER and two times daily • Liraglutide • Lixisenatide • Dulaglutide • Albiglutide (see Table 57 for dosing)	[redacted]
Outcome	Change from baseline in: • A1C • fasting plasma glucose • postprandial glucose • body weight • BMI • SBP Proportion of patients achieving: • < 7% A1C • ≤ 6.5% A1C • ≥ 5% weight loss • ≥ 10% weight loss • composite end point (< 7% A1C, no weight gain, and no hypoglycemia)	Incidence of: • discontinuations due to adverse events • nausea • vomiting • diarrhea • pancreatitis • overall hypoglycemia • severe hypoglycemia • non-severe hypoglycemia • nocturnal hypoglycemia
Study design	RCTs with at least a 20-week duration[b]	[redacted]
Publication characteristics	English language Published from 1994 to August 16, 2017 Conferences up to August 16, 2017	[redacted]
Exclusions	Trials where > 90% of patients were inadequately controlled on MET monotherapy, or 100% of patients were inadequately controlled with two OADs, or patients were inadequately controlled on one OAD other than MET. Excluded trials that were restricted to those with CV disease or high proportion of CV risk factors.	[redacted]

A1C = glycated hemoglobin; BMI = body mass index; CV = cardiovascular; DBP = diastolic blood pressure; ER = extended release; GLP-1 = glucagon-like peptide-1; MET = metformin; OAD = oral antidiabetic drug; RCT = randomized controlled trial; SBP = systolic blood pressure; SEM = semaglutide; SGLT2 = sodium-glucose cotransporter-2; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.

[a] Not available in Canada.

[b] Crossover studies were included if data were reported prior to crossover and after at least 20 weeks of therapy.

Source: Manufacturer-submitted NMAs.[47,48,53]

ITC for Semaglutide Versus Other GLP-1 Agonists as Add-On to One or Two OADs

NMA Methods

Bayesian models were used to conduct the NMA (WinBUGS software). Continuous outcomes were analyzed using a normal likelihood, identity link, shared parameter model to account for arm-level and trial-level data reported within trials. Dichotomous outcomes were analyzed using a binomial likelihood assuming a normal distribution and logit link. Data were reported as odds ratios or mean treatment differences and 95% credible intervals, and treatment effects were assumed to be statistically significant if the 95% credible intervals excluded the null.

Fixed and random effects models were run and the model was selected based on the deviance information criterion (DIC) (assuming a 3- to 5-point difference was important) and average posterior residual deviance. The models use uninformative prior distributions. Three Markov chain Monte Carlo methods were used, and convergence was assessed by analyzing history and density plots and Brooks-Gelman-Rubin diagnostic plots. Autocorrelation plots were assessed to detect autocorrelation in the chains. Parameter estimates were taken from the 20,000 iterations following the assessment of autocorrelation. Inconsistency between direct and indirect evidence was assessed using the Bucher method.

Exploratory meta-regression analyses were conducted for the change from baseline in glycated hemoglobin (A1C), systolic blood pressure (SBP), weight, and fasting plasma glucose (FPG) outcomes, however limited details on these analyses were provided. A sensitivity analysis was also conducted that included eight trials with patient populations deemed to be outliers (see below). The report does not describe any analyses to explore the potential impact of including studies of second-line therapy with studies of mixed populations of second-line and third-line treatment. There was no mention of conducting a standard meta-analysis to explore potential heterogeneity between studies.

The most commonly reported follow-up time-point was selected for the analyses. Thus 24 weeks' follow-up plus or minus four weeks was chosen as all included studies reported at least one outcome within this window.

Evidence Network

For the indirect comparison of GLP-1 agonists, a total of 75 studies met the inclusion criteria for the systematic review, of which 40 were considered for the analysis (Table 67). Another six studies were excluded as they did not include common secondary comparators that connected the network, thus 34 trials were included in the NMA. Of these, eight trials were considered potential outliers due to study design or patient characteristics and were excluded from the base-case analysis. This included six trials in Asian patients, one trial in a treatment-naive population, and one trial that enrolled young obese patients. These six trials were included in a sensitivity analysis.

The risk of bias related to randomization or allocation concealment was rated as unclear or high for 40% and 60% of studies respectively. More than 40% of trials were rated as high risk of bias related to blinding, and 20% had high risk of bias related to drop-outs.

Table 67: Study Disposition for Indirect Comparisons

	SEM Versus GLP-1 Analogues as Add-On to 1 to 2 OADs	SEM Versus SGLT2 Inhibitors as Add-On to 1 to 2 OADs
Number of trials included in the systematic review	75	[redacted]
Number of trials excluded from the NMA	35	[redacted]
Reason for exclusion		
100% patients inadequately controlled on 2 OADs	8	
< 90% of patients inadequately controlled on MET	6	
Patients with CV risk factors or CV disease	4	
Patients inadequately controlled on insulin	12	[redacted]
Study did not clearly report titration of GLP-1 agonist	2	
No placebo group	1	
Patients received prior MET + SIT then EXE + 1 OAD or EXE + SIT + MET	1	
Patients inadequately controlled on 1 to 2 OADs then MET + randomized treatment	1	
Number of trials relevant to the NMA	40	[redacted]
Number of trials included in NMA feasibility assessment	34[a]	[redacted]
Number of trials included in the base-case analysis	26[b]	[redacted]

CV = cardiovascular; EXE = exenatide; GLP-1 = glucagon-like peptide -1; MET = metformin; NMA = network meta-analysis; OAD = oral antidiabetic drug; SEM = semaglutide; SGLT2 = sodium-glucose cotransporter-2; SIT = sitagliptin.

[a] Placebo, sitagliptin, and insulin glargine were secondary comparators that provided connections between the primary comparators of interest. Lixisenatide plus insulin glargine was also retained as a secondary comparator. Studies or treatment arms for other secondary comparators were removed from the analysis (i.e., pioglitazone, glimepiride, glibenclamide, and biphasic insulin aspart) if they were not common comparators and did not connect with any other treatment nodes.

[b] Eight trials were considered potential outliers due study design or patient characteristics and were excluded from the base-case analysis. This included six trials in Asian patients, one trial in a treatment-naive population, and one trial that enrolled young obese patients. All trials were included in a sensitivity analysis.

Source: Manufacturer-submitted NMAs.[47,48,53]

Of the 34 included studies, 15 were designed as superiority trials and seven as non-inferiority studies. Six trials were non-inferiority and superiority trials and in another six, the design was not reported. Sixteen trials were double-blind and 18 were open label. The mean age across trials ranged from 43 years to 58 years, and 29% to 60% of patients were female. Six trials were conducted exclusively in Asian patients and one was exclusively in white patients. Among other trials, the proportion of patients who were white ranged from 34% to 92%. The mean BMI was 26 kg/m^2 to 36.8 kg/m^2 and disease duration ranged from 0.6 years to 11.3 years (after excluding the trial in treatment-naive patients the duration ranged from 4.4 years to 11.3 years). At baseline, the mean A1C ranged from 7.9% to 8.7%.

The treatment history of patients enrolled in the included studies is described in Table 68. Fourteen trials (41%) enrolled patients who were inadequately controlled on metformin monotherapy. One trial (3%) enrolled treatment-naive patients who were administered metformin for eight months prior to randomization. The other 19 trials (56%) enrolled a mixed population that had received metformin with or without sulfonylureas, thiazolidinediones, insulin, or other combinations of OADs. Among the mixed population trials, the proportion of patients on monotherapy ranged from 75% to 99% in seven studies, from 50% to 74% in six studies, from 25% to 49% in five studies, and in two trials the proportion was unspecified. With the exclusion of the eight trials deemed to be outliers (six studies in Asian patients, one in treatment-naive patients who underwent eight months of MET monotherapy prior to randomization, and one trial in young obese patients), the authors concluded that the patient and study characteristics were sufficiently similar to conduct the NMA.

Table 68: Prior Treatment Experience for Studies Included in NMAs

	SEM Versus GLP-1 Analogues as Add-On to 1 to 2 OADs	SEM Versus SGLT2 Inhibitors as Add-On to 1 to 2 OADs
Prior treatment experience	**N studies (%)**	**N studies (%)**
Total N (base case)	34 (100)	[redacted]
100% of population inadequately controlled on 1 OAD	14 (41)[a]	[redacted]
Mixed population (prior therapy with 1 or 2 OADs)	19 (56)	[redacted]
Percentage of mixed trial population inadequately controlled on MET monotherapy 75% to 99% 50% to 74% 25% to 49% Unspecified	 7 (21) 6 (18) 5 (15) 2 (6)	[redacted]
100% of population inadequately controlled on 2 OADs	0[c]	[redacted]
Other	1 (3)[e]	[redacted]

GLP-1 = glucagon-like peptide -1; MET = metformin; NMA = network meta-analysis; NR = not reported; OAD = oral antidiabetic drug; SEM = semaglutide; SGLT2 = sodium-glucose cotransporter-2.

[a] All trials on MET monotherapy.

[b] In seven trials (33%), patients were inadequately controlled on MET. Other monotherapies were used in the other two trials.

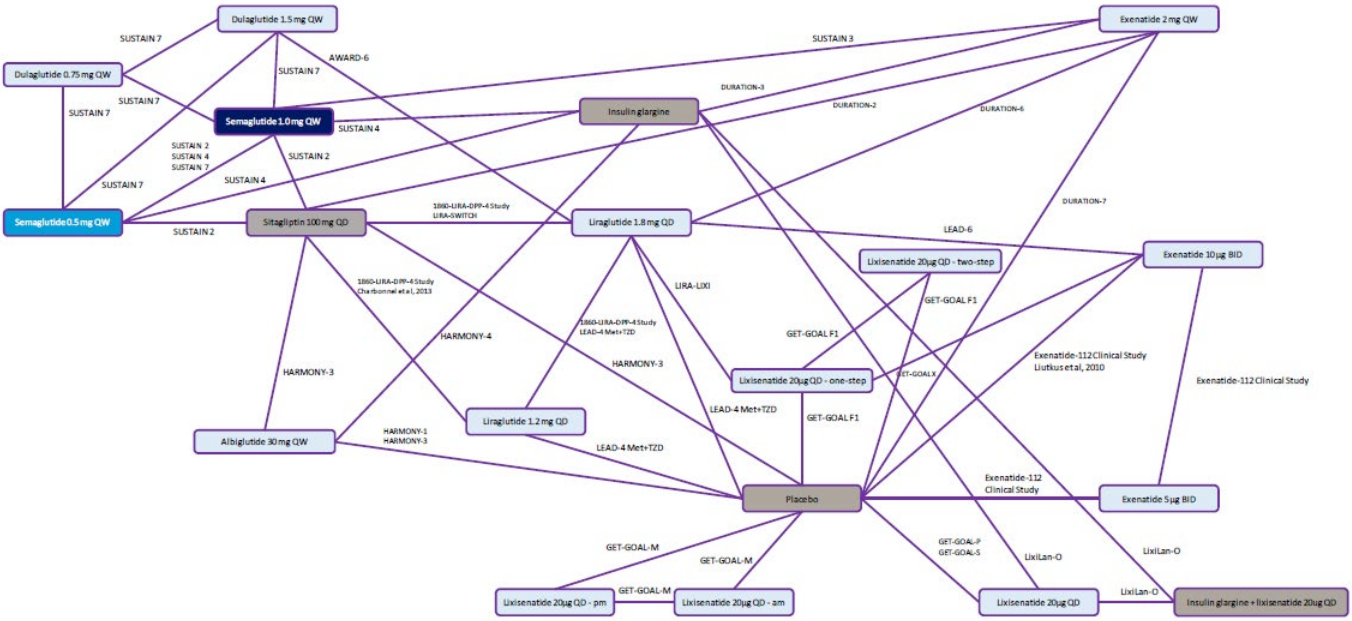
[c] Trials where patients had been inadequately controlled on two OADs were excluded (N = 8).

[d] In four trials patients had received MET plus a sulfonylurea.

[e] One study enrolled patients who were treatment -naive who received MET for eight-month run-in period prior to randomization.

Source: Manufacturer-submitted NMAs.[47,48,53]

Figure 8: Evidence Network for Change in A1C of GLP-1 Agonists as Second- or Third-Line Therapy



Source: Manufacturer-submitted NMA of SEM versus other GLP-1 agonists as add-on to 1 or 2 OADs.[47]

[redacted]

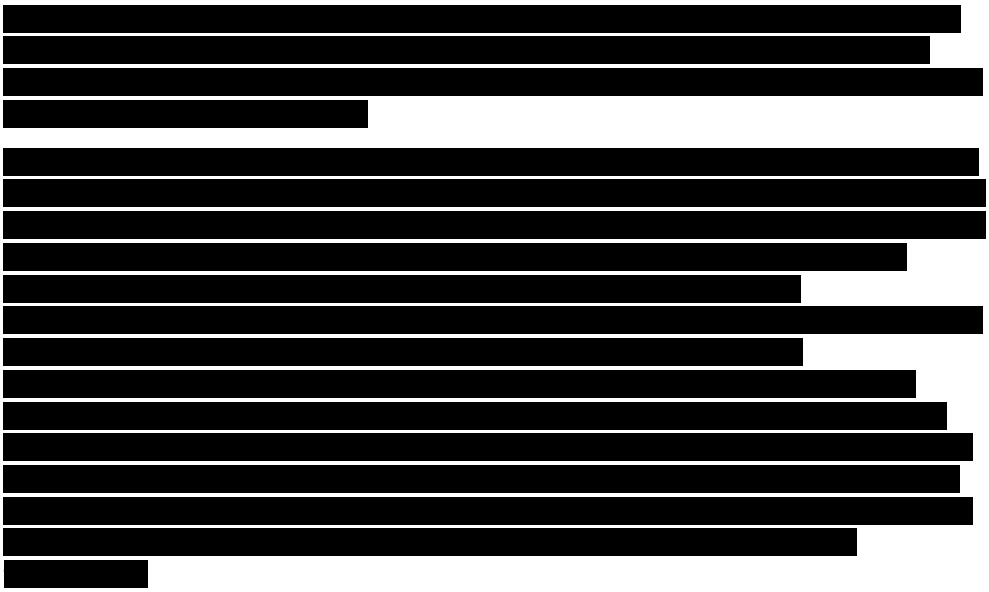


Figure 9: Evidence Network for Change in A1C of SGLT2 Inhibitors as Second- or Third-Line Therapy

FIGURE CONTAINED CONFIDENTIAL INFORMATION AND WAS REDACTED AT THE REQUEST OF THE MANUFACTURER

Critical Appraisal

A key assumption for indirect treatment comparisons (ITCs) is that the patients enrolled are comparable between trials.[66,68] As stated in the documents provided by the manufacturer, "*An imbalance in the distribution of effect modifiers between studies that compare different interventions results in transitivity violation and therefore biased indirect comparisons.*"[48] The selection of studies for the ITCs was driven by the need to match the inclusion criteria of the SUSTAIN trials, rather than patient populations that were clinically homogenous. Input from clinical experts affirm that patients who are inadequately controlled on two prior OADs represent a more advanced diabetes population than those with inadequate glycemic control on one OAD. It is our assertion that the patient and study characteristics of the trials included in the NMAs of second- and third-line therapy were clinically heterogeneous and the manufacturer has not supplied sufficient evidence that pooling these data does not violate the transitivity assumption.

The manufacturer provided the following arguments to support their analysis:

- The baseline patient characteristics of patients in SUSTAIN-2, 3, 4, and 7 do not consistently differ between second- and third-line patients.
- The treatment effects do not consistently vary between patients treated as second- and third-line.
- The NMAs were adjusted for treatment-effect modifiers.[64]

[redacted] In the NMA of the GLP-1 agonists the authors limited heterogeneity by restricting the evidence base, and cite the need to match the population in SUSTAIN-3 and SUSTAIN-4 as justification for excluding eight trials of patients inadequately controlled on two OADs. In addition, another eight trials deemed to be outliers were excluded (Table 67). It is unclear what impact the exclusion of these trials may have had on the findings of the NMAs.

[redacted] The CDR reviewer conducted a meta-analysis comparing semaglutide doses and this showed statistical heterogeneity (I^2 = 72%) for the change from baseline in A1C data for 26 weeks (Figure 10). [redacted] These data suggest heterogeneity in treatment effects may be present within the semaglutide studies. [redacted]

The manufacturer stated that the meta-regression analyses conducted based on the number of prior OADs showed minimal impact on treatment effects, which justified the inclusion of a mixed patient population.[64] First, prior OADs was a covariate in the meta-regression analyses of the SGLT2 inhibitors only. The NMA of GLP-1 agonists ignored this potential effect modifier and there were no meta-regression, subgroup, or sensitivity analyses to examine the potential impact of including this mixed patient population. Second, it is unclear if the categorical variables used in the regression analysis of SGLT2 inhibitors would be adequate to control for disease severity. Meta-regression based on study level data have low power to detect differences and an NMA that included individual patient data may have been a more robust means to identify the effect of potential effect modifiers.

Figure 10: Meta-Analysis of SUSTAIN Trials by Semaglutide Dose

FIGURE CONTAINED CONFIDENTIAL INFORMATION AND WAS REDACTED AT THE REQUEST OF THE MANUFACTURER

CI = confidence interval; IV = inverse variance; SD = standard deviation; SEM = semaglutide.

The manufacturer stated that it was necessary to include trials for mixed populations because it was not possible to create a connected network if studies were restricted to patients inadequately controlled on two OADs.[64] As was noted in Appendix 5, the manufacturer-submitted NMAs were designed as separate networks for each drug class, rather than a single connected network. This is not best practice, as ideally networks should include all relevant comparators.[66,67] Since comparative data for semaglutide versus other GLP-1 agonists and SGLT2 inhibitors was needed to inform the economic analysis, a comprehensive network that included all these drugs and the DPP-4 inhibitors would have been more appropriate. As a result of the fragmented approach, not all relevant evidence was included in the models. Both reports describe excluding studies with secondary comparators that did not connect the primary comparators of interest. [redacted] Had the authors included all relevant comparators, a connected network may have been possible, as others have shown.[59]

An additional limitation is that these ITCs do not address the approved indication as third-line therapy (as add-on to metformin plus sulfonylurea), which is the proposed listing request and was the population modelled in the pharmacoeconomic analysis. It appears that the results of these NMAs were assumed to represent treatment effects as add-on to metformin plus sulfonylureas, with no justification to support this extrapolation. As documented in Table 68, the majority of the data for the NMA of GLP-1 agonists was based on patients previously treated with metformin alone. Eight trials where 100% of the population were inadequately controlled on two OADs were excluded from the analysis. [redacted]

Conclusion

The manufacturer-submitted NMAs in patients inadequately controlled on one or two OADs pooled data from heterogeneous patient populations, which may violate the transitivity assumption. In addition, they provided limited evidence for the approved indication of semaglutide as add-on therapy to metformin plus a sulfonylurea. As a result of these limitations, the validity and utility of the findings are uncertain. No conclusions can be drawn from these ITCs.

Appendix 7: Summary of Indirect Comparison Evaluating Mortality

Introduction

The objective of the indirect comparison by Zheng et al. 2018[52] was to assess the efficacy and safety of sodium-glucose cotransporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1 (GPL-1) agonists in reducing mortality and cardiovascular outcomes in patients with type 2 diabetes.

Methods

The authors conducted a systematic review of the literature based on the inclusion criteria and methods described in Table 69. A search was conducted for English language randomized controlled trials (RCTs) (greater than and equal to 12 weeks duration) in patients with type 2 diabetes that compared SGLT2 inhibitors, DPP-4 inhibitors, and GPL-1 agonists to each other or to placebo or no-treatment control groups. The primary outcome of interest was all-cause mortality. Secondary outcomes included cardiovascular mortality, myocardial infarction, stroke, and heart failure.

For the indirect comparison, both fixed and random Bayesian hierarchical models (GeMTC package on R) were run, with the model selected based on lowest deviance information criterion (DIC) value. The results were reported as hazard ratios (HR) and 95% credible interval (CrI). For studies that reported data as event counts only, the differences in follow-up duration between studies were incorporated using the trial patient-years follow-up to estimate HRs using the Poisson likelihood and log link. Non-informative priors were used for all parameters. Markov chain Monte Carlo methods were used with a 5,000 iteration burn-in and 100,000 iterations for parameter estimation based on four chains. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic, using a cut-off of 1.05.

Transitivity was assessed by qualitatively examining the clinical similarity of the trial populations. Network consistency was assessed by a node splitting analysis and by calculating the ratio of direct and indirect treatment effects within each comparison with their 95% CrI. The I^2 statistic was used to evaluate between-study heterogeneity (less than and equal to 0.25 defined as low heterogeneity). Studies with no events in any treatment group were excluded from the network as these trials do not contribute to the effect estimates.

The primary analysis pooled drugs within drug class and estimated the differences between classes. A sensitivity analysis was conducted for all-cause mortality by individual drug, and one that included only cardiovascular outcome trials. Sensitivity analyses were also conducted based on trial duration (excluded trials less than 12 months), population (excluded post-acute coronary syndrome or low cardiovascular risk trials), and risk of bias (included only low-risk studies, or excluded open-label trials). A frequentist random effects network meta-analysis (NMA) was also performed (NetMeta package in R), which reported results are relative risks with 95% confidence interval (CI). Frequentist pairwise meta-analysis was conducted for some adverse events.

The analysis was limited to market-approved doses, and data were pooled for all doses of a drug.

Table 69: Inclusion Criteria and Methods for Zheng 2018

Criteria	Zheng 2018
Population	Patients with type 2 diabetes
Intervention	SGLT2 inhibitors GLP-1 agonists DPP-4 inhibitors At market-approved doses
Comparator	One of the treatments above or control (placebo or no treatment)
Outcome	Primary: All-cause mortality Secondary: Cardiovascular mortality, heart failure events, myocardial infarction (all and non-fatal), unstable angina, stroke (all and non-fatal) Safety: Adverse events (any, serious, leading to study withdrawal) and hypoglycemia (minor and major), lower limb amputation, urinary tract infection, genital infection, pancreatitis, and retinopathy.
Study design	RCTs of at least 12 weeks in duration
Publication characteristics	English
Literature search methods	Systematic search of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to October 2017. Reference lists of relevant articles were searched.
Screening, extraction, and quality assessment methods	Titles and abstracts were screened for inclusion by one author. Full-text articles of selected abstracts were screening independently by two researchers according to predetermined criteria. Disagreements were resolved through discussion. Data extraction completed independently in duplicate using piloted extraction forms. Risk of bias assessed by two researchers using the Cochrane tool. Publication bias was assessed using the Egger test for funnel plot asymmetry.

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; RCT = randomized controlled trial; SGLT2 = sodium-glucose cotransporter-2.

Source: Zheng et al.[52]

Results

Summary of Included Studies

A total of 236 RCTs (176,310 patients and 310,166 patient-years) met the inclusion criteria for the indirect comparison. Twenty-three of these RCTs directly compared active treatments; the other 213 trials compared an active agent to placebo. Nine trials were designed as cardiovascular outcome studies and contributed 247,034 patient-years to the analysis (N = 87,162).

The authors reported that the baseline characteristics of the studies (age, sex, body mass index [BMI], glycated hemoglobin [A1C]) were deemed sufficiently similar to permit NMA. Among the 236 trials, 1% were at a high risk of bias for allocation concealment, 7% for blinding, and 25% for attrition bias. Forty-four per cent were low risk of bias for all domains. No evidence of publication bias was observed (Egger test 0.10, $P = 0.27$).

The primary analysis of all-cause mortality included data from 97 RCTs and 134,160 patients. The SGLT2 inhibitors and GLP-1 agonist drug class were associated with a reduction in all-cause mortality compared with control, with 95% CrI that did not include the null. In the comparison to the DPP-4 inhibitors, the SGLT2 inhibitors (HR 0.78, 95% CrI 0.68 to 090) and the GLP-1 agonists (HR 0.86, 95% CrI 0.77 to 0.96) were associated with a statistically significant reduction in all-cause mortality. The DPP-4 inhibitors were not associated with a reduction in mortality relative to control. These findings were consistent across the sensitivity analyses conducted including the analysis restricted to cardiovascular outcome trials.

Of interest to this review is the analysis comparing the individual drugs (Table 70) which included data from 98 trials. Semaglutide was not associated with statistically significant differences in all-cause mortality versus the control (placebo or no treatment), other GLP-1 agonists, SGLT2 inhibitors (canagliflozin or dapagliflozin) or DPP-4 inhibitors, based on the Bayesian fixed effect model. Semaglutide was associated with an increased risk of death compared with empagliflozin (HR 1.49, 95% CrI 1.01 to 2.20).

Table 70: NMA Results for All-Cause Mortality

	All-Cause Mortality HR (95% CrI) (FE) SEM vs. Comparator
Number of Studies (Patients)	98 (134,301)
SGLT2 inhibitors	
Canagliflozin	1.16 (0.80, 1.70)
Dapagliflozin	0.92 (0.44, 1.98)
Empagliflozin	**1.49 (1.01, 2.20)**
DPP-4 inhibitors	
Alogliptin	1.14 (0.76, 1.72)
Linagliptin	1.27 (0.45, 3.69)
Saxagliptin	0.92 (0.64, 1.34)
Sitagliptin	1.00 (0.70, 1.44)
GLP-1 agonists	
Dulaglutide	1.64 (0.16, 17.24)
Exenatide	1.18 (0.82, 1.70)
Liraglutide	1.19 (0.82, 1.73)
Lixisenatide	1.11 (0.75, 1.64)
Other	
Control	1.02 (0.72, 1.44)

CrI = credible interval; DPP-4 inhibitor = dipeptidyl peptidase-4; FE = fixed effects; GLP-1 = glucagon-like peptide -1; HR = hazard ratio; NMA = network meta-analysis; SEM = semaglutide; SGLT2 = sodium-glucose cotransporter-2.

Note: Comparisons where the 95% CrI exclude the null are shown in bold.

Source: Zheng et al.[52]

Critical Appraisal

The ITC was based on a systematic review that followed accepted methods for study selection, data extraction, and quality assessment of studies. A comprehensive evidence base was used to inform the analysis (236 RCTs), however the search was limited to published English language studies available as of October 2017, thus more recent clinical trials may be missing. The authors appear to have used standard Bayesian methods to conduct the NMA. Of note, event rates were imputed for trials that reported only the number of events and follow-up times (rather than HR) and the imputation method used assumed a constant event rate over time, which may not be true. It is unclear what impact this may have had on the results.

Although the authors stated that baseline characteristics were similar across trials, some differences were noted. For example, the analysis pooled data from cardiovascular outcome trials, which were designed to assess major adverse cardiovascular events (MACE) in a higher risk population, with trials designed to assess glycemic control in patients with a generally lower risk of cardiovascular events. The authors presented some information on the patient characteristics of the included trials but there was no discussion of the background therapies that patients received, or how differences in these co-interventions

may affect the results. The duration of the trials was heterogeneous and ranged from 12 weeks to 161 weeks, and although the duration of short-term trials would be insufficient to show any impact of treatment on mortality, many of these trials were likely dropped from the analysis if they had no events in any of the treatment groups. In order to evaluate the potential impact of these sources of heterogeneity, the authors conducted several sensitivity analyses (i.e., excluding trials less than one year in duration or in low cardiovascular risk patients, and including only low-risk-of-bias studies), and the results of these analyses were consistent with the primary analysis. The authors, however, did not explore the impact of variations in age, which may be an important predictor of mortality.

There was only one analysis that was directly relevant to this review, but this was conducted as a sensitivity analysis and so not all details of interest were provided (e.g., DIC values, assessment of inconsistency). Moreover, there was no exploration of potential effect modifiers for this analysis, or a sensitivity analyses that included only data from cardiovascular outcome trials. The credible intervals were wide, suggesting there is considerable uncertainty in the results.

Although not an issue for the analysis of all-cause mortality, the methods used to ascertain cardiovascular events may not have been consistent across trials, particularly those trials not designed to assess cardiovascular safety.

Conclusion

The ITC that examined all-cause mortality among patients with type 2 diabetes mellitus treated with GLP-1 agonists, DPP-4 inhibitors or SGLT2 inhibitors suggested that the risk of death among those who received semaglutide was similar to other therapies with the exception of empagliflozin. These data should be interpreted with caution due to potential heterogeneity in-trial and patient characteristics of the included studies that was not adequately explored in the NMA.

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