Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value

Draft Evidence Report

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This draft evidence report was updated on September 12, 2019 to revise the costs for oral semaglutide presented in Table 4.7.

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit:
https://icer-review.org/material/diabetes-stakeholder-list/

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List of Acronyms Used in this Report

AACE	American Association of Clinical Endocrinologists
ACE	American College of Endocrinology
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetes Association
ADD	Antidiabetic drug
ASCVD	atherosclerotic cardiovascular disease
BCBSMA	Blue Cross Blue Shield of Massachusetts
CDC	Centers for Disease Control and Prevention
CEMR	Centricity Electronic Medical Records
CEPAC	Comparative Effectiveness Public Advisory Council
CHF	Congestive heart failure
CI	Confidence interval
CrI	Credible interval
CKD	Chronic kidney disease
CMS	Centers for Medicare and Medicaid Services
CV	Cardiovascular
CVD	Cardiovascular disease
CVOT	Cardiovascular outcomes trial
DPP-4	Dipeptidyl peptidase-4
eCVD	Established cardiovascular disease
eGFR	Estimated glomerular filtration rate
evLYG	Equal-value life year gained
EASD	European Association of the Study of Diabetes
ESC	European Society of Cardiology
ESRD	End stage renal disease
ETD	Estimated treatment difference
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GIP	Glucose-dependent insulinotropic polypeptide
GLP1	Glucagon-like peptide 1
HbA1c	Glycated hemoglobin
HRQoL	Health-related quality of life
ICER	Institute for Clinical and Economic Review
IHD	Ischemic heart disease
MACE	Major Adverse Cardiovascular Event
MI	Myocardial infarction
NCD	National coverage decision
NMA	Network meta-analysis
OM1	Outcomes Model 1
OM2	Outcomes Model 2
LCD	Local coverage decision
LY	Life year
PICOTS	Population, Intervention, Comparator, and Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
RCT	Randomized control trial
SAE	Severe adverse event
SGLT-2	Sodium-glucose cotransporter 2

SF-36	The Short Form (36) Health Survey
SU	Sulfonylurea
T2DM	Type 2 diabetes mellitus
UKPDS	United Kingdom Prospective Diabetes Study
US	United States
USD	United States dollar
USPSTF	United States Preventive Services Task Force
WAC	Wholesale acquisition cost
WTP	Willingness to pay

1. Introduction

1.1 Background

Background

In the US, approximately 30 million individuals have diabetes mellitus, of whom 95% have Type 2 diabetes (T2DM).[1] T2DM is characterized by insulin resistance, a condition in which the body does not respond to insulin appropriately. Insulin, a hormone produced by beta cells in the pancreas, is central to the control of blood glucose levels. Patients with diabetes have elevations in blood glucose (hyperglycemia) and are at increased risk for damage to blood vessels both large (macrovascular disease) and small (microvascular disease). Many of the complications of diabetes are the result of vascular disease, including microvascular damage to the eyes and kidneys, and macrovascular complications including myocardial infarction, stroke, limb ischemia, and cardiovascular (CV) death.[2] Better control of hyperglycemia reduces the risk of microvascular complications and may reduce the risk of macrovascular complications, particularly in individuals newly diagnosed with diabetes.[3]

In 2014, 7.2 million hospital discharges were reported among individuals with diabetes in the United States, including hospitalizations for major cardiovascular disease (CVD) and lower-extremity amputation.[1] The annual cost of managing diabetes in the United States (US) is approximately $245 billion, including both direct medical costs and lost productivity resulting from complications.[1] Costs to individual patients can create substantial financial toxicity. The Centers for Disease Control (CDC) reported that in surveys covering 2017-2018, a quarter of patients with diabetes asked their physicians to prescribe a lower cost medication, and 13% of patients did not take their medications as prescribed to reduce costs.[4]

Management of T2DM typically begins with a foundation of medical nutrition therapy and physical activity ("lifestyle changes"), and this may be sufficient in some individuals to achieve adequate blood glucose control. Control of blood glucose is generally assessed over the long term by measuring levels of glycated hemoglobin (HbA1c).[5] High levels of blood glucose can cause glucose molecules to bind to hemoglobin in red blood cells; the percentage of HbA1c, therefore, reflects glycemic control over the lifespan of the red blood cells (typically three to four months).[5] Levels of HbA1c are generally used as "glycemic targets" in patients with T2DM, with somewhat less intense control being accepted for with a history of severe hypoglycemia, limited life expectancy, advanced micro or macrovascular complications, important comorbid conditions, or long-standing diabetes where the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.[5] In addition to lifestyle changes, many individuals with T2DM will require antihyperglycemic

medications to achieve and sustain glycemic control.[2,6] Some of these medications require close monitoring of blood glucose levels, up to multiple times per day with certain forms of insulin.

Metformin is generally the preferred first-line medication option and has a favorable safety profile in that it does not increase weight or the risk of hypoglycemia (low blood glucose) when used as a single agent.[2,6] If lifestyle changes and metformin do not achieve a desired glycemic target, another glucose-lowering drug may be added.[2,6] Additional management options include oral agents (e.g., sulfonylureas, thiazolidinediones, sodium-glucose cotransporter 2 [SGLT-2] inhibitors, dipeptidyl peptidase-4 [DPP-4] inhibitors) and injectable medications (e.g., glucagon-like peptide 1 [GLP-1] receptor agonists, insulin).[2,6]

Diabetes management also involves management of the risks of microvascular and macrovascular complications of T2DM, including screening and treating diabetic eye disease, managing CV risk factors, and preventing and treating diabetic foot infections.[2]

In 2008, the US Food and Drug Administration (FDA) issued recommendations to evaluate the CV effects of new antihyperglycemic therapies because of concerns that some therapies that lower blood glucose may increase the risk for adverse CV events over time.[7] These recommendations generally require the conduct of large randomized trials of these new agents in patients at high risk for CV events.[8,9] Since then, several CV outcome trials (CVOTs) have been conducted, and this evidence has allowed for greater certainty in considering the relative benefits and risks of each therapy.[8] An updated guideline from the American Diabetes Association suggests that many patients who do not achieve adequate glycemic control with metformin should be subsequently treated by adding a GLP-1 receptor agonist or SGLT-2 inhibitor to the regimen. However, the guideline suggests use of older agents if cost is a major issue, highlighting the importance of considering cost effectiveness in assessing the newer therapies for T2DM.[6]

A new oral form of the GLP-1 receptor agonist semaglutide (Novo Nordisk) is currently being evaluated for the treatment of patients with T2DM; an injectable form of semaglutide that is administered subcutaneously once weekly has been available in the US since 2017.[10] The manufacturer filed for FDA approval of oral semaglutide in March 2019 for two indications. A decision is expected by September 2019 for the first indication – to control blood glucose in patients with T2DM – and by January 2020 for the second indication – to reduce major CV events in adults with T2DM and established CV disease.[11] If approved, oral semaglutide would be the first oral formulation of a GLP-1 receptor agonist to become available.

Newer Treatments for T2DM

DPP-4 Inhibitors

DPP-4 is an enzyme that deactivates almost 100 peptides including several relevant to glucose homeostasis including incretin hormones such as GLP-1 and glucose-dependent insulinotropic

polypeptide (GIP).[12] DPP-4 inhibitors are oral medications that are generally well tolerated, but with very modest effects in lowering blood glucose levels; they are not believed to have important effects on weight or CV risk apart from their effects on blood glucose.[6] In some trials, treatment with DPP-4 inhibitors has increased the risk of hospitalization for heart failure.[13]

SGLT-2 Inhibitors

SGLT-2 is a protein in the proximal tubules of the kidney responsible for reabsorbing filtered glucose.[14] SGLT-2 inhibitors are oral medications that block glucose reabsorption in the kidney resulting in the loss of glucose in the urine. SGLT-2 inhibitors have modest effects in lowering blood glucose and can increase the risk for both mild and severe genitourinary infections, but also appear to result in weight loss and have favorable effects on CV disease, heart failure, and kidney disease.[6]

GLP-1 Receptor Agonists

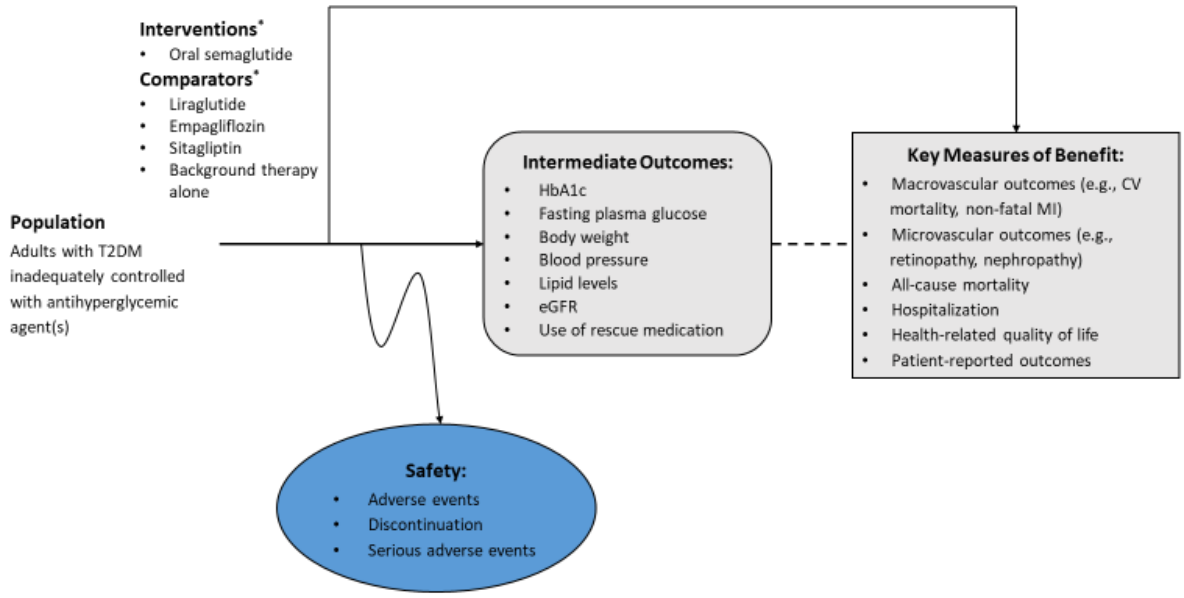
GLP-1 is released by cells in the gastrointestinal tract and stimulates pancreatic release of insulin in response to glucose; it also slows gastric emptying and reduces glucagon levels.[15] All approved GLP-1 receptor agonists are administered by injection weekly, daily, or twice daily. GLP-1 receptor agonists substantially lower blood glucose levels and result in weight loss and appear to have favorable effects on CV disease and kidney disease.[6] Gastrointestinal side effects are common with these agents, and they carry a warning for a risk of promoting thyroid C-cell tumors based on studies in animals.[16]

1.2 Scope of the Assessment

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.1.

Figure 1.1. Analytic Framework: Oral Semaglutide for T2DM



CV: cardiovascular, eGFR: estimated glomerular filtration rate, HbA1c: glycated hemoglobin, MI: myocardial infarction, T2DM: type 2 diabetes mellitus

*Oral semaglutide, liraglutide, empagliflozin, and sitagliptin will be evaluated as add-on therapies to current antihyperglycemic treatment(s).

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., HbA1C levels), and those within the squared-off boxes are key measures of benefit (e.g., death). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.[17]

Populations

The population of interest for this review is adults with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s). Data permitting, we intended to examine subgroups including, but not limited to, the following:

1. Patients at high risk for CV events
2. Patients with moderate-to-severe renal impairment
3. Patients requiring a second antihyperglycemic agent (i.e., second-line therapy)
4. Patients requiring a third antihyperglycemic agent (i.e., third-line therapy)

We found evidence on the effect of oral semaglutide in patients at high risk for CV events and in patients with moderate renal impairment. However, we did not find evidence stratified by line of therapy.

Interventions

Our intervention of interest for this review was oral semaglutide added to current antihyperglycemic treatment.

Comparators

We compared add-on oral semaglutide to ongoing background treatment (e.g., metformin with or without sulfonylureas) alone and to each of the following add-on agents:

- Liraglutide (Victoza®, Novo Nordisk), an injectable GLP-1 receptor agonist
- Empagliflozin (Jardiance®, Boehringer Ingelheim and Eli Lilly), an SGLT-2 inhibitor
- Sitagliptin (Januvia®, Merck), a DPP-4 inhibitor

These three agents were chosen in part because they were active comparators in the trials of oral semaglutide.

Outcomes

We sought evidence on the following outcomes listed below.

Efficacy

Intermediate Outcomes

- HbA1c
- Fasting plasma glucose
- Body weight

- Blood pressure
- Lipid levels
- Estimated glomerular filtration rate (eGFR)
- Use of rescue medication (e.g., additional glucose-lowering medication)

Key Measures of Benefit

- Macrovascular outcomes including:
    - CV mortality
    - Stroke
    - Myocardial infarction
    - Heart failure
    - Other CV events
- Microvascular outcomes including:
    - Retinopathy
    - Nephropathy
    - Neuropathy
    - Other renal or eye events (e.g., chronic kidney disease progression, visual deterioration)
- All-cause mortality
- Hospitalization
- Health-related quality of life and activities of daily living
- Patient-reported outcomes

Safety

- Adverse events including:
    - Hypoglycemia
    - Weight gain
    - Pancreatitis
    - Urogenital infections
    - Gastrointestinal effects
    - Fractures
    - Thyroid tumors
    - Renal effects
    - CV events
    - Other treatment-emergent adverse events
- Discontinuation (all-cause, due to adverse events)
- Serious adverse events (SAEs)

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least three months' duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings.

1.3 Definitions

Diagnosis of Diabetes: Standard diagnostic criteria for diabetes include a fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L), or a two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) following a 75-gram oral glucose challenge, or an HbA1c ≥6.5% (48 mmol/mol), or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL(11.1 mmol/L).[18] Except for the last criterion, diagnosis requires two abnormal test results.[18]

Glycated Hemoglobin (HbA1c): The percentage of hemoglobin in the blood that is glycated. The HbA1c percentage generally acts as an average measure of a patient's blood glucose levels over the preceding two to four months.[19]

Fasting Plasma Glucose (FPG): The level of glucose in a patient's blood after having no caloric intake for at least eight hours.[18]

3-Point Major Adverse Cardiovascular Events (MACE): A composite outcome consisting of non-fatal stroke, non-fatal myocardial infarction, and CV death.[20]

The Short Form (36) Health Survey (SF-36): A 36-item quality of life instrument that measures eight domains of health status (physical functioning, vitality, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health).[21]

Diabetes Treatment Satisfaction Questionnaire: A diabetes specific eight-item instrument assessing patient's satisfaction with their diabetes treatment.[22]

Impact of Weight on Quality of Life Questionnaire: A 74-item self-reported instrument that assesses the impact of weight on quality of life across eight domains.[23]

Control of Eating Questionnaire: A 21-item instrument that assesses food cravings from the previous seven days.[24]

1.4 Insights Gained from Discussions with Patients and Patient Groups

In discussions with patients and patient groups we heard about the difficulties of living with T2DM, particularly when on complex insulin regimens. We heard about the discomfort of frequently monitoring blood glucose by finger stick, the discomfort and complexity of injecting insulin on a daily or multiple-times-per-day basis, and the stress of monitoring dietary intake. We heard of the fear and worry about the damage that diabetes can do to the body and the discomfort of living with chronic neuropathy. We also heard about the financial toxicity of diabetes with one older patient explaining how he continues to work many hours per week to qualify for employer-based insurance in addition to his Medicare benefits. That same patient, however, stated he would be willing to pay more for an oral medication to avoid even one injection per week.

1.5. Potential Cost-Saving Measures in T2DM

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). These services are ones that would not be directly affected by therapies for T2DM (e.g., reduction in nephropathy), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of T2DM beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with T2DM that could be reduced, eliminated, or made more efficient. As an example, through the Choosing Wisely initiative, both the American Association of Family Physicians and the Society of General Internal Medicine suggest not routinely recommending daily home glucose monitoring for patients with T2DM who are not using insulin.[25]

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

To understand the insurance landscape for the interventions and comparators in this report, we reviewed National and Local Coverage Determinations (NCDs and LCDs) from the Centers for Medicare and Medicaid Services (CMS); publicly available coverage policies from representative public plans of MassHealth (Massachusetts Medicaid) and Neighborhood Health Plan of Rhode Island (NHPRI; Rhode Island Medicaid); and national and regional private payers (Blue Cross Blue Shield of Massachusetts [BCBSMA], Caremark, Express Scripts, and Humana). We surveyed each plan's coverage policies for the comparators reviewed in this report, including liraglutide (Victoza), empagliflozin (Jardiance), and sitagliptin (Januvia). At the time this report was published, the FDA had yet to issue a decision on oral semaglutide, precluding a survey of its coverage policies. We instead reviewed the coverage policies for injectable semaglutide (Ozempic), which may serve as a model for coverage of the new agent.

We were unable to identify any NCDs or LCDs relating to the use of any of these therapies.[26] A summary of our findings is as follows:

Liraglutide (Victoza)

Liraglutide is listed as a tier two product on the Rhode Island Medicaid and Humana plans, while Massachusetts Medicaid, Caremark and Express Scripts do not list the associated tier (Table 2.1).[27-31] Liraglutide is not covered on BCBSMA's plan, however, there were other GLP-1 receptor agonists that were covered as preferred agents.[32] Of the surveyed plans, only Rhode Island Medicaid and Humana did not require a prior authorization for liraglutide (Table 2.1) .

Empagliflozin (Jardiance)

Empagliflozin is listed as a tier two product on the Rhode Island Medicaid and Humana plans and as a tier three option under BCBSMA, while Massachusetts Medicaid, Caremark, and Express Scripts do not list the associated tier (Table 2.1).[27-32] Neither Medicaid plan surveyed required step therapy or prior authorization for empagliflozin, while of the private payers, only BCBSMA and Caremark required both step therapy and prior authorization (Table 2.1).

Sitagliptin (Januvia)

Sitagliptin is listed as a tier two product on the Rhode Island Medicaid and Humana plans and as a tier three option on the BCBSMA plan, while Massachusetts Medicaid, Caremark, and Express

Scripts do not list the associated tier (Table 2.1).[27-32] Neither Medicaid plan surveyed required step therapy or prior authorization for sitagliptin, while of the private payers, only BCBSMA and Caremark required both step therapy and prior authorization (Table 2.1).

Injectable Semaglutide (Ozempic)

Injectable semaglutide is listed as a tier two product on the Rhode Island Medicaid and Humana plans while Massachusetts Medicaid, Caremark, and Express Scripts do not list the associated tier (Table 2.1).[27-31] Injectable semaglutide is not covered on BCBSMA's plan, however, other GLP-1 receptor agonists were covered as preferred agents.[32] Of the surveyed plans, only Rhode Island Medicaid and Humana did not require a prior authorization for injectable semaglutide (Table 2.1).

Table 2.1. Private and Public Coverage Policies for Comparators of Oral Semaglutide*

	BCBSMA (Tier 4)	Caremark	Express Scripts	Humana (Tier 4)	MassHealth	NHPRI
Injectable Semaglutide (Ozempic)						
Tier	NC	NL	NL	2	NL	2
ST	Yes	Yes	No	No	No	No
PA	Yes	Yes	Yes	No	Yes	No
Preferred Agent	No	Yes	No	NL	NL	NL
Liraglutide (Victoza)						
Tier	NC	NL	NL	2	NL	2
ST	Yes	Yes	No	No	No	No
PA	Yes	Yes	Yes	No	Yes	No
Preferred Agent	No	Yes	No	NL	NL	NL
Empagliflozin (Jardiance)						
Tier	3	NL	NL	2	NL	2
ST	Yes	Yes	No	No	No	No
PA	Yes	Yes	No	No	No	No
Preferred Agent	Yes	Yes	Yes	NL	NL	NL
Sitagliptin (Januvia)						
Tier	3	NL	NL	2	NL	2
ST	Yes	Yes	No	No	No	No
PA	Yes	Yes	No	No	No	No
Preferred Agent	Yes	Yes	Yes	NL	NL	NL

BCBSMA: Blue Cross Blue Shield of Massachusetts, N/A: Not available, NC: Not covered, NHPRI: Neighborhood Health Plan of Rhode Island, NL: Not listed

*Coverage policies for oral semaglutide are not provided since the FDA has yet to issue a decision on its approval

2.2 Clinical Guidelines

Below is a summary of clinical guidelines for the treatment and monitoring of T2DM from the American Diabetes Associates (ADA), and the European Society of Cardiology (ESC) and the European Association of the Study of Diabetes.

The American Diabetes Association (ADA)[6]

The ADA's Standards of Medical Care in Diabetes guidelines recommend that at time of diagnosis of T2DM, all patients, except when contraindicated, should be started on metformin in addition to comprehensive lifestyle modifications (e.g., healthy eating patterns, medical nutrition therapy, regular physical activity, weight management, smoking cessation).[33] A recommended HbA1c target is less than 7.0% for most nonpregnant adults. However, the guidelines suggest accounting for patient-specific factors, including but not limited to risk of hypoglycemia, comorbidities, disease duration, and patient preference, through which a patients' individualized target HbA1c may be higher or lower than 7.0%.[5] Dual pharmacologic therapy should be considered at initiation of newly diagnosed T2DM patients if their HbA1c is greater than or equal to 1.5% of the HbA1c target. These guidelines recommend a patient-centered approach to help guide selection of pharmacologic agents with considerations for comorbidities, risk of hypoglycemia, risk of side effects, cost, and impact on patient weight, along with patient preferences.

If the patient does not have chronic kidney disease (CKD), atherosclerotic cardiovascular disease (ASCVD), or concerns regarding weight management, and the HbA1c target is not achieved after three months of therapy, it is recommended to have a combination of metformin and any of six preferred medication classes which include basal insulin, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, sulfonylureas, or thiazolidinediones, dependent upon patient factors and drug-specific effects. When there is a compelling need to either minimize weight gain or help promote weight loss, use of either GLP-1 receptor agonists or SGLT-2 inhibitors are preferred.

For T2DM patients who also have established ASCVD and who do not achieve HbA1c target after three months, use of either SGLT-2 inhibitors or GLP-1 receptor agonists are recommended as part of the treatment regimen. Among T2DM patients who have established ASCVD and heart failure or are at high risk of developing heart failure, use of SGLT-2 inhibitors are preferred. For T2DM patients who also have CKD, use of GLP-1 receptor agonists or SGLT-2 inhibitors are preferred.

The European Society of Cardiology (ESC) and the European Association of the Study of Diabetes (EASD)[34]

The ESC and EASD guidelines on diabetes, pre-diabetes, and CVD recommend the use of metformin along with lifestyle modifications (e.g., healthy eating patterns, regular physical activity, smoking cessation, weight management) as first-line therapy in patients with T2DM without established

ASCVD or at high CV risk.[34] A recommended HbA1c target is less than 7.0% for most adults, however, target goals should be individualized on a per-patient basis.

For patients with T2DM and CVD or at high CV risk, the use of GLP-1 receptor agonists or SGLT-2 inhibitors are recommended to reduce the risk of CV events. For patients with T2DM and heart failure, SGLT-2 inhibitors are recommended to reduce the risk of hospitalization from heart failure. Saxagliptin is not recommended for use in patients with heart failure. For patients with T2DM and CKD, SGLT-2 inhibitors are recommended to reduce progression of CKD.

3. Comparative Clinical Effectiveness

3.1 Overview

To inform our review of the comparative clinical effectiveness of oral semaglutide for the treatment of T2DM, we abstracted evidence from available studies of this agent, whether in published or unpublished forms (e.g., conference abstracts). As stated in the Background Section, the comparators of interest were liraglutide, empagliflozin, sitagliptin, and no treatment beyond ongoing background antihyperglycemic treatment. Our review focused on the clinical benefits in terms of intermediate outcomes (e.g., HbA1c) and key measures of benefit (e.g., CV outcomes), as well as potential harms.

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on oral semaglutide for T2DM followed established best methods.[35,36] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[37] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix Table A1.

We searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings that were published in 2017 and later. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design (PICOTS) elements described above. The search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Appendix Table A2 and A3.

We also searched MEDLINE and Cochrane Database of Systematic Reviews for recent systematic reviews of the other DPP-4 inhibitors, SGLT-2 inhibitors, or GLP-1 receptor agonists to provide context around how the comparator treatments compare to other agents within the same drug class. The search strategy is presented in Appendix Table A4. These systematic reviews are summarized in Appendix B.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from

conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Study Selection

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection was accomplished through two levels of screening, at the abstract and full-text level. Two reviewers independently screened the titles and abstracts of all publications identified using DistillerSR (Evidence Partners, Ottawa, Canada). No study was excluded at abstract level screening due to insufficient information. Citations accepted during abstract-level screening were reviewed as full text. Reasons for exclusion were categorized according to the PICOTS elements.

Data Extraction and Quality Assessment

Two reviewers extracted key information from the full set of accepted studies. Data elements included a description of patient populations, sample size, duration of follow-up, study design features (e.g., double-blind), interventions (e.g., drug, dosage, frequency), outcome assessments (e.g., timing, definitions, and methods of assessment), results, and quality assessment for each study. We used criteria employed by the US Preventive Services Task Force (USPSTF) that included presence of comparable groups, non-differential loss to follow-up, use of blinding, clear definition of interventions and outcomes, and appropriate handling of missing data to assess the quality of clinical trials. For more information on data extraction and quality assessment, refer to Appendix D.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among oral semaglutide relative to comparators of interest.[38]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for oral semaglutide using ClinicalTrials.gov. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies may indicate whether there is bias in the published literature . Search terms include “semaglutide” and “NN 9924.” For this review, we found no evidence of any study completed more than two years ago that has not subsequently been published.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were abstracted into evidence tables (see Appendix Tables D1-D9) and are described in the text below. Data informing the comparison of oral semaglutide and comparators of interests on CV and renal benefits were synthesized quantitatively in network meta-analyses (NMAs). The outcomes analyzed were 3-point MACE (a composite of CV death, nonfatal MI, or nonfatal stroke), hospitalization for heart failure, and new or worsening nephropathy. We included data from the cardiovascular outcomes trial (CVOT) of oral semaglutide (PIONEER 6) and injectable semaglutide (SUSTAIN 6) to inform the CV and renal effects of semaglutide as a molecule. We conducted a random effects meta-analysis of treatment effects from these two trials using the metafor package in R.[39] The rationale for the decision to synthesize data from the oral and injectable semaglutide CVOTs is discussed later. The results from the meta-analysis along with results from the CVOTs of the comparator treatments were synthesized in NMAs to obtain indirect estimates of semaglutide compared to the comparator treatments. The NMAs were conducted in a Bayesian framework with fixed effects on treatment parameters using the gemtc package in R.[40] The log hazard ratios for outcomes were analyzed using a normal likelihood and identity link. Tabular results are presented for the treatment effects (hazard ratio) of each intervention with 95% credible intervals (95% CrI).

3.3 Results

Study Selection

Our literature search identified 3,602 potentially relevant references (see Appendix Figure A1), of which 14 references[41-54] relating to 12 unique randomized controlled trials (RCTs) met the full inclusion criteria. Primary reasons for exclusion included intervention not of interest, comparison not of interest, and wrong study population. As stated in our research protocol, we searched for RCTs comparing our active comparators of interest to each other or ongoing background treatment in order to assess the feasibility of conducting NMAs. As mentioned above, we decided to conduct NMAs on CV and renal outcomes since there were no head-to-head data available for oral semaglutide versus our active comparators of interest for these endpoints. We decided not to conduct NMAs on intermediate outcomes such as HbA1c or body weight since we did have head-to-head data for these endpoints. We, therefore, only included trials of the comparator treatments if they measured CV or renal effects.

Key Studies

PIONEER Trials

Data to inform our assessment of oral semaglutide were primarily drawn from six publications[49-52,54] and two conference abstracts[42,53] relating to eight trials. These eight trials were part of the

PIONEER program, a Phase III clinical development program designed to assess the efficacy and safety of oral semaglutide in patients with T2DM. The PIONEER program was comprised of ten trials (PIONEER 1 through PIONEER 10). The PIONEER trials included in this review (PIONEER 1 through PIONEER 8)[42,49-54] were multinational RCTs comparing oral semaglutide to sitagliptin, empagliflozin, liraglutide, and placebo. Two of the PIONEER trials (PIONEER 9 and 10) are not included in this review because the results are currently only available in press releases. Both trials were conducted exclusively in Japanese patients and compared oral semaglutide to liraglutide 0.9 mg and placebo (PIONEER 9) and to dulaglutide 0.75 mg (PIONEER 10).

Table 3.1 presents the study design and key baseline characteristics of the PIONEER trials included in this review. The trials generally enrolled patients with T2DM with inadequate glycemic control (HbA1c ≥ 7.0%). Most trials assessed oral semaglutide as an add-on therapy to current antihyperglycemic treatment, while one trial assessed oral semaglutide as monotherapy (PIONEER 1).[53] Four trials had active controls and were conducted in patients inadequately controlled on one to two oral antihyperglycemic agents (PIONEER 2, 3, 4, and 7). PIONEER 2 compared oral semaglutide 14 mg to empagliflozin 25 mg added to metformin;[48] PIONEER 3 compared oral semaglutide 3, 7, and 14 mg to sitagliptin 100 mg added to metformin ± a sulfonylurea;[54] PIONEER 4 compared oral semaglutide 14 mg to liraglutide 1.8 mg and placebo added to metformin ± an SGLT-2 inhibitor;[49] and PIONEER 7 compared oral semaglutide flexible dose to sitagliptin 100 mg added to one to two oral antihyperglycemic agents (primarily metformin ± a sulfonylurea).[50] These head-to-head trials had randomized phases that lasted either 52 or 78 weeks. The primary outcome for PIONEER 2, 3, and 4 was the change in HbA1c at 26 weeks, and the primary outcome for PIONEER 7 was the proportion of patients achieving HbA1c <7.0% at 52 weeks. PIONEER 2 and 7 were open-label trials, and PIONEER 3 and 4 were blinded. Key exclusion criteria included: renal impairment (eGFR <60 mL/min/1.73m^2); MI, stroke, hospitalization for unstable angina, or transient ischemic attack within 180 days; stage IV heart failure; and history of pancreatitis. See Appendix Table D2 for the full details of eligibility criteria. Among the four head-to-head trials, the mean age at baseline ranged from 56 years to 58 years, the mean duration of diabetes ranged from 7.4 years to 8.8 years, and the mean HbA1c ranged from 8.0% to 8.3%.

The remaining four trials were placebo-controlled. Two placebo-controlled trials were conducted in higher risk populations (PIONEER 5 and 6). PIONEER 5 was a 26-week double-blind trial of oral semaglutide 14 mg versus placebo in patients with moderate renal impairment.[51] The study and results are described below in the section on subgroups of interest. PIONEER 6 was an event-driven CVOT of oral semaglutide 14 mg versus placebo conducted in patients with established CVD or CKD (85% of enrolled) or CV risk factors only.[52] The primary outcome was a composite of nonfatal stroke, nonfatal MI, and CV death in a time-to-first-event analysis. Additional detail on the study design and characteristics of PIONEER 6 is provided alongside the description of the other included CVOTs. The other two placebo-controlled trials were conducted in patients at earlier and later stages in T2DM treatment (PIONEER 1 and 8). PIONEER 1 was a 26-week double-blind trial of oral

semaglutide 3, 7, and 14 mg versus placebo conducted in drug-naïve patients inadequately controlled on diet and exercise.[53] At baseline, the mean age was 55 years, mean duration of diabetes was 3.5 years, and mean HbA1c was 8.0%. PIONEER 8 was a 52-week double-blind trial of oral semaglutide 3, 7, and 14 mg versus placebo conducted in patients inadequately controlled with insulin therapy; the dose of insulin was not allowed to increase above baseline levels for the first 26 weeks and unrestricted adjustments were allowed for the remainder of the trial.[42] The mean age was 61 years, mean duration of diabetes was 15.0 years, and the mean HbA1c was 8.2%. The primary outcome in both PIONEER 1 and PIONEER 8 was change in HbA1c at 26 weeks.

In the PIONEER trials, patients were instructed to take the study drug in the morning in a fasting state. In the fixed dose trials (all but PIONEER 7), oral semaglutide was initiated at 3 mg, escalated to 7 mg after four weeks, and escalated to 14 mg after another four weeks until the randomized dose was achieved. In the flexible dose trial (PIONEER 7), patients initiated oral semaglutide at 3 mg, and the dose could be adjusted based on HbA1c and tolerability every eight weeks. The dose was escalated if HbA1c≥7.0%, unless the patient experienced moderate-to-severe nausea or vomiting for three or more days in the preceding week. If the patient reported moderate-to-severe nausea or vomiting, the dose could be decreased at the investigator's discretion. In the PIONEER trials, patients could be offered rescue medication in the presence of persistent hyperglycemia. The criteria to initiate rescue medication varied across trials. See Appendix Table D2 for trial-specific criteria. If a patient discontinued the study drug, they were switched to another antihyperglycemic agent that was chosen at the investigator's discretion.

The PIONEER trials used two estimands to evaluate treatment efficacy. The treatment policy estimand evaluated the effect of treatment regardless of study drug discontinuation or use of rescue medication, while the trial product estimand evaluated the effect of treatment while patients were on treatment and not receiving rescue medication. In our review, we summarize treatment policy estimand results as it more closely resembles the intention-to-treat principle. The treatment policy estimand included all data collected post-randomization regardless of study drug discontinuation or use of rescue medication. To handle missing data, this estimand employed a pattern mixture model that assumed patients with missing data would have similar results as the patients with the same treatment assignment and treatment status (e.g., discontinued treatment).

Table 3.1. Study Design and Key Characteristics of Included PIONEER Trials

Trial	Arms*	Inclusion Criteria	Key Baseline Characteristics	Phases	Primary Outcome
Head-to-Head Trials					
PIONEER 2 (N=821)	1. Oral semaglutide 14 mg 2. Empagliflozin 25 mg	• Treated with metformin • HbA1c of 7.0%-10.5%	Age: 57 years HbA1c: 8.1% T2DM Duration: 7.4 years	52-week open-label	Change in HbA1c at week 26
PIONEER 3 (N=1864)	1. Oral semaglutide 3 mg 2. Oral semaglutide 7 mg 3. Oral semaglutide 14 mg 4. Sitagliptin 100 mg	• Treated with metformin ± sulfonylurea • HbA1c of 7.0%-10.5%	Age: 58 years HbA1c: 8.3% T2DM Duration: 8.6 years	78-week blinded	Change in HbA1c at week 26
PIONEER 4 (N=711)	1. Oral semaglutide 14 mg 2. Liraglutide 1.8 mg 3. Placebo	• Treated with metformin ± SGLT-2 inhibitor • HbA1c of 7.0%-9.5%	Age: 56 years HbA1c: 8.0% T2DM Duration: 7.6 years	52-week blinded	Change in HbA1c at week 26
PIONEER 7 (N=504)	1. Oral semaglutide [flexible, 3, 7, or 14 mg] 2. Sitagliptin 100 mg	• Treated with 1-2 oral antihyperglycemic agents • HbA1c of 7.5%-9.5%	Age: 57 years HbA1c: 8.3% T2DM Duration: 8.8 years	52-week open-label + 52-week extension	Proportion with HbA1c<7.0 % at week 52
Placebo-Controlled Trials					
PIONEER 1 (N=703)	1. Oral semaglutide 3 mg 2. Oral semaglutide 7 mg 3. Oral semaglutide 14 mg 4. Placebo	• Treated with diet & exercise • HbA1c of 7.0%-9.5%	Age: 55 years HbA1c: 8.0% T2DM Duration: 3.5 years	26-week blinded	Change in HbA1c at week 26
PIONEER 5 (N=324)	1. Oral semaglutide 14 mg 2. Placebo	• Moderate renal impairment • Treated with metformin ± sulfonylurea; or basal insulin ± metformin • HbA1c of 7.0%-9.5%	Age: 70 years HbA1c: 8.0% T2DM Duration: 14.0 years	26-week blinded	Change in HbA1c at week 26
PIONEER 6 (N=3183)	1. Oral semaglutide 14 mg 2. Placebo	•≥50 years old with eCVD or CKD, or ≥60 years old with CV risk factors	Age: 66 years HbA1c: 8.2% T2DM Duration: 14.9 years	Event-driven; blinded	3-point composite MACE*
PIONEER 8 (N=731)	1. Oral semaglutide 3 mg 2. Oral semaglutide 7 mg 3. Oral semaglutide 14 mg 4. Placebo	• Treated with insulin • HbA1c of 7.0%-9.5%	Age: 61 years HbA1c: 8.2% T2DM Duration: 15.0 years	52-week blinded	Change in HbA1c at week 26

CKD: chronic kidney disease, eCVD: established cardiovascular disease, HbA1c: glycated hemoglobin, MACE: major adverse cardiovascular events, mg: milligram, T2DM: type 2 diabetes

*All agents were administered once daily, †Nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death

Cardiovascular Outcome Trials

While the head-to-head PIONEER trials provided results regarding the efficacy of oral semaglutide compared to our active comparators of interest on intermediate outcomes such as HbA1c, they did not measure the comparative effects on key measures of benefit such as CV and renal outcomes. In

order to understand the effect of oral semaglutide compared to our active comparators of interest on key measures of benefit, we conducted NMAs that included PIONEER 6 and CVOTs of our comparator therapies.[44-46] In addition, we included evidence from the CVOT of injectable semaglutide (SUSTAIN 6).[43] Table 3.2 presents the study design and key baseline characteristics of the included CVOTs.

PIONEER 6 was an event-driven, placebo-controlled CVOT of oral semaglutide 14 mg conducted in 3183 patients with established CVD or CKD (85% of enrolled) or CV risk factors only.[52] The primary outcome was first occurrence of nonfatal MI, nonfatal stroke, or CV death (i.e., 3-point MACE). The primary objective was to rule out an 80% excess risk for CV events compared to placebo (noninferiority margin 1.8 for the upper bound of the 95% confidence interval (CI) for 3-point MACE). Patients were randomly assigned to oral semaglutide 14 mg (n=1591) or placebo (n=1592) and were followed for a median of 1.3 years. At baseline, the mean age was 66 years and the mean duration of diabetes was 14.9 years. Although there were no enrollment criteria regarding HbA1c, the mean HbA1c at baseline was 8.2% which is similar to that of the other PIONEER trials that enrolled patients with inadequate glycemic control.

SUSTAIN 6 was a 104-week placebo-controlled CVOT of injectable semaglutide conducted in 3297 patients with established CVD or CKD (83% of enrolled) or CV risk factors only.[43] Patients were required to have inadequate glycemic control (HbA1c ≥7.0%) to be enrolled. The primary outcome was 3-point MACE, and the primary objective was to rule out an 80% excess risk for CV events compared to placebo. Patients were randomly assigned to injectable semaglutide 0.5 mg or 1.0 mg (n=1648) or volume-matched placebo (n=1649) and were followed for a median of 2.1 years. At baseline, the mean age was 65 years, the mean duration of diabetes was 13.9 years, and the mean HbA1c was 8.7%.

The CVOTs of comparator therapies included in this review were LEADER (liraglutide vs. placebo), EMPA-REG OUTOME (empagliflozin vs. placebo), and TECOS (sitagliptin vs. placebo). LEADER randomized 9340 patients with established CVD or CKD (81% of enrolled) or CV risk factors only to liraglutide 1.8 mg (n=4668) or placebo (n=4672); the median follow-up was 3.8 years.[46] EMPA-REG OUTCOME randomized 7020 patients with established CVD to empagliflozin 10 mg or 25 mg (n=4687) or placebo (n=2333); the median follow-up was 3.1 years.[44] TECOS randomized 14671 patients with established CVD to sitagliptin 100 mg (n=7332) or placebo (n=7339); the median follow-up was 3.0 years.[45] The primary objective of all three trials was to rule out a 30% excess risk for CV events compared to placebo (noninferiority margin 1.3 for the upper bound of the 95% CI for the primary outcome). The primary outcome in LEADER and EMPA-REG OUTCOME was 3-point MACE, and the primary outcome in TECOS was a composite of 3-point MACE plus hospitalization for unstable angina; the key secondary outcome in TECOS was 3-point MACE. LEADER and EMPA-REG OUTCOME enrolled patients with inadequate glycemic control (HbA1c ≥7.0%), whereas TECOS enrolled patients with an HbA1c between 6.5% and 8.0%. The mean HbA1c in TECOS was 7.2% compared to 8.7% in LEADER and 8.2% in EMPA-REG OUTCOME. The mean duration of diabetes

was 12.8 years in LEADER, 11.9 years in TECOS, and 57.1% of patients in EMPA-REG OUTCOME had diabetes for more than 10 years.

At baseline, the proportion of patients receiving metformin was generally similar across the included CVOTs, ranging from 73.2% in SUSTAIN 6 to 81.6% in TECOS; however, the proportion of patients using insulin and sulfonylureas at baseline varied across the trials (Table 3.2). The majority of patients in all CVOTs were also receiving antihypertensives and lipid-lowering drugs (Table 3.2). All of the included CVOTs encouraged investigators to intensify antihyperglycemic and CV medications in line with standard of care guidelines.

Although we are primarily interested in the CV and renal outcomes measured in the CVOTs, we will also report the effect of the agents on intermediate outcomes such as HbA1c, weight, and use of rescue medication as well as on safety parameters that were observed in these trials.

Table 3.2. Key Characteristics of Included CVOTs

	PIONEER 6 (N=3183)	SUSTAIN 6 (N=3297)	LEADER (N=9340)	EMPA-REG (N=7020)	TECOS (N=14671)
CV Risk	≥50 years old with eCVD or CKD, or ≥60 years old with CV risk factors			≥18 years old with eCVD	≥50 years old with eCVD
HbA1c Criteria	None	≥7.0%	≥7.0%	≥7.0%	6.5-8.0%
Arms	1. Oral SEM 14 mg 2. PBO	1. Inj SEM 0.5 mg 2. Inj SEM 1.0 mg 3. PBO	1. LIR 1.8 mg 2. PBO	1. EMP 25 mg 2. EMP 10 mg 3. PBO	1. SIT 100 mg* 2. PBO
Follow-up, median	1.3 years	2.1 years	3.8 years	3.1 years	3.0 years
Age, mean	66 years	65 years	64 years	63 years	66 years
HbA1c, mean	8.2%	8.7%	8.7%	8.1%	7.2%
T2DM Duration, mean	14.9 years	13.9 years	12.8 years	>10 years: 57.1%	11.6 years
Established CVD	84.7% (CVD or CKD)	83.0% (CVD or CKD)	81.3% (CVD or CKD)	99.2% (CVD)	100% (CVD)
Renal Impairment	eGFR 30-59:28.2%	eGFR 30-59:25.2% eGFR <30: 3.2%	eGFR 30-59: 20.7% eGFR <30: 2.4%	eGFR 30-59: 25.9%	eGFR <50: 9.4%
Background Medications					
Metformin	77.4%	73.2%	76.5%	74.0%	81.6%
Insulin	60.6%	58.0%	44.6%	48.2%	23.2%
Sulfonylurea	32.3%	42.8%	50.7%	42.8%	45.3%
Anti-hypertensive	93.9%	93.5%	92.4%	94.9%	ACE or ARB: 78.8% BB: 63.5%
Lipid-lowering drug	85.2%	76.5%	75.8%	81.0%	Statin: 79.9% Ezetimibe: 5.2%

ACE: angiotensin-converting-enzyme inhibitor, ARB: angiotensin receptor blockers, BB: beta blockers, CKD: chronic kidney disease, CVD: cardiovascular disease, eCVD: established cardiovascular disease, eGFR: estimated glomerular filtration rate, HbA1c: glycated hemoglobin, Inj: injectable, T2DM: type 2 diabetes

*50 mg if eGFR ≥30 and <50

Quality of Individual Studies

Using criteria from the U.S. Preventive Services Task Force (USPSTF), we rated all of the included RCTs as good quality. The trials had comparable groups at baseline, generally non-differential follow-up, clear definition of interventions and outcomes, and appropriate handling of missing data.

We noted that PIONEER 2 and PIONEER 7 were open-label while all others were blinded (Appendix D).

Clinical Benefits

Intermediate Outcomes

Oral semaglutide reduced HbA1c more than placebo, empagliflozin, and sitagliptin, and more than liraglutide at 52 weeks but not at 26 weeks. Oral semaglutide reduced body weight more than placebo, liraglutide, and sitagliptin; reductions in body weight were similar with oral semaglutide and empagliflozin.

HbA1c

HbA1c is reported as a percentage (the percentage of hemoglobin that is glycated). Changes in HbA1c during trials reflect the absolute change in the percentage of glycated hemoglobin.

At 26 weeks, oral semaglutide 14 mg had greater reductions in HbA1c compared to placebo when added to metformin ± SGLT-2 inhibitor (PIONEER 4, -1.2% vs -0.2%),[49] when added to insulin therapy (PIONEER 8, -1.3% vs. -0.1%),[42] and when used as a monotherapy (PIONEER 1, -1.4% vs. -0.3%)[53] (Table 3.3). Significant reductions with oral semaglutide 14 mg compared to placebo were also observed at 52 weeks in PIONEER 4 and PIONEER 8 (-1.2% vs -0.2% for both)(Table 3.3). Oral semaglutide 3 mg and 7 mg also reduced HbA1c more than placebo at all timepoints in PIONEER 1 and PIONEER 8 (Table 3.3 and Appendix Table D6).

Reductions in HbA1c at 26 weeks were similar with oral semaglutide 14 mg and liraglutide 1.8 mg when added to metformin ± SGLT-2 inhibitor (PIONEER 4, -1.2% vs. -1.1%).[49] Oral semaglutide 14 mg reduced HbA1c at 26 weeks more than empagliflozin 25 mg when added to metformin (PIONEER 2, -1.3% vs. -0.9%)[48] and sitagliptin 100 mg when added to metformin ± sulfonylurea (PIONEER 3, -1.3% vs. -0.8%).[54] At 52 weeks, oral semaglutide 14 mg continued to reduce HbA1c more than empagliflozin 25 mg (-1.3% vs. -0.9%) and sitagliptin 100 mg (-1.2% vs -0.7%) and also more than liraglutide 1.8 mg (-1.2% vs. -0.9%)(Table 3.3). 78-week results from PIONEER 3 continued to show greater reductions with oral semaglutide 14 mg than sitagliptin 100 mg (-1.1% vs. -0.7%)(Appendix Table D5). Additionally, results from PIONEER 3 showed greater reductions in HbA1c with oral semaglutide 7 mg than sitagliptin 100 mg at 26 and 52 weeks but not at 78 weeks; oral semaglutide 3 mg did not reduce HbA1c more than sitagliptin 100 mg at any timepoint (Table 3.3 and Appendix Table D5). In PIONEER 7, oral semaglutide flexible dose reduced HbA1c more than sitagliptin 100 mg at 52 weeks (-1.3% vs -0.8%);[50] results at 26 weeks were not reported (Table 3.3).

Table 3.3. Change from Baseline in HbA1c at Week 26 and 52

Trial	Arm	Week 26		Week 52	
		Change	ETD (95% CI)	Change	ETD (95% CI)
Head-to-Head Trials					
PIONEER 2 52-week RCT MET	Semaglutide 14 mg	-1.3*	-0.4 (-0.6, -0.3)	-1.3*	-0.4 (-0.5, -0.3)
	Empagliflozin 25 mg	-0.9	—	-0.9	—
PIONEER 3 78-week RCT MET ± SU	Semaglutide 7 mg	-1.0*	-0.3 (-0.4 , -0.1)	-1.0*	-0.3 (-0.4 , -0.1)
	Semaglutide 14 mg	-1.3*	-0.5 (-0.6 , -0.4)	-1.2*	-0.5 (-0.6 , -0.3)
	Sitagliptin 100 mg	-0.8	—	-0.7	—
PIONEER 4 52-week RCT MET ± SGLT-2i	Semaglutide 14 mg	-1.2	-0.1 (-0.3, 0) vs. liraglutide -1.1 (-1.2, -0.9) vs. placebo	-1.2	-0.3 (-0.5, -0.1) vs. liraglutide -1.0 (-1.2, -0.8) vs. placebo
	Liraglutide 1.8 mg	-1.1		-0.9*	
	Placebo	-0.2*		-0.2*	
PIONEER 7 52-week RCT 1-2 Oral ADs	Semaglutide flexible	*NR*		-1.3*	-0.5 (-0.7, -0.4)
	Sitagliptin 100 mg			-0.8	—
Placebo-Controlled Trials					
PIONEER 1 26-week RCT Diet & exercise	Semaglutide 7 mg	-1.2*	-0.9 (-1.1, -0.6)	*N/A*	
	Semaglutide 14 mg	-1.4*	-1.1 (-1.3, -0.9)		
	Placebo	-0.3	—		
PIONEER 8 52-week RCT Insulin therapy	Semaglutide 7 mg	-0.9*	-0.9 (-1.1, -0.7)	-0.8*	-0.6 (-0.8, -0.4)
	Semaglutide 14 mg	-1.3*	-1.2 (-1.4, -1.0)	-1.2*	-0.9 (-1.1, -0.7)
	Placebo	-0.1	—	-0.2	—

Data are mean change from baseline, estimated treatment difference (95% CI)
*p<0.001
95% CI: 95% confidence interval, ADs: antidiabetics, ETD: estimated treatment difference, MET: metformin, mg: milligram, N/A: not applicable, NR: not reported, RCT: randomized controlled trial, SGLT-2i: SGLT-2 inhibitor, SU: sulfonylurea

More patients treated with oral semaglutide 14 mg achieved HbA1c<7.0% compared to placebo when added to metformin ± SGLT-2 inhibitor at 26 weeks (PIONEER 4, 67.6% vs. 14.2%) and 52 weeks (60.7% vs. 15.0%)[49] and as a monotherapy at 26 weeks (PIONEER 1, 76.9% vs 31.0%)[53](Table 3.4). Oral semaglutide 3 mg and 7 mg were also shown to have higher rates of achieving HbA1c<7.0% compared to placebo in PIONEER 1 (Table 3.4 and Appendix Table D6). Results for the comparison of oral semaglutide 3, 7, and 14 mg and placebo added to insulin therapy from PIONEER 8 are not available.

The rates of achieving HbA1c<7.0% were similar with oral semaglutide 14 mg and liraglutide 1.8 mg at 26 weeks (PIONEER 4, 67.6% vs 61.8%) and 52 weeks (60.7% vs 55.0%)[49](Table 3.4). More patients treated with oral semaglutide 14 mg achieved HbA1c<7.0% compared to empagliflozin 25 mg at 26 weeks (PIONEER 2, 66.8% vs 40.0%) and 52 weeks (66.1% vs. 43.2%)[48] and compared to sitagliptin 100 mg at 26 weeks (PIONEER 3, 55% vs 32%), 52 weeks (53% vs 31%), and 78 weeks (44% vs 29%)[54](Table 3.4 and Appendix Table D5). More patients treated with oral semaglutide

flexible dose achieved HbA1c<7.0% compared to sitagliptin 100 mg at 52 weeks (PIONEER 7, 58% vs 25%);[50] results at 26 weeks were not reported.

Table 3.4. Proportion Achieving HbA1c<7.0% at Week 26 and 52

Trial	Arm	Week 26		Week 52	
		%	OR (95% CI)	%	OR (95% CI)
Head-to-Head Trials					
PIONEER 2 52-week RCT MET	Semaglutide 14 mg	66.8*	3.39 (2.47, 4.65)	66.1*	2.71 (1.99, 3.69)
	Empagliflozin 25 mg	40	—	43.2	—
PIONEER 3 78-week RCT MET ± SU	Semaglutide 7 mg	42*	1.54 (1.18, 2.02)‡	38†	1.37 (1.04, 1.79)‡
	Semaglutide 14 mg	55*	2.61 (2.00, 3.41)‡	53*	2.49 (1.91, 3.26)‡
	Sitagliptin 100 mg	32	—	31	—
PIONEER 4 52-week RCT MET ± SGLT2i	Semaglutide 14 mg	67.6	1.31 (0.91, 1.89) vs. liraglutide 17.1 (9.5, 30.77) vs. placebo	60.7	1.33 (0.93, 1.91) vs. liraglutide 11.36 (6.4, 20.19) vs. placebo
	Liraglutide 1.8 mg	61.8		55	
	Placebo	14.2*		15*	
PIONEER 7 52-week RCT 1-2 Oral ADs	Semaglutide flexible	*NR*		58*	4.40 (2.89, 6.70)
	Sitagliptin 100 mg			25	—
Placebo-Controlled Trials					
PIONEER 1 26-week RCT Diet & exercise	Semaglutide 7 mg	68.8*	5.79 (3.50, 9.59)	*N/A*	
	Semaglutide 14 mg	76.9*	8.36 (4.86, 14.41)		
	Placebo	31	—		
PIONEER 8 52-week RCT Insulin therapy	Semaglutide 7 mg	*Data not currently available*			
	Semaglutide 14 mg				
	Placebo				

Data are percentage of patients, odds ratio (95% CI)
*p<0.001
†p=0.04
‡odds ratios were calculated for PIONEER 3 as the trial only reported estimated treatment differences.
95% CI: 95% confidence interval, ADs: antidiabetics, ETD: estimated treatment difference, MET: metformin, mg: milligram, N/A: not applicable, NR: not reported RCT: randomized controlled trial, SGLT-2i: SGLT-2 inhibitor, SU: sulfonylurea

Changes in HbA1c were reported in PIONEER 6 as well as the other CVOTs included in this review. In PIONEER 6, HbA1c was decreased by -1.0% in the oral semaglutide 14 mg arm compared to -0.3% in the placebo arm at 1.3 years of follow-up.[52] In SUSTAIN 6, HbA1c was decreased by -1.1% and -1.4% in patients receiving injectable semaglutide 0.5 mg and 1.0 mg, respectively, compared to a reduction of -0.4% for both volume-matched placebo arms at two years.[43] In LEADER, the mean difference in HbA1c reduction between liraglutide 1.8 mg and placebo was -0.4% at three years. In EMPA-REG OUTCOME, the mean difference in HbA1c reduction with empagliflozin 10 mg and 25 mg

compared to placebo was -0.42% and -0.47%, respectively, at 1.8 years and -0.24% and -0.36% , respectively, at four years.[44] In TECOS, the mean difference in HbA1c reduction between sitagliptin 100 mg and placebo was -0.29% at three years.[45]

Body Weight

Oral semaglutide 14 mg reduced body weight more than placebo at 26 weeks when added to metformin ± SGLT-2 inhibitor (PIONEER 4, -4.4 kg vs. -0.5 kg),[49] when added to insulin therapy (PIONEER 8, -3.7 kg vs. -0.4 kg),[42] and as a monotherapy (PIONEER 1, -3.7 kg vs. -1.4 kg)[53](Table 3.5). Greater weight reductions with oral semaglutide 14 mg compared to placebo were shown at 52 weeks in PIONEER 4 (-4.3 kg vs -1.0 kg) and PIONEER 8 (-3.7 kg vs 0.5 kg)(Table 3.5). Oral semaglutide 3 mg and 7 mg reduced weight more than placebo when added to insulin therapy (PIONEER 8) but not when used as monotherapy (PIONEER 1)(Appendix Table D6).

Oral semaglutide 14 mg reduced body weight more than liraglutide 1.8 mg at 26 weeks when added to metformin ± SGLT-2 inhibitor (PIONEER 4, -4.4 kg vs. -3.1 kg)[49] and sitagliptin 100 mg when added to metformin ± sulfonylurea (PIONEER 3, -3.1 kg vs. -0.6 kg).[54] Oral semaglutide 14 mg and empagliflozin 25 mg had similar reductions in weight when added to metformin at 26 weeks (PIONEER 2, -3.8 kg vs. -3.7 kg)[48](Table 3.5). At 52 weeks, weight loss remained greater with oral semaglutide 14 mg compared to liraglutide 1.8 mg (-4.3 kg vs. -3.0 kg) and sitagliptin 100 mg (-3.4 kg vs. -0.8 kg); no significant differences between oral semaglutide 14 mg and empagliflozin 25 mg were observed (-3.8 kg vs. -3.6 kg)(Table 3.5). 78-week results from PIONEER 3 showed continued greater reductions with oral semaglutide 14 mg compared to sitagliptin 100 mg (-3.2 kg vs. -1.0 kg)(Appendix Table D5). Additionally, results from PIONEER 3 showed greater reductions with oral semaglutide 3 mg and 7 mg than sitagliptin 100 mg at all timepoints (Table 3.5 and Appendix Table D5). In PIONEER 7, oral semaglutide flexible dose reduced weight more than sitagliptin 100 mg at 52 weeks (-2.6 kg vs. –0.7 kg);[50] results at 26 weeks were not reported (Table 3.5).

Table 3.5. Change from Baseline in Body Weight (kg) at Week 26 and 52

Trial	Arm	Week 26		Week 52	
		Change	ETD (95% CI)	Change	ETD (95% CI)
Head-to-Head Trials					
PIONEER 2 52-week RCT MET	Semaglutide 14 mg	-3.8	-0.1 (-0.7, 0.5)	-3.8	-0.2 (-0.9, 0.5)
	Empagliflozin 25 mg	-3.7	—	-3.6	—
PIONEER 3 78-week RCT MET ± SU	Semaglutide 7 mg	-2.2*	-1.6 (-2.0, -1.1)	-2.4*	-1.7 (-2.3, -1.1)
	Semaglutide 14 mg	-3.1*	-2.5 (-3.0, -2.0)	-3.4*	-2.7 (-3.3, -2.1)
	Sitagliptin 100 mg	-0.6	—	-0.8	—
PIONEER 4 52-week RCT MET ± SGLT2i	Semaglutide 14 mg	-4.4	-1.2 (-1.9, -0.6) vs. liraglutide -3.8 (-4.7, -3.0) vs. placebo	-4.3	-1.3 (-2.1, -0.5) vs. liraglutide -3.3 (-4.3, -2.4) vs. placebo
	Liraglutide 1.8 mg	-3.1*		-3.0†	
	Placebo	-0.5*		-1.0*	
PIONEER 7 52-week RCT 1-2 Oral ADs	Semaglutide flexible	*NR*		-2.6*	-1.9 (-2.6 to -1.2)
	Sitagliptin 100 mg			-0.7	—
Placebo-Controlled Trials					
PIONEER 1 26-week RCT Diet & exercise	Semaglutide 7 mg	-2.3	-0.9 (-1.9, 0.1)	*N/A*	
	Semaglutide 14 mg	-3.7*	-2.3 (-3.1, -1.5)		
	Placebo	-1.4	—		
PIONEER 8 52-week RCT Insulin therapy	Semaglutide 7 mg	-2.4*	-2.0 (-3.0, -1.0)	-2.0*	-2.5 (-3.6, -1.4)
	Semaglutide 14 mg	-3.7*	-3.3 (-4.2, -2.3)	-3.7*	-4.3 (-5.3, -3.2)
	Placebo	-0.4	—	0.5	—

Data are change in body weight (kg), estimated treatment difference (95% CI)
*p<0.001
†p=0.0019 95% CI: 95% confidence interval, ADs: antidiabetics, ETD: estimated treatment difference, MET: metformin, mg: milligram, N/A: not applicable, NR: not reported RCT: randomized controlled trial, SGLT-2i: SGLT-2 inhibitor, SU: sulfonylurea

More patients achieved ≥5% weight loss with oral semaglutide 14 mg than placebo when added to metformin ± SGLT-2 inhibitor at 26 weeks (PIONEER 4, 43.5% vs. 7.5%) and at 52 weeks (44.7% vs 12.0%)[49] and as a monotherapy at 26 weeks (PIONEER 1, 41.3% vs 14.9%)[53](Table 3.6). Oral semaglutide 7 mg but not 3 mg had significantly higher rates compared to placebo when used as a monotherapy (Table 3.6 and Appendix Table D6). Results for the comparison of oral semaglutide 3, 7, and 14 mg and placebo added to insulin therapy from PIONEER 8 are not available.

More patients achieved ≥5% weight loss with oral semaglutide 14 mg compared to sitagliptin 100 mg at 26 weeks (PIONEER 3, 30% vs. 10%), 52 weeks (34% vs 12%), and 78 weeks (33% vs 14%)[54] and compared to liraglutide 1.8 mg at 26 weeks (PIONEER 4, 43.5% vs. 27.7%) and at 52 weeks (44.7% vs. 24.5%).[49] This was also seen with oral semaglutide flexible dose compared to sitagliptin 100 mg at 52 weeks (PIONEER 7, 27.0% vs 12.0%);[50] results at 26 weeks were not reported (Table 3.5). Results for the comparison of oral semaglutide 14 mg and empagliflozin 25 mg from PIONEER 2 are not available.

Table 3.6. Proportion Achieving ≥5% Weight Loss at Week 26 and 52

Trial	Arm	Week 26		Week 52	
		%	OR (95% CI)	%	OR (95% CI)
Head-to-Head Trials					
PIONEER 2 52-week RCT MET	Semaglutide 14 mg	*Data not currently available*			
	Empagliflozin 25 mg				
PIONEER 3 78-week RCT MET ± SU	Semaglutide 7 mg	19*	2.09 (1.43-3.05)§	27*	2.73 (1.93-3.86)§
	Semaglutide 14 mg	30*	3.85 (2.68-5.52)§	34*	3.78 (2.69-5.30)§
	Sitagliptin 100 mg	10	—	12	—
PIONEER 4 52-week RCT MET ± SGLT2i	Semaglutide 14 mg	43.5	1.95 (1.36, 2.8) vs. liraglutide 9.4 (4.71, 18.77) vs. placebo	44.7	5.64 (3.17, 10.02) vs. liraglutide 2.38(1.65, 3.43) vs. placebo
	Liraglutide 1.8 mg	27.7*		24.5*	
	Placebo	7.5*		12.0*	
PIONEER 7 52-week RCT 1-2 Oral ADs	Semaglutide flexible	*NR*		27.0*	2.71 (1.65, 4.45)
	Sitagliptin 100 mg			12.1	—
Placebo-Controlled Trials					
PIONEER 1 26-week RCT Diet & exercise	Semaglutide 7 mg	26.9†	2.05 (1.16, 3.63)	*N/A*	
	Semaglutide 14 mg	41.3*	3.74 (2.18, 6.41)		
	Placebo	14.9	—		
PIONEER 8 52-week RCT Insulin therapy	Semaglutide 7 mg	*Data not currently available*			
	Semaglutide 14 mg				
	Placebo				

Data are percentage of patients, odds ratio (95% CI)

95% CI: 95% confidence interval, ADs: antidiabetics, ETD: estimated treatment difference, MET: metformin, mg: milligram, N/A: not applicable, NR: not reported RCT: randomized controlled trial, SGLT-2i: SGLT-2 inhibitor, SU: sulfonylurea

*p<0.001

†p=0.01

§odds ratios were calculated for PIONEER 3 as the trial only reported estimated treatment differences.

Body weight was decreased more with oral semaglutide 14 mg compared to placebo in PIONEER 6 at 1.3 years (-4.2 kg vs -0.8 kg)[52] and with injectable semaglutide 0.5 mg and 1.0 mg compared to volume-matched placebo at in SUSTAIN 6 at two years (-3.6 kg vs -0.7 kg and -4.9 vs -0.5 kg, respectively).[43] The mean difference in weight reduction between liraglutide 1.8 mg and placebo was -2.3 kg at three years in LEADER.[46] The mean reduction in body weight was not reported in EMPA-REG OUTCOME, but examination of the curve of mean body weight evidences greater reductions with empagliflozin 10 mg and 25 mg compared to placebo.[44] Changes in body weight were not reported in TECOS.[45]

Fasting Plasma Glucose

Oral semaglutide 14 mg reduced fasting plasma glucose (FPG) levels more than placebo when added to metformin ± SGLT-2 inhibitor at 26 weeks and 52 weeks (PIONEER 4)[49] and when used a monotherapy at 26 weeks (PIONEER 1)[53](Appendix Table D6). Oral semaglutide 3 mg and 7 mg also

reduced FPG more than placebo in PIONEER 1 (Appendix Table D6). Results for the comparison of oral semaglutide 3, 7, and 14 mg and placebo added to insulin therapy from PIONEER 8 are not available.

There were significant reductions in FPG with oral semaglutide 14 mg compared to liraglutide 1.8 mg when added to metformin ± SGLT-2 inhibitor at 52 weeks but not at 26 weeks[49](Appendix Table D5). Oral semaglutide 14 mg reduced FPG more compared to sitagliptin 100 mg when added to metformin ± sulfonylurea at 26, 52, and 78 weeks[54](Appendix Table D5). Results for the comparison of oral semaglutide 14 mg and empagliflozin 25 mg from PIONEER 2 are not available. Oral semaglutide flexible dose reduced FPG levels significantly more than sitagliptin 100 mg at 52 weeks; results at 26 weeks were not reported[50](Appendix Table D5).

Changes in FPG were not reported in the CVOTs included in this review.

Blood Pressure

There were greater decreases in systolic blood pressure with oral semaglutide 14 mg compared to placebo when added to metformin ± SGLT-2 inhibitor at 52 weeks but not at 26 weeks (PIONEER 4)[49](Appendix Table D6). No significant changes in systolic blood pressure were observed with oral semaglutide as a monotherapy compared to placebo at 26 weeks in PIONEER 1.[53] Results for the comparison of oral semaglutide 3, 7, and 14 mg and placebo added to insulin therapy from PIONEER 8 are not available.

No significant changes in systolic blood pressure with oral semaglutide 14 mg compared to liraglutide 1.8 mg were observed in PIONEER 4[49](Appendix Table D5). Oral semaglutide 7 mg and 14 mg reduced systolic blood pressure more than sitagliptin 100 mg when added to metformin ± sulfonylurea at 52 and 78 weeks but not at 26 weeks (PIONEER 3)[54](Appendix Table D6). Results for the comparison of oral semaglutide 14 mg and empagliflozin 25 mg from PIONEER 2 are not available.

There were no notable changes in diastolic blood pressure observed in the PIONEER trials.

In the CVOTs, there were significant reductions in systolic blood pressure compared to placebo with oral semaglutide 14 mg at 1.3 years (PIONEER 6),[52] injectable semaglutide 1.0 mg at 104 weeks (SUSTAIN 6),[43] liraglutide 1.8 mg at three years (LEADER),[46] and empagliflozin 10 mg/25 mg at four years (EMPA-REG OUTCOME).[44] Diastolic blood pressure was increased with liraglutide 1.8 mg at three years, decreased with empagliflozin 10 mg/25 mg at four years, and was unchanged with both oral semaglutide 14 mg and injectable semaglutide 0.5 mg/1.0 mg. Changes in blood pressure were not reported in TECOS.

Lipid Levels

The PIONEER trials reported the change in total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein levels cholesterol (HDL-C), and triglycerides.

Total cholesterol and triglycerides were significantly reduced with oral semaglutide 14 mg compared to placebo as a monotherapy at 26 weeks; no significant changes with oral semaglutide 3

mg or 7 mg were observed (PIONEER 1)[53](Appendix Table D6). Total cholesterol and triglycerides were reduced with oral semaglutide 14 mg compared to placebo when added to metformin ± SGLT2-inhibitor at 26 and 52 weeks; LDL-C was reduced at 52 weeks but not at 26 weeks (PIONEER 4)[49](Appendix Table D6). Results for the comparison of oral semaglutide 3, 7, and 14 mg and placebo added to insulin therapy from PIONEER 8 are not available.

No significant changes in lipid levels with oral semaglutide 14 mg compared to liraglutide 1.8 mg were observed.[49] Oral semaglutide 14 mg reduced total cholesterol and LDL-C more than sitagliptin 100 mg when added to metformin ± sulfonylurea at 26 weeks but not at 52 or 78 weeks; triglyceride levels were reduced at 26 and 52 weeks but not at 78 weeks (Table D5). Results for the comparison of oral semaglutide 14 mg and empagliflozin 25 mg from PIONEER 2 are not available. Oral semaglutide flexible dose reduced total cholesterol and LDL-C more than sitagliptin 100 mg when added to one to two oral antihyperglycemic agents at 52 weeks (PIONEER 7).[50]

In PIONEER 6, examination of the curves of lipid levels suggest there were modest decreases in total cholesterol, LDL-C, and triglycerides and a modest increase in HDL-C with oral semaglutide 14 mg compared to placebo. In SUSTAIN 6, there were greater reductions in triglycerides and greater increases in HDL-C with injectable semaglutide 1.0 mg compared to placebo and greater reductions in total cholesterol and LDL-C with injectable semaglutide 0.5 mg compared to placebo at 104 weeks. In EMPA-REG, examination of the curves of lipid levels suggest there were modest increases HDL-C and decreases in LDL-C with empagliflozin; the effect on total cholesterol and triglycerides levels were not reported. The effect on lipid levels was not reported in LEADER or TECOS.

Adherence and Use of Rescue Medication

More patients treated with placebo compared to oral semaglutide 14 mg used rescue medication to control T2DM in PIONEER 4 (41.6% vs. 21.8%),[49] PIONEER 8 (31.0% vs. 15.5%),[42] and PIONEER 1 (15.2% vs 1.1%)[53](Table 3.7). There were also higher rates of rescue medication use with oral semaglutide 3 mg and 7 mg compared to placebo in PIONEER 1 and PIONEER 8 (Table 3.7).

In the head-to-head trials, the proportion of patients treated with oral semaglutide 14 mg who used rescue medication to control T2DM ranged from 21.8% to 28%.[48,49,54] The proportion of patients using rescue medication was similar for liraglutide 1.8 mg and oral semaglutide 14 mg (PIONEER 4, 18.7% vs. 21.8%)[49] and for empagliflozin 25 mg and oral semaglutide 14 mg (PIONEER 2, 21.5% vs 24.6%).[48] Numerically more patients treated with sitagliptin 100 mg used rescue medication during the trial compared to oral semaglutide 14 mg (PIONEER 3, 39.4% vs 28.0%).[54] In PIONEER 7, a similar proportion of patients treated with oral semaglutide flexible dose and sitagliptin 100 mg used rescue medication (20% vs. 24%).[50]

In all trials, the proportion of patients using rescue medication increased over the course of the trials (Table 3.7). In trials that evaluated multiple doses of oral semaglutide, there were higher rates of rescue medication with lower doses.

Rates of all-cause trial product discontinuation were higher with oral semaglutide 14 mg compared to placebo as well as all active comparators. In the head-to-head trials, all cause trial product

discontinuation rates with oral semaglutide 14 mg ranged from 15.4% to 19.1% and rates with active comparators ranged from 11% to 13.1% (Table 3.7).[48,49,54] In trials that evaluated multiple doses of oral semaglutide, there were lower rates of study drug discontinuation with lower doses. Gastrointestinal side-effects were the most common reason for study drug discontinuation with oral semaglutide 14 mg.

Table 3.7. Use of Rescue Medication and Discontinuation Rates

Trial	Arm	Rescue Medication			All-Cause D/C of Trial Product	Did Not Complete Trial
		Week 26	Week 52	Overall	End of Trial	End of Trial
Head-to-Head Trials						
PIONEER 2 52-week RCT MET	Semaglutide 14 mg	*Not currently available*		24.6	17.5	2.7
	Empagliflozin 25 mg			21.5	11.0	5.6
PIONEER 3 78-week RCT MET ± SU	Semaglutide 7 mg	2.4	15.7	35.4	15.0	6.4
	Semaglutide 14 mg	1.1	6.7	28.0	19.1	5.8
	Sitagliptin 100 mg	2.8	20.1	39.4	13.1	3.4
PIONEER 4 52-week RCT MET ± SGLT2i	Semaglutide 14 mg	3.5	7.0	21.8	15.4	2.8
	Liraglutide 1.8 mg	3.2	6.3	18.7	12.7	3.5
	Placebo	7.7	30.3	41.6	12.0	5.6
PIONEER 7 52-week RCT 1-2 Oral ADs	Semaglutide flexible	NR	3.2	20	16.6	4.7
	Sitagliptin 100 mg	NR	15.9	24	9.2	2.8
Placebo-Controlled Trials						
PIONEER 1 26-week RCT Diet & exercise	Semaglutide 7 mg	2.3	*N/A*		10.3	8.0
	Semaglutide 14 mg	1.1			13.7	6.9
	Placebo	15.2			10.7	4.5
PIONEER 8 52-week RCT Insulin therapy	Semaglutide 7 mg	*Not currently available*		16.5	18.7	4.9
	Semaglutide 14 mg			15.5	20.4	3.3
	Placebo			31.0	12.0	4.9

D/C: discontinuation, ETD: estimated treatment difference, MET: metformin, mg: milligram, N/A: not available, RCT: randomized controlled trial, SGLT-2i: SGLT-2 inhibitor, SU: sulfonylurea

All of CVOTs reported the proportion of patients using any rescue medication throughout the trial except for PIONEER 6 which only reported the proportions using specific types of rescue medication. Where reported, 19.5% to 21.7% of patients receiving active agents compared to 27.9% to 40.6% receiving placebo used any rescue medication throughout the trials with the largest between-arm difference observed in SUSTAIN 6 (Table 3.8). In PIONEER 6, over twice as many patients receiving placebo compared to those treated with oral semaglutide 14 mg used insulin, sulfonylureas, and SGLT-2 inhibitors during the trial; a roughly similar trend was observed in SUSTAIN 6 and EMPA-REG OUTCOME with the exception of no additional SGLT-2 inhibitor use allowed in EMPA-REG OUTCOME (Table 3.8). In LEADER and TECOS, more similar rates of rescue medication were observed with active agents and placebo.

The proportion of patients discontinuing the trial product was higher with active agents compared to placebo in all CVOTs except for TECOS in which there were similar rates of all-cause

discontinuation of the trial product between the arms (Table 3.8). The proportion of patients not completing the trial were generally similar between the placebo and active arms in all CVOTs (Table 3.8).

Table 3.8. Use of Rescue Medication* and Discontinuation Rates in CVOTs

Trial	Arm	Any Rescue Medication	Insulin	SU	SGLT-2 inhibitor	All-Cause D/C of Trial Product	Did Not Complete Trial
PIONEER 6	Oral Semaglutide 14 mg	NR	11.2	3.5	3.1	15.3	0.3
	Placebo	NR	23.6	7.8	7.0	9.8	0.4
SUSTAIN 6	Injectable Semaglutide 0.5/1.0 mg	20.1	9.4	3.7	2.7	21.2	1.5
	Placebo	40.6	24.0	7.7	5.6	18.8	2.4
LEADER	Liraglutide 1.8 mg	21.7	28.8	7.5	2.1	NR	3.0
	Placebo	29.1	43.2	10.8	2.8	NR	3.4
EMPA-REG OUTCOME	Empagliflozin 10/25 mg	19.5	5.8	3.8	N/A	26.5	3.2
	Placebo	31.5	11.5	7.0	N/A	23.1	2.7
TECOS	Sitagliptin 100 mg	21.7	9.7	NR	NR	22.5	4.9
	Placebo	27.9	13.2	NR	NR	23.2	5.9

*Rescue medication was defined as the use of any antihyperglycemic agent for three or more weeks in PIONEER 6 and SUSTAIN 6 and for one or more week in EMPA-REG OUTCOME; no criteria in TECOS or LEADER was identified, but insulin use was defined as use longer than three months in TECOS.

Key Measures of Benefit

The rates of MACE were numerically lower with oral semaglutide compared to placebo, but the difference was not statistically significant. Injectable semaglutide, liraglutide, and empagliflozin reduced MACE compared to placebo, while sitagliptin had no effect on MACE. An NMA found that semaglutide (oral and injectable) reduced MACE compared to sitagliptin; no statistically significant differences in MACE were found between semaglutide and liraglutide or empagliflozin.

3-Point MACE: Nonfatal stroke, Nonfatal MI, and CV Death

After a median follow-up of 1.3 years, 3-point MACE was lower with oral semaglutide 14 mg compared to placebo but the difference was not statistically significant (3.8% vs. 4.8%; HR 0.79, 95% CI: 0.57 to 1.11).[52] Point estimates for the components of MACE showed reductions in CV death (HR 0.49) and nonfatal stroke (HR 0.74) but an increase in nonfatal MI (HR 1.18). These component

analyses were not controlled for multiple testing or for the statistical non-significance of the overall HR for MACE.

After a median follow-up of 2.1 years, injectable semaglutide 0.5 mg/1.0 mg (pooled) reduced the risk for 3-point MACE compared with placebo (6.6% vs 8.9%; HR 0.74; 95% CI 0.58 to 0.95).[43] Although this overall estimate of reduction in MACE is similar to that seen with oral semaglutide, the point estimates of the components of MACE do not appear similar: CV death (HR 0.98), nonfatal stroke (HR 0.66), nonfatal MI (HR 0.74).

While the similar point estimates for overall MACE for oral and injectable semaglutide provide additional support for this benefit, the disparate estimates of the components make it appear that these are unlikely to be reliable and may reflect imprecision related to small numbers of events. This concern affected decisions below about how quantitative analyses used for comparative clinical effectiveness and economic modeling were performed.

In the CVOTs of comparator therapies, 3-point MACE was lower for liraglutide 1.8 mg compared to placebo after a median follow-up of 3.8 years (13.0% vs. 14.9%; HR 0.87; 95% CI 0.78 to 0.97)[46] and with empagliflozin 10 mg/25 mg (pooled) compared to placebo after a median follow-up of 3.1 years (10.5% vs. 12.1%; HR 0.86; 95% CI 0.74, 0.99).[44] The effect of sitagliptin 100 mg on 3-point MACE after 3.0 years was similar to placebo (10.2% vs 10.2%; HR 0.99; 95% CI: 0.89-1.10).[45]

Hospitalization for Heart Failure

Neither oral semaglutide 14 mg or injectable semaglutide 0.5 mg/1.0 mg clearly affected the risk for hospitalization for heart failure (HHF) compared to placebo (HR 0.86; 95% CI: 0.48 to 1.55 and HR 1.11; 95% CI: 0.77 to 1.61, respectively).[43,52] Of the comparators, there was a significant risk reduction with empagliflozin 10 mg/25 mg compared to placebo (HR 0.65; 95% CI: 0.50 to 0.85)[44], a nonsignificant risk reduction with liraglutide 1.8 mg compared to placebo (HR 0.87; 95% CI: 0.73 to 1.05),[46] and no difference between sitagliptin 100 mg and placebo (HR 1.00; 95% CI: 0.83 to 1.20).[45]

New or Worsening Nephropathy

The effect of oral semaglutide on nephropathy was not reported in PIONEER 6. In the SUSTAIN 6 trial of injectable semaglutide, the risk for new or worsening nephropathy, generally defined as persistent macroalbuminuria, doubling of serum creatinine level and creatinine clearance <45 mL/min/1.73 m^2, need for renal replacement therapy, or death due to renal disease, was significantly reduced with injectable semaglutide 0.5/1.0 mg compared to placebo (HR 0.64; 95% CI: 0.46 to 0.88).[43] Liraglutide 1.8 mg and empagliflozin 10 mg/25 mg reduced the risk for new or worsening nephropathy compared with placebo (HR 0.78; 95% CI 0.67 to 0.92 and HR 0.61; 95% CI 0.53 to 0.69, respectively).[44,46] The incidence of nephropathy was not reported in TECOS.

All-Cause Death

Compared to placebo, significant reductions in all-cause death were observed with oral semaglutide 14 mg (1.4% vs 2.8%; HR 0.51; 95%: 0.31 to 0.84), liraglutide 1.8 mg (8.2% vs. 9.6%; HR 0.85; 95% CI: 0.74 to 0.97), and empagliflozin 10/25 mg (5.7% vs 8.3%; HR 0.68; 95% CI: 0.57 to 0.82). Injectable

semaglutide 0.5 mg/1.0 mg and sitagliptin 100 mg had similar rates of all-cause death compared to placebo in their respective trials (3.8% vs 3.6%; HR 1.05; 95% CI: 0.74 to 1.50 and 7.4% vs. 7.3%; HR 1.01; 95% CI: 0.90 to 1.14, respectively).

Neuropathy

We did not find evidence from any of the included CVOTs on the incidence of neuropathy.

Table 3.9. Key Outcomes in Included CVOTs

	PIONEER 6	SUSTAIN 6	LEADER	EMPA-REG OUTCOME	TECOS
Median follow-up	1.3 years	2.1 years	3.8 years	3.1 years	3.0 years
CV death, nonfatal MI, or nonfatal stroke† HR (95% CI)	Oral SEM: 3.8% PBO: 4.8% 0.79 (0.57-1.11)	Inj SEM: 6.6% PBO: 8.9% 0.74 (0.58-0.95)	LIR: 13.0% PBO: 14.9% 0.87 (0.78-0.97)	EMP: 10.5% PBO: 12.1% 0.86 (0.74-0.99)	SIT: 10.2% PBO: 10.2% 0.99 (0.89-1.10)
All-cause death HR (95% CI)	Oral SEM: 1.4% PBO: 2.8% 0.51 (0.31-0.84)	Inj SEM: 3.8% PBO: 3.6% 1.05 (0.74-1.50)	LIR: 8.2% PBO: 9.6% 0.85 (0.74-0.97)	EMP: 5.7% PBO: 8.3% 0.68 (0.57-0.82)	SIT: 7.5% PBO: 7.3% 1.01 (0.90-1.14)
CV death HR (95% CI)	Oral SEM: 0.9% PBO: 1.9% 0.49 (0.27-0.92)	Inj SEM: 2.7% PBO: 2.8% 0.98 (0.65-1.48)	LIR: 4.7% PBO: 6.0% 0.78 (0.66-0.93)	EMP: 3.7% PBO: 5.9% 0.62 (0.49-0.77)	SIT 5.2% PBO: 5.0% 1.03 (0.89-1.19)
Nonfatal stroke HR (95% CI)	Oral SEM: 0.8% PBO: 1.0% 0.74 (0.35-1.57)	Inj SEM: 1.6% PBO: 2.7% 0.61 (0.38-0.99)	LIR: 3.4% PBO: 3.8% 0.89 (0.72-1.11)	EMP: 3.2% PBO: 2.6% 1.24 (0.92-1.67)	SIT 2.0%* PBO: 2.2% NR
Nonfatal MI HR (95% CI)	Oral SEM: 2.3% PBO: 1.9% 1.18 (0.73-1.90)	Inj SEM: 2.9% PBO: 3.9% 0.74 (0.51-1.08)	LIR: 6.0% PBO: 6.8% 0.88 (0.75-1.03)	EMP: 4.5% PBO: 5.2% 0.87 (0.70-1.09)	SIT 3.9%* PBO: 4.0% NR
Hospitalization for heart failure HR (95% CI)	Oral SEM: 1.3% PBO: 1.5% 0.86 (0.48-1.55)	Inj SEM: 3.6% PBO: 3.3% 1.11 (0.77-1.61)	LIR: 4.7% PBO: 5.3% 0.87 (0.73-1.05)	EMP: 2.7% PBO: 4.1% 0.65 (0.50-0.85)	SIT: 3.1% PBO: 3.1% 1.00 (0.83-1.20)
Nephropathy HR (95% CI)	Not reported	Inj SEM: 3.8% PBO: 6.1% 0.64 (0.46-0.88)	LIR: 5.7% PBO: 7.2% 0.78 (0.67-0.92)	EMP: 11.2% PBO: 16.6% 0.61 (0.53-0.69)	Not reported

*Only reported as the number of patients with event contributing to secondary composite outcome (3-point MACE)

Network Meta-Analysis

We conducted network meta-analyses (NMAs) to compare oral semaglutide 14 mg to our active comparators of interest on CV and microvascular outcomes since these key benefits were not measured in the head-to-head PIONEER trials. For CV outcomes, we chose to analyze 3-point MACE and not the individual components due to the small number of events that occurred in some trials; we did not attempt to analyze all-cause death for similar concerns. In addition to 3-point MACE, we also analyzed hospitalization for heart failure (HHF) to understand the CV effects of these agents. For microvascular outcomes, we analyzed new or worsening nephropathy. In the absence of long-term outcomes data, we did not analyze retinopathy. In our NMAs, we included data from both PIONEER 6 and SUSTAIN 6 to inform the CV and renal benefits of semaglutide as a molecule. Results from a 26-week, open-label Phase II dose-finding trial showed oral semaglutide 20 mg and 40 mg had similar effects on HbA1c and body weight compared to injectable semaglutide 1.0 mg, while the 10 mg dose of oral semaglutide showed slightly lower changes in HbA1c and body weight compared to injectable semaglutide 1.0 mg.[55] Although this trial provides information around the

effect of oral semaglutide compared to injectable semaglutide on intermediate outcomes, there is still uncertainty of the comparability of these two formulations of semaglutide on key measures of benefit. We conducted a random effects meta-analysis of 3-point MACE and HHF results from PIONEER 6 and SUSTAIN 6 to estimate the overall effect of semaglutide; for nephropathy, we used data from SUSTAIN 6 in our analyses as no data were reported in PIONEER 6. Results from the random effects meta-analysis are reported in Appendix Table D11.

The uncertainty of whether oral and injectable formulations of semaglutide have the same effect on key benefits, along with differences in trial lengths, sample size, and enrollment criteria among all included CVOTs raise concerns about the validity of our analysis. We acknowledge these limitations and emphasize the need to interpret the results with caution.

Results from our NMA showed overall semaglutide (both oral and injectable) significantly reduced the risk for 3-point MACE compared to sitagliptin 100 mg (HR 0.77; 95% CI: 0.61 to 0.96). Results also showed a nonsignificant risk reduction of semaglutide compared to empagliflozin 10/25 mg (HR 0.88; 95% CI 0.69 to 1.13) and liraglutide 1.8 mg (HR 0.87; HR 0.70 to 1.09). Empagliflozin 10 mg/25 mg significantly reduced the risk for HHF compared to semaglutide (HR 0.63; 95% CI: 0.42 to 0.95). There were no significant differences with semaglutide and any of the active comparators of interest on nephropathy (Appendix Table D17) .

Table 3.10. League Table of Hazard Ratios for 3-point MACE

Semaglutide	1.13 (0.89, 1.44)	1.14 (0.91, 1.43)	**1.3 (1.04, 1.63)**	**1.32 (1.08, 1.6)**
0.88 (0.69, 1.13)	**Empagliflozin**	1.01 (0.84, 1.21)	1.15 (0.96, 1.38)	**1.16 (1.01, 1.34)**
0.87 (0.7, 1.09)	0.99 (0.82, 1.18)	**Liraglutide**	1.14 (0.98, 1.32)	**1.15 (1.03, 1.28)**
0.77 (0.61, 0.96)	0.87 (0.73, 1.04)	0.88 (0.75, 1.02)	**Sitagliptin**	1.01 (0.91, 1.12)
0.76 (0.63, 0.93)	**0.86 (0.74, 0.99)**	**0.87 (0.78, 0.97)**	0.99 (0.89, 1.1)	**Placebo**

Data are hazard ratio (95% credible interval). Estimates in bold signify that the 95% credible interval does not contain one.

Table 3.11. League Table of Hazard Ratios for Hospitalization for Heart Failure

Semaglutide	**0.63 (0.42, 0.95)**	0.84 (0.59, 1.21)	0.97 (0.68, 1.4)	0.97 (0.71, 1.32)
1.59 (1.05, 2.38)	**Empagliflozin**	1.34 (0.97, 1.85)	**1.54 (1.11, 2.13)**	**1.54 (1.18, 2.01)**
1.18 (0.83, 1.7)	0.75 (0.54, 1.03)	**Liraglutide**	1.15 (0.89, 1.49)	1.15 (0.96, 1.38)
1.03 (0.72, 1.48)	**0.65 (0.47, 0.9)**	0.87 (0.67, 1.13)	**Sitagliptin**	1 (0.83, 1.2)
1.03 (0.76, 1.4)	**0.65 (0.5, 0.85)**	0.87 (0.72, 1.04)	1 (0.83, 1.2)	**Placebo**

Data are hazard ratio (95% credible interval). Estimates in bold signify that the 95% credible interval does not contain one.

Health-Related Quality of Life and Patient-Reported Outcomes

The impact of oral semaglutide on health-related quality of life (HRQoL) outcomes and patient reported outcomes (PROs) were not reported in PIONEER 6 and were variably measured in the head-to-head PIONEER trials. PIONEER 3 and 7 measured the change from baseline in the Short

Form-36 Version 2 (Acute Version). In PIONEER 3, oral semaglutide 14 mg did not improve scores in any domain more than sitagliptin 100 mg; the only significant improvement observed with any dose of oral semaglutide compared to sitagliptin 100 mg was with oral semaglutide 7 mg at 78 weeks on the physical functioning domain. In PIONEER 7, oral semaglutide flexible dose did not result in any improvements compared to sitagliptin 100 mg.

PIONEER 4 and 7 measured the change in the Diabetes Treatment Satisfaction Questionnaire scores. In PIONEER 4, oral semaglutide 14 mg resulted in greater improvements in the total score compared to placebo but not liraglutide 1.8 mg at both 26 and 52 weeks. In PIONEER 7, there was no difference in the improvement in total score with oral semaglutide flexible dose compared to sitagliptin 100 mg.

PIONEER 3 also measured changes in the Impact of Weight on Quality of Life Questionnaire and the Control of Eating Questionnaire. The only significant improvement with any dose of oral semaglutide compared to sitagliptin 100 mg on the total Impact of Weight on Quality of Life score was with oral semaglutide 7 mg at 52 weeks; a significant improvement was not seen at 78 weeks. There were no significant changes with any dose of oral semaglutide compared to sitagliptin 100 mg on the Control of Eating Questionnaire domains.

PIONEER 1 did not measure any HRQoL outcomes or PROs, and data for PIONEER 2 and PIONEER 8 are not available.

Harms

Adverse events experienced with oral semaglutide were generally mild to moderate in severity. Gastrointestinal effects including nausea, vomiting, and diarrhea were the most common adverse events experienced with oral semaglutide. A considerable portion of patients discontinued oral semaglutide due to adverse events, specifically gastrointestinal events. Semaglutide may increase rates of retinopathy.

In the head-to-head PIONEER trials, the rate of adverse events with oral semaglutide 14 mg ranged from 70.5% to 80% compared to 69.2% to 83.3% with the comparator therapies. Most adverse events were mild-to-moderate in severity, and the most common adverse events were related to gastrointestinal disorders. Across the head-to-head trials, the rate of nausea with oral semaglutide 14 mg ranged from 15.1% to 20%. Liraglutide 1.8 mg had a similar rate of nausea in PIONEER 4 (18%), while empagliflozin 25 mg and sitagliptin 100 mg had lower rates (2.4% and 6.9%, respectively). Diarrhea was also commonly reported among patients receiving oral semaglutide 14 mg, ranging from 9.3% to 15%, as was vomiting, ranging from 7.3% to 9%; rates were lower with comparator therapies for both events. In PIONEER 7, similar rates of adverse events occurred with oral semaglutide flexible dose compared to oral semaglutide 14 mg in other trials. In PIONEER 1, the rate of adverse events was lower compared to the head-to-head trials (56.6% vs 55.6% for oral semaglutide 14 mg and placebo, respectively), and the most common adverse events were also related gastrointestinal disorders (Table 3.12). In PIONEER 8, more patients treated with oral

semaglutide 14 mg compared to placebo experienced adverse events (83.4% vs. 75.5% for oral semaglutide 14 mg vs. placebo, respectively); limited data are currently available for PIONEER 8.

In the trials evaluating multiple doses of oral semaglutide, the 3 mg and 7 mg doses had similar rates of overall adverse events compared to the 14 mg dose, but the rate of gastrointestinal adverse events were generally lower. Across the trials, the rate of severe hypoglycemia was low (<1%). The rate of any hypoglycemia (i.e., blood-glucose confirmed symptomatic or severe) was also generally low with the highest rates observed in trials in which around half of the patients were receiving background sulfonylurea therapy (PIONEER 3 and 7).

In the head-to-head trials, adverse events leading to discontinuation of the study drug occurred in approximately 11% of patients treated with oral semaglutide 14 mg compared to 4% to 5.2% of patients treated with comparator therapies. In PIONEER 7, the rate of adverse events leading to discontinuation were slightly lower with oral semaglutide flexible dose (9%) as compared to the rates observed with oral semaglutide 14 mg. The rate of discontinuation of oral semaglutide 14 mg was 7.4% in PIONEER 1 and 13.3% in PIONEER 8 compared to approximately 2% to 3% with placebo. The most common adverse events leading to discontinuation of oral semaglutide across all trials were related to gastrointestinal disorders. In the Phase II dose-finding trial, there were generally similar rates of adverse events including gastrointestinal effects for most doses of oral semaglutide compared to injectable semaglutide.[55]

In the head-to-head trials, the incidence of SAEs ranged from 6.6% to 11% with oral semaglutide 14 mg compared to 8% to 12.4% with comparator therapies. In PIONEER 7, 9% of patients treated with semaglutide flexible dose experienced SAEs compared to 10% with placebo. In both PIONEER 1 and PIONEER 8, oral semaglutide 14 mg was shown to have lower rates of SAEs compared to placebo. In trials that evaluate multiple doses of oral semaglutide, there was no clear pattern of fewer SAEs with lower doses. Across all trials, the rate of death was low with the highest incidence reported in PIONEER 4 (1.1% for oral semaglutide).

Table 3.12. Safety in the PIONEER Trials

Arm	PIONEER 1			PIONEER 2		PIONEER 3			PIONEER 4			PIONEER 7		PIONEER 8		
	SEM 7 mg	SEM 14 mg	PBO	SEM 14 mg	EMP 25 mg	SEM 7 mg	SEM 14 mg	SIT 100 mg	SEM 14 mg	LIR 1.8 mg	PBO	SEM flex	SIT 100 mg	SEM 7 mg	SEM 14 mg	PBO
Week	26			52		78			52			52		52		
Any AE	53.1	56.6	55.6	70.5	69.2	78.2	79.6	83.3	80	74	67	78	69	78.5	83.4	75.5
SAE	1.7	1.1	4.5	6.6	9.0	10.1	9.5	12.4	11	8	11	9	10	10.5	6.6	9.2
Death	0	0	0	0	0.2	0.6	0.2	0.6	1.1	1.4	0.7	0	0.4			
Severe AE	0.6	1.7	2.8	5.9	5.6	8.0	8.6	11.4	8	8	5	6	7			
AE leading to D/C	4.0	7.4	2.2	10.7	4.4	5.8	11.6	5.2	11	9	4	9	3	8.8	13.3	2.7
GI AE leading to D/C	2.3	5.1	0.6	8.0	0.7	3.4	6.9	2.6	8	6	2	6	1			
Hypoglycemia	1.1	0.6	0.6	1.7	2.0	5.2	7.7	8.4	1	2	2	5.5	5.6			
Severe hypoglycemia	0.6	0	0	0.2	0.2	0	0.2	0.9	0	0	0	0	0			
Nausea	5.1	16	5.6	19.8	2.4	13.4	15.1	6.9	20	18	4	21	2			
Diarrhea	5.1	5.1	2.2	9.3	3.2	11.4	12.3	7.9	15	11	8	9	3			
Vomiting	4.6	6.9	2.2	7.3	1.7	6.0	9.0	4.1	9	5	2	6	1			
Headache	5.7	5.1	5.1	—	—	6.5	8.0	7.7	9	6	6	10	6			
Decreased appetite	1.7	5.1	0.6	5.1	0.5	3.0	6.9	3.0	6	7	0	—	—			
Urinary tract infection	—	—	—	—	—	4.5	4.9	5.6	0.4	0.4	0	—	—			
Diabetic retinopathy	3.4	1.1	1.7	—	—	5.2	3.4	5.8	2.8	1.1	1.4	1.2	1.6			

AE: adverse event, D/C: discontinuation, EMP: empagliflozin, GI: gastrointestinal, LIR: liraglutide, mg: milligram, PBO: placebo, SAE: severe adverse event, SIT: sitagliptin

*Severe or blood-glucose confirmed symptomatic

Safety parameters were variably reported in the CVOTs. Similar proportions of patients experienced any adverse event in the active and placebo arms in SUSTAIN 6 (injectable semaglutide), LEADER (liraglutide), and EMPA-REG OUTCOME (empagliflozin); these rates were not reported in PIONEER 6 (oral semaglutide) or TECOS (sitagliptin). Compared to placebo, AEs leading to discontinuation occurred more frequently in patients treated with oral semaglutide, injectable semaglutide, and liraglutide and less frequently with empagliflozin in their respective trials; the rate was not reported for sitagliptin. For both oral and injectable semaglutide, the majority of AEs leading to discontinuation were reported to be related to gastrointestinal effects.

SAEs were reported in numerically more patients treated with placebo compared to active agents in PIONEER 6, SUSTAIN 6, LEADER and EMPA-REG OUTCOME; the majority of SAEs were related to cardiac disorders. The rate of SAEs was not reported in TECOS. Where reported, the rates of acute kidney injury, acute renal failure, and acute pancreatitis were numerically lower with active agents compared to placebo, except for the rate of acute pancreatitis with sitagliptin in TECOS. Acute gallstone disease occurred in more patients treated with empagliflozin compared to placebo in EMPA-REG OUTCOME (3.1% vs 1.9%, respectively). The rate of complicated urinary tract infections was similar with empagliflozin and placebo (1.7% vs 1.8%, respectively), although there was a higher incidence of urosepsis with empagliflozin (0.4% vs 0.1%).

Retinopathy

The proportion of patients experiencing adverse events related to diabetic retinopathy was higher with oral semaglutide 14 mg compared to placebo (7.1% vs 6.3%); no statistical test comparing these rates were reported. Most events were categorized as nonproliferative (89%) and did not require additional therapy (76%). Treatment with injectable semaglutide 0.5 mg/1.0 mg resulted in an increased risk for retinopathy compared to placebo, defined as vitreous hemorrhage, new onset diabetes-related blindness, or need for new treatment (3.0% vs 1.8%; HR 1.76; 95% CI 1.11 to 2.78). Under the same definition, liraglutide 1.8 mg showed a nonsignificant increased risk for retinopathy compared to placebo (2.3% vs 2.0%; HR 1.15; 95% CI: 0.87 to 1.52), and empagliflozin 10 mg/25 mg showed a nonsignificant reduction compared to placebo (1.6% vs 2.1%; HR 0.78; 95% CI: 0.54 to 1.12)[47]. Numerically more patients treated with sitagliptin 100 mg experienced adverse events related to diabetic retinopathy compared to those receiving placebo (2.8% vs. 2.0%); no statistical test comparing these rates was reported.

Table 3.13. Safety in CVOTs

Trial	PIONEER 6		SUSTAIN 6		LEADER		EMPA-REG OUCTOME		TECOS	
Arm	SEM 14 mg	PBO	SEM 0.5/1.0	PBO	LIR 1.8 mg	PBO	EMPA 10/25	PBO	SIT 100 mg	PBO
Any AE	NR	NR	89.4	90.0	62.3	60.8	90.2	91.7	NR	NR
GI AE	NR	NR	51.5	35.4	NR	NR	NR	NR	NR	NR
SAE	18.9	22.5	34.3	38.0	49.7	50.4	38.2	42.3	NR	NR
AE leading to D/C	11.6	6.5	13.0	6.7	9.5	7.3	17.3	19.4	NR	NR
GI AE leading to D/C	6.8	1.6	7.5	1.1	NR	NR	NR	NR	NR	NR
Acute kidney injury	2.0	2.3	NR	NR	NR	NR	1.0	1.6	NR	NR
Acute renal failure	NR	NR	4.0	4.2	NR	NR	5.2	6.6	1.4	1.5
Acute pancreatitis	0.1	0.2	0.6	0.8	0.4	0.5	NR	NR	0.3	0.2
Severe hypo-glycemia	1.4	0.8	NR	NR	2.4	3.3	1.3	1.5	2.2	1.9
Malignant neoplasms	2.6	3.0	4.0	4.2	6.3	6.0	NR	NR	NR	NR
Thyroid neoplasms	0.1	0	0.1	0.1	0.1	0.1	NR	NR	NR	NR

AE: adverse event, D/C: discontinuation, EMP: empagliflozin, GI: gastrointestinal, LIR: liraglutide, mg: milligram, NR: not reported, PBO: placebo, SAE: severe adverse event, SIT: sitagliptin

Subgroups

We found evidence on the efficacy and safety of oral semaglutide in two of our prespecified subgroups of interest: patients at high risk for CV events and patients with moderate renal impairment. Data informing the effect of oral semaglutide in patients at high risk for CV events were primarily derived from PIONEER 6 which is discussed above. We did not find evidence stratified by line of therapy.

Moderate Renal Impairment

PIONEER 5 was a 26-week double-blind trial of oral semaglutide 14 mg versus placebo conducted in patients with moderate renal impairment (eGFR of 30-59 mL/min/1.73m^2).[51] Of the enrolled population, 60% had stage 3A CKD (eGFR 45-59 mL/min/1.73m^2), and 40% had stage 3B CKD (eGFR 30-44 mL/min/1.73m^2). The mean age at baseline was 70 years, mean duration of diabetes was 14.0 years, and mean HbA1c was 8.0%. The primary outcome was change in HbA1c at 26 weeks.

In PIONEER 5, compared to placebo patients treated with oral semaglutide 14 mg had greater reductions in HbA1c (-1.0% vs -0.2%) and body weight (-3.4 kg vs -0.9 kg) at 26 weeks.[51] At 26 weeks, more patients on oral semaglutide 14 mg achieved an HbA1c<7.0% (57.8% vs 22.6%) and had weight loss ≥5.0% (35.7% vs 9.7%). Over the course of the trial, renal function appeared to remain consistent from baseline: the median ratio of eGFR at 31 weeks compared with baseline with oral semaglutide was 1.02 (range 0.27-1.96) and with placebo was 1.00 (range 0.68-2.17). A higher proportion of patients on oral semaglutide 14 mg discontinued the study drug due to adverse events compared with placebo (15% vs. 5%). Approximately 75% of patients on oral semaglutide experienced an adverse event compared to 68% for placebo; there were similar rates of SAEs in both arms (12% vs. 11%).

Controversies and Uncertainties

The highest quality evidence comparing semaglutide with newer antidiabetic agents comes from the PIONEER trials that involved head-to-head comparisons. While these trials clearly show greater reductions in blood glucose with semaglutide than with empagliflozin and sitagliptin, this is a surrogate outcome. The most important clinical outcomes, including CV outcomes and renal outcomes, could only be assessed by indirect comparisons that are potentially susceptible to effect modification, particularly given the differences at baseline in the populations studied.

The CVOT of oral semaglutide was shorter than the comparator CVOTs. In comparing results, we are assuming that the proportional hazards assumption holds. Additionally, in combining results from the CVOTs of oral and injectable semaglutide and using results of injectable semaglutide to make inferences about the renal effects of oral semaglutide, we are assuming these inferences are reasonable because the therapies are similar. However, it is possible that the different absorption patterns of injectable and oral medications could result in different biologic effects.

In looking at the comparators from the PIONEER studies, we are assuming in part that these comparators provide some information about the classes they represent: DPP-4 inhibitors, SGLT-2 inhibitors, and injectable GLP-1 receptor agonists. While some systematic reviews of these agents suggest this is generally reasonable,[56] it creates another level of indirectness in assessing the benefits and harms of oral semaglutide.

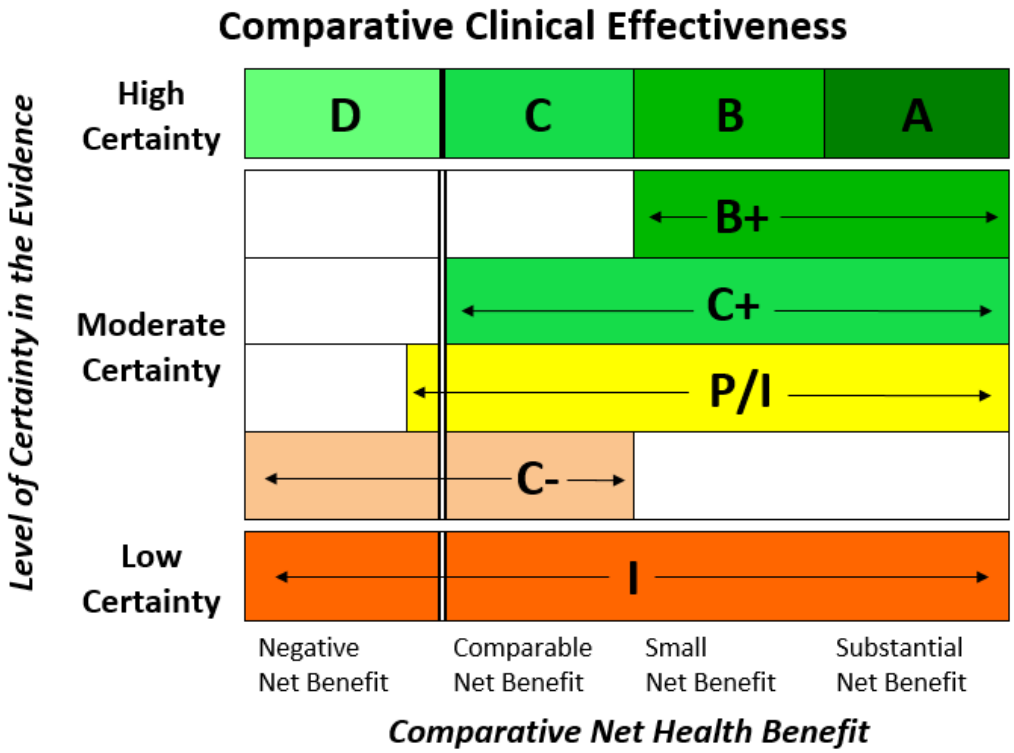
Adherence in the real world is important to the effectiveness of the therapies under review. The higher rates of gastrointestinal side effects with GLP-1 receptor agonists, including oral semaglutide, is likely to result in higher rates of discontinuation in real world use than in clinical trials. Thus, randomized trials may overstate the real-world comparative effectiveness of these therapies. Additionally, oral semaglutide is administered on an empty stomach, which may affect adherence and acceptability.

Both injectable and oral semaglutide were shown to have numerically higher rates of diabetic retinopathy events compared to placebo in CVOTs, with a significant risk increase reported for injectable semaglutide (HR 1.76).[43] A manufacturer-sponsored post-hoc analysis suggested the increased risk for retinopathy could be partly attributed to rapid reductions in HbA1c during the first 16 weeks of treatment; the mean reductions with injectable semaglutide 1.0 mg were -1.8% compared to -1.4% for patients experiencing diabetic retinopathy complications and the overall trial population, respectively.[57] Patients who developed diabetic retinopathy complications throughout the trial generally had pre-existing diabetic retinopathy and higher mean HbA1c levels at baseline. An increased risk for retinopathy has not been consistently shown in other trials of GLP-1 receptor agonists. The ongoing FOCUS trial is a five-year blinded trial that is measuring the effects of injectable semaglutide on diabetic eye disease (Appendix C).

Additionally, rates of rare harms may be important in assessing the comparative effectiveness of the therapies under review, but randomized trials provide only limited evidence in this regard. GLP-1 receptor agonists, including oral semaglutide, may induce thyroid tumors, and SGLT-2 inhibitors can cause severe genitourinary infections and may increase the risk for diabetic ketoacidosis and limb amputations. Full understanding of the rates of these adverse events could influence patient and clinician decisions in choosing between these options.

3.4 Summary and Comment

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable" *- High certainty of a comparable net health benefit*
D = "Negative" *- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

In this review, we compared oral semaglutide to an injectable GLP-1 receptor agonist (liraglutide), an SGLT-2 inhibitor (empagliflozin), and DPP-4 inhibitor (sitagliptin). We have evidence on blood glucose control, weight change, common side effects, and adherence from head-to-head

randomized trials for each of these comparisons. However, evidence on important macrovascular and microvascular outcomes is indirect, and there is significant statistical uncertainty in these comparisons as well as uncertainties created by the trials being performed in different populations. Additionally, we are uncertain on the impact of semaglutide on retinopathy both in the short and long term. We are rating the evidence for the comparison between the 14 mg daily dose of oral semaglutide as this was the primary dose evaluated in the CVOT.

For the comparison between oral semaglutide and liraglutide, semaglutide appears to result in greater reductions in HbA1c and body weight. Point estimates of MACE were lower with semaglutide, but confidence in this comparison is low. Gastrointestinal side effects appeared somewhat more common with semaglutide raising potential concerns about adherence. Overall, given the similar mechanism of action and the improved blood glucose control and body weight, but taking into account uncertainty about MACE and about real world adherence, we judge that we have moderate certainty that oral semaglutide provides comparable, small, or substantial net health benefit compared with liraglutide, but that there is a small likelihood of worse net health benefit and so judge oral semaglutide promising but inconclusive ("P/I") for this comparison.

For the comparison between oral semaglutide and empagliflozin, semaglutide lowers HbA1c and controls blood glucose better than empagliflozin with similar effects on weight. Point estimates of MACE were lower with semaglutide, but confidence in this comparison is low. Empagliflozin and injectable semaglutide appear to have similar effects on nephropathy; we do not have evidence on oral semaglutide. Hospitalization for heart failure appears to be lower with empagliflozin and we have moderate confidence in this comparison. Rates of discontinuation are higher with semaglutide, with much higher rates of gastrointestinal side effects. Rare, severe genitourinary infection risk could affect patient choices about using empagliflozin, however we have no good estimates of risk. Given these competing risks and benefits, overall we have low certainty in the net health benefit of oral semaglutide compared with empagliflozin and judge the evidence insufficient ("I").

For the comparison between oral semaglutide and sitagliptin, semaglutide lowers HbA1c and controls blood glucose better than sitagliptin and also results in greater reductions in weight. Semaglutide appears to reduce MACE while sitagliptin appears to have no effects on MACE, and confidence in this comparison is moderate. Rates of discontinuation are higher with semaglutide with higher rates of gastrointestinal side effects. Although overall benefits appear greater with semaglutide, we have some concerns about adherence in the real world given the higher rates of side effects. As such, we have moderate certainty that oral semaglutide provides a small or substantial net health benefit compared with sitagliptin, with high certainty of at least a small net health benefit and judge oral semaglutide incremental or better ("B+") for this comparison.

For the comparison between oral semaglutide and continued background therapy in patients inadequately controlled on background therapy, we have high quality evidence that semaglutide

improves blood glucose control and lowers weight. We have moderate quality evidence that semaglutide improves MACE, however that certainty is increased by extrapolating from evidence on injectable semaglutide. Semaglutide has significant rates of gastrointestinal side effects and, as mentioned, may increase the risk of retinopathy. Overall, we judge that we have high certainty that oral semaglutide provides substantial net health benefits compared with continuing background therapy alone in patients inadequately controlled on background therapy and judge oral semaglutide superior ("A") for this comparison.

Table 3.14. Evidence Ratings

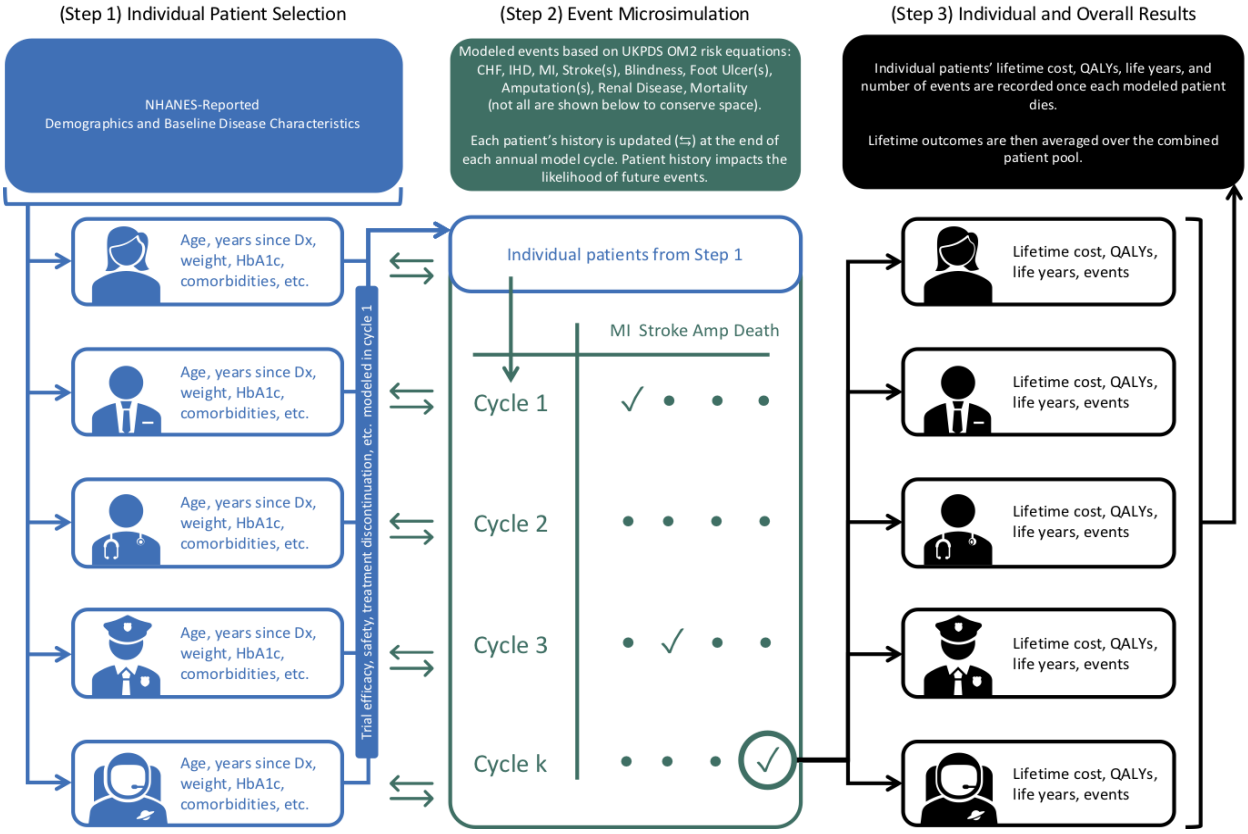
Comparison	ICER Evidence Rating
Oral semaglutide vs. *liraglutide*	Moderate certainty of a comparable, small, or substantial net health benefit, with a small likelihood of worse net health benefit ("P/I")
Oral semaglutide vs. *empagliflozin*	Low certainty in the net health benefit ("I")
Oral semaglutide vs. *sitagliptin*	Moderate certainty of a small or substantial net benefit, with high certainty of at least a small net benefit ("B+")
Oral semaglutide vs. *ongoing background therapy*	High certainty of a substantial net benefit ("A")

4. Long-Term Cost Effectiveness

4.1 Overview

The primary aim of this analysis was to estimate the lifetime cost effectiveness of oral semaglutide added to current antihyperglycemic treatment for T2DM using a decision analytic model. Oral semaglutide added to current antihyperglycemic treatment was separately compared to four modeled comparators, including: (1) ongoing background antihyperglycemic treatment (e.g., metformin with or without sulfonylureas), (2) sitagliptin, (3) empagliflozin, and (4) liraglutide; comparators (2), (3), and (4) are also added to current antihyperglycemic treatment. The model estimates outcomes that include life years (LYs) gained as an estimate of equal value life years gained (evLYGs), QALYs gained, clinical events, cost per MACE avoided, and total costs for each intervention over a lifetime time horizon. The base-case analysis used a health care sector perspective (i.e., direct medical care costs only), and a lifetime time horizon. All costs and outcomes were discounted at 3% per year. We modeled a variety of scenarios beyond the base case, and plan to also include a modified societal perspective in a future version of the report. The analytic framework for this assessment is depicted in Figure 4.1 below.

Figure 4.1. Model Framework



4.2 Methods

We developed an adaptation of a published microsimulation model[58] based on the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model 2 (OM2)[59] for this evaluation, informed by the PIONEER clinical trials,[42,48-54] relevant quality of life literature,[60,61] and other prior economic models.[62-66] The model was developed in Microsoft® Excel® for Office 365 (Version 1906).

Model Structure

The model (Figure 4.1) is an individual patient-level, Monte Carlo-based microsimulation of costs, quality of life, clinical events, and mortality associated with T2DM among adults in the US diagnosed with the disease. This modeling approach was chosen due to the complexity of co-occurring co-morbidities in people with T2DM. Three modeling steps were used: (1) individual patient simulation of PIONEER trial results; (2) event microsimulation; and (3) calculation of mean results from the pool of simulated patients' lifetime outcomes. Simulated patients were run through the modeling steps for each comparator versus oral semaglutide added to current ongoing background antihyperglycemic treatment. The three model steps are explained below:

(1) Individual patient simulation of trial results. Individual patients with T2DM from the 2013-14 and 2015-16 NHANES survey populations were extracted using patient demographics and clinical characteristics.[58] In the first model cycle, we utilized the UKPDS OM2 risk equations[59] for the individual components of MACE and nephropathy to estimate the risk of these events in the ongoing background antihyperglycemic treatment comparator. We applied the hazard ratio results from the network meta-analysis (NMA) of CV and renal outcomes to estimate these outcomes among patients treated with oral semaglutide, sitagliptin, empagliflozin, and liraglutide. We also applied the results of the PIONEER trials for HbA1c change, weight change, hypoglycemia, and trial discontinuation due to adverse events during this first cycle.

(2) Event microsimulation. Each simulated patient from step 1 was then sequentially run through the event microsimulation. Each model cycle was one year in duration. The UKPDS OM2 risk equations[59] were used along with hazard ratios from the NMA of CV and renal outcomes to calculate the incidence of a clinical event and/or mortality in each year until the simulated patient died. We also included modules to account for (a) gradual increases in HbA1c and weight, (b) hypoglycemia, and (c) the addition of or transition to insulin treatment. All event and/or mortality associated costs and health state utility weights were applied concurrently. The UKPDS OM2 risk equations account for patient history upon entering the model as well as new clinical events that occurred during the microsimulation.

(3) Calculation of mean results. After each simulated patient died, the model recorded the patient's lifetime cost, QALYs, life years, and clinical event history. Each outcome was then

averaged over the entire pool of simulated patients to derive overall model results. Unlike a traditional Markov cohort model with deterministic results, we performed 2,500 microsimulations per patient (1,862,500 total simulations) to get each base-case result plus a 95% credible range (CR); the number of simulations was chosen to ensure statistical convergence.

Target Population

The population of interest for this review was adults with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s). Therefore, we utilized a representative population of patients from the U.S., drawing patient-level data from the NHANES program, which surveys approximately 5,000 people across the U.S. each year in two-year survey populations. The survey population consists of people from counties across the U.S.[67] A cohort of U.S. adults aged ≥30 years with self-reported diabetes from NHANES 2013-14 and 2015-16 surveys (n=745) served as the population for our microsimulations. The demographic and clinical characteristics of the patient population for our microsimulations are summarized in Table 4.1.

Table 4.1. Base-Case Model Cohort Characteristics

NHANES 2013-14 and 2015-16 Diabetes Patient Characteristics (n=745)	Value
Age (years), mean (SD)	62.7 (12.8)
Female, %	47.9%
Black Race, %	44.0%
Current Smoker, %	33.3%
Duration of Diabetes (years), mean (SD)	11.7 (9.6)
Body Mass Index (kg/m^2), mean (SD)	33.5 (7.8)
Estimated Glomerular Filtration Rate (ml/min/m^2), mean (SD)	77.5, (29.4)
Hemoglobin A1c (%), mean (SD)	7.4 (1.8)
Myocardial Infarction, %	11.8%
Stroke, %	0.2%
Heart Failure, %	11.8%
Ischemic Heart Disease, %	11.5%
Angina, %	7.1%
Renal Complications, %	19.3%

SD: standard deviation

Treatment Strategies

We compared the treatment of patients with oral semaglutide added to background treatment to each of the following treatments:

- Ongoing background antihyperglycemic treatment (e.g., metformin with or without sulfonylureas) alone
- Sitagliptin (Januvia, Merck), a DPP-4 inhibitor, added to ongoing background treatment
- Empagliflozin (Jardiance, Boehringer Ingelheim and Eli Lilly), a SGLT-2 inhibitor, added to ongoing background treatment
- Liraglutide (Victoza, Novo Nordisk), an injectable GLP-1 receptor agonist, added to ongoing background treatment

The three add-on agents were chosen in part because they were active comparators in the trials of oral semaglutide and to ensure that the comparisons included one agent from each class of the newer T2DM medications. Doses for each treatment used in the model are shown in Table 4.2.

Table 4.2. Treatment Regimen Modeled Dosages

	Oral Semaglutide	Sitagliptin	Empagliflozin	Liraglutide
Brand Name		Januvia®	Jardiance®	Victoza®
Manufacturer	Novo Nordisk	Merck	Boehringer Ingelheim & Eli Lilly	Novo Nordisk
Route of Administration	oral	oral	oral	subcutaneous
Dosing	14 mg daily	100 mg daily	10 mg or 25 mg daily	1.8 mg daily

mg: milligram

Key Model Characteristics and Assumptions

Key model assumptions are listed in Table 4.3, along with the rationale for each.

Table 4.3. Key Model Assumptions

Assumption	Rationale
The incremental rate of kidney function decline, MACE, and congestive heart failure (CHF) is independent of patient characteristics including HbA1c control.	Contemporary clinical trials have demonstrated an independent relationship between T2DM treatments and both renal failure and MACE beyond the impact based on changes in HbA1c.
Hazard ratio adjustment of UKPDS OM2 risk estimates for MACE and renal outcomes, based on NMA results, was maintained over each patient's lifetime.	Long-term effectiveness is currently unknown.
The relative risks of MACE and renal outcomes between the treatment regimens are uniformly distributed across all people with T2DM.	Effectiveness in non-trial populations is currently unknown, but the relative effectiveness is assumed to be similar across patient populations.
In model cycle 1, HbA1c change, weight change, severe hypoglycemia, and trial discontinuation due to adverse event were modeled independently of NHANES patient characteristics.	It Is impossible to predict which individual patients will experience a given outcome or to what degree. Therefore, we assigned each individual's cycle 1 outcome(s) based on a random draw from each outcome parameter's probabilistic distribution.
All patients entering the model are assumed to have no prior history of amputation(s), blindness, foot ulcer(s), or hypoglycemia.	Patient history of these outcomes was not reported in NHANES data.
Atrial fibrillation and peripheral artery disease, which have UKPDS OM2 coefficients and are thus necessary inputs, are independently simulated for each patient based on national incidence estimates that is non-specific to T2DM.	Patient history of these outcomes was not reported in NHANES data.
The model did not capture any cost or disutility from adverse events other than hypoglycemia.	The PIONEER trials do not present disaggregated adverse event data, and we chose not to assign a nonspecific cost and disutility for the aggregated adverse events.

Model Inputs

Clinical Inputs

Clinical inputs regarding the efficacy of oral semaglutide compared to ongoing background antihyperglycemic treatment, sitagliptin, empagliflozin, and liraglutide on intermediate outcomes such as HbA1c and body weight were derived from the head-to-head PIONEER trials.[48,49,54] We also utilized the NMA of PIONEER 6, SUSTAIN 6, and the comparator CVOTs[44-46,52] to obtain hazard ratios

for each comparator for MACE, CHF, and renal failure outcomes (Table 4.4); hazard ratios were applied to the UKPDS OM2 estimated baseline rate from each NHANES patient's individual characteristics (utilized as the estimated event rates for the ongoing background antihyperglycemic treatment) to derive the outcome rates for oral semaglutide, sitagliptin, empagliflozin, and liraglutide in the model. Specifically, the NMA-derived hazard ratios for oral semaglutide versus placebo were applied to the baseline UKPDS OM2 equations to derive rates for oral semaglutide, while the rates for sitagliptin (except for nephropathy), empagliflozin, and liraglutide were derived by applying the oral semaglutide versus placebo hazard ratios and each comparators' hazard ratio versus oral semaglutide. We assumed no effect on nephropathy for sitagliptin because no data exist for this outcome. No hazard ratio calibration was used for the background treatment comparator.

Table 4.4. Hazard Ratios from Network Meta-Analysis

Hazard Ratio	Mean	Lower	Upper	Source
Composite MACE				
Oral Semaglutide HR vs. Background Tx	0.76	0.63	0.93	NMA
Sitagliptin HR vs. Oral Semaglutide	1.30	1.04	1.63	NMA
Empagliflozin HR vs. Oral Semaglutide	1.13	0.89	1.44	NMA
Liraglutide HR vs. Oral Semaglutide	1.14	0.91	1.43	NMA
Congestive Heart Failure				
Oral Semaglutide HR vs. Background Tx	1.03	0.76	1.40	NMA
Sitagliptin HR vs. Oral Semaglutide	0.97	0.68	1.40	NMA
Empagliflozin HR vs. Oral Semaglutide	0.63	0.42	0.95	NMA
Liraglutide HR vs. Oral Semaglutide	0.84	0.59	1.21	NMA
Nephropathy				
Oral Semaglutide HR vs. Background Tx	0.64	0.46	0.89	NMA
Sitagliptin HR vs. Background Tx	1.00	0.80	1.20	NMA
Empagliflozin HR vs. Oral Semaglutide	0.95	0.67	1.35	NMA
Liraglutide HR vs. Oral Semaglutide	1.22	0.85	1.75	NMA

HR = hazard ratio; Tx = treatment

We modeled PIONEER trial outcomes in cycle 1 only. Weighted averages and pooled proportions were calculated for oral semaglutide 14 mg using data from PIONEER 2, 3, and 4. (Table 4.5). In order to account for between-study differences, we then calculated weighted adjusted changes to derive estimates for the comparators.

Table 4.5. Clinical Trial Outcomes Modeled in Cycle 1

Estimate	Mean	Lower (-20%)	Upper (+20%)	Source
Change in HbA1c				
Oral Semaglutide	-1.24	-0.99	-1.48	PIONEER 2,3,4
Sitagliptin	-0.74	-0.59	-0.88	PIONEER 3
Empagliflozin	-0.84	-0.67	-1.00	PIONEER 2
Liraglutide	-0.94	-0.75	-1.12	PIONEER 4
Background Treatment	-0.24	-0.19	-0.28	PIONEER 4
Change in Weight				
Oral Semaglutide	-3.8 kg	-3.0 kg	-4.5 kg	PIONEER 2,3,4
Sitagliptin	-1.2 kg	-0.9 kg	-1.4 kg	PIONEER 3
Empagliflozin	-3.6 kg	-2.9 kg	-4.3 kg	PIONEER 2
Liraglutide	-2.5 kg	-2.0 kg	-3.0 kg	PIONEER 4
Background Treatment	-0.5 kg	-0.4 kg	-0.6 kg	PIONEER 4
Severe Hypoglycemia				
Oral Semaglutide	0.002	0.001	0.002	PIONEER 2,3,4
Sitagliptin	0.007	0.006	0.008	PIONEER 3
Empagliflozin	0.002	0.001	0.002	PIONEER 2
Liraglutide	0.0	0.0	0.0	PIONEER 4
Background Treatment	0.0	0.0	0.0	PIONEER 4
Discontinuation Due to Adverse Event				
Oral Semaglutide	0.111	0.089	0.133	PIONEER 2,3,4
Sitagliptin	0.049	0.039	0.059	PIONEER 3
Empagliflozin	0.046	0.036	0.055	PIONEER 2
Liraglutide	0.094	0.075	0.112	PIONEER 4
Background Treatment	0.036	0.029	0.043	PIONEER 4

HbA1c: glycated hemoglobin, kg: kilogram

UKPDS OM2 Diabetes-Related Complication and Mortality Probabilities

We modeled diabetes-related complications and mortality based on risk equations from the UKPDS OM2.[59] The UKPDS OM2 risk equations are widely used in diabetes simulation models, and have been shown to accurately predict results for the population in which it was developed as well as other diabetes populations.[59,68-70] The UKPDS OM2 complications (13 risk equations) include congestive heart failure (CHF), ischemic heart disease (IHD), first MI for females, first MI for males, subsequent MI, first stroke, subsequent stroke, blindness, foot ulcer, first amputation without prior ulcer, first amputation with prior ulcer, subsequent amputation, and end stage renal disease (ESRD).[59] In the microsimulation, patients were able to experience multiple and concurrent complications during each modeled year. The UKPDS OM2 mortality risk equations predict that previous T2DM-related complications (except foot ulcer and blindness) increase the probability of death. The four mortality risk equations included were death without history of complication(s),

death in the year of a clinical event, death in subsequent year of prior event(s), and death with history of clinical event(s).[59]

Additional Modules

- Treatment Discontinuation and Insulin Uptake. We applied pooled estimates of treatment discontinuation due to adverse events in cycle 1 (Table 4.5). Patients discontinuing their primary modeled treatment were assumed to transition to insulin therapy. This choice was made to facilitate head-to-head comparator evaluations as opposed to evaluating differences in multiple potential treatment pathways. All patients who discontinued used insulin in addition to background treatment for the remainder of the model time horizon. After cycle 1, we assumed that oral semaglutide, empagliflozin, and liraglutide patients added insulin therapy while remaining on their current treatment if their HbA1c reached 8.5 or above; sitagliptin patients were assumed to discontinue treatment and transition to insulin if their HbA1c reached 8.5 or above. Insulin treatment costs were modeled using mean doses from a multivariate prediction model for HbA1c change, weight change, and hypoglycemic events associated with insulin rescue medication.[71] After cycle 1, clinical characteristics for patients pre- and post-insulin were modeled using the equations for HbA1c and weight change,[71] which then influenced the UKPDS OM2 complication risk equations for those patients. The hypoglycemia equations from the Willis et al. prediction model were not used due to their substantial uncertainty.
- Hypoglycemia. Mild, moderate, and severe hypoglycemia were modeled in cycles 2+ based on the previous UKPDS OM2 adaptation from Laiteerapong et al.[58] Patients not yet receiving insulin were assumed to have a 5% probability for a severe hypoglycemic event and a 33% probability for a mild or moderate event each year. Patients receiving insulin were assumed to have a 21% probability of a severe hypoglycemic event and a 52% probability of a mild or moderate hypoglycemic event each year. Patients were assumed to have no more than one mild or moderate hypoglycemic event and one severe hypoglycemic event per year but could have multiple hypoglycemic events during their lifetime.
- Atrial Fibrillation and Peripheral Artery Disease. The UKPDS OM2 equations have coefficients for atrial fibrillation and peripheral vascular (artery) disease but the NHANES patient dataset did not provide this information. Therefore, we utilized age-based cumulative incidence estimates from the US population[72,73] and (for atrial fibrillation) relative risk estimates based on patients' HbA1c [74] to simulate these patient characteristics prior to each microsimulation.

Utilities

We used consistent health state utility values across treatments evaluated in the model. Each patient's specific utility value for a given year is derived from a baseline utility and applicable regression coefficients for: (1) complications in the year of an event, (2) history of complications, and (3) demographic characteristics; the regression coefficients should not be interpreted as disutility values. The primary utility source was Shao et al.[60] We added missing regression coefficients for foot ulcer and amputation events from a recent diabetes utility study by Sullivan and Ghushchyan.[61] In Shao et al., the Health Utilities Index Mark 3 (HUI-3) was used to measure heath utility in a sample of 8,713 patients from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of high CVD risk T2DM patients.[75] Sullivan and Ghushchyan mapped EQ-5D-3L questionnaire responses to the Short Form-12 health survey responses of 20,705 individuals with diabetes (types 1 and 2) in the Medical Expenditure Panel Survey (MEPS) database from 2000 to 2011.[61] Lastly, we modeled an annual disutility for daily injection of insulin (for patients who discontinue treatment) and liraglutide based on Boye et al., who used standard gamble interviews of T2DM patients in Scotland to estimate the utility values for injection-related attributes.[76]

Table 4.6. Utility Calculation for Health States

	Estimate	SE	Lower	Upper
Baseline Utility	0.800	0.023	0.755	0.845
Macrovascular complication coefficients				
Congestive heart failure event[60]	-0.089	0.022	-0.132	-0.047
Congestive heart failure history[60]	-0.041	0.010	-0.060	-0.022
Ischemic heart disease history*[60]	-0.016	0.005	-0.026	-0.006
Myocardial infarction event[60]	-0.042	0.016	-0.074	-0.010
Myocardial infarction history[60]	-0.011	0.006	-0.022	0.001
Stroke event[60]	-0.204	0.035	-0.272	-0.136
Stroke history[60]	-0.101	0.008	-0.117	-0.086
Microvascular complication coefficients				
Blindness history[60]	-0.057	0.009	-0.074	-0.040
Foot ulcer event[61]	-0.024	0.005	-0.033	-0.015
Amputation event[61]	-0.051	0.029	-0.108	0.005
Renal disease history[60]	-0.024	0.016	-0.056	0.008
Hypoglycemia event[60]	-0.036	0.010	-0.056	-0.016
Hypoglycemia history[60]	-0.033	0.011	-0.054	-0.011
Demographic characteristic coefficients[60]†				
Annual disutility of daily injection (liraglutide and insulin only)[76]	-0.054		-20%	+20%

SE: standard error

*Disutility for ischemic heart disease is based on "revascularization history" from Shao et al.[60]

†Refer to Shao et al. for full list of multivariate regression results by patient demographics.

Economic Inputs

Drug Acquisition Costs

Because oral semaglutide is not approved by the FDA, the drug price is not yet available. We used the net price of injectable semaglutide as a placeholder price, as well as calculating the threshold prices at three willingness to pay (WTP) thresholds: $50,000 per QALY gained, $100,000 per QALY gained, and $150,000 per QALY gained.

For each treatment strategy, we obtained net pricing estimates from SSR Health, LLC, which combines data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs, to derive a net price.[77] We estimated net prices by comparing the most recent four-quarter averages (i.e., second quarter of 2018 through first quarter of 2019) of both net prices and wholesale acquisition cost (WAC) per unit to arrive at a mean discount from WAC for the drug. Finally, we applied this average discount to the most recent available WAC (accessed July 2019) to arrive at an estimated net price per unit (Table 4.7).

Table 4.7. Drug Cost Inputs

Drug	WAC per 4-Week-Pill Bottle/Pen[78]	Net Price per 4-Week-Pill Bottle/Pen/Insulin Unit	Discount from WAC[77]	Net Price per Year‡
Oral Semaglutide*	$772.42§	$501.54§	35%	$6,520.02
Sitagliptin (Januvia®)	$451.20	$123.62	72.6%	$1,505.07
Empagliflozin (Jardiance®)	$492.85	$171.51	65.2%	$2,088.13
Liraglutide (Victoza®)†	$307.26	$219.38	28.6%	$5,341.90
Metformin				$917.19[58]
Sulfonylureas				$578.54[58]
Insulin				
Basal		$0.22		Varies by patient weight
Bolus		$0.28		
Premix		$0.14		

WAC: wholesale acquisition cost

*As a placeholder, we used Ozempic (injectable semaglutide) prices. The placeholder price is for 2 mg/1.5 ml pens at a dose of 1 mg per week.

†Prices for liraglutide are per 3 ml pen, and the annual price calculation assumes a 1.2mg/day dosage.

‡1 year = 365.25 days or 52 weeks

§This table was updated to revise the costs for oral semaglutide. This change does not impact the model results, as the model uses net price per year as the price input.

Non-Drug Costs

Costs for T2DM-related complications and hypoglycemia were obtained from Ward et al., who estimated direct medical costs from data sources including inpatient and emergency department databases, national physician and laboratory fee schedules, government reports, and published literature.[79] Complication costs in the year of the event reflect acute care and any subsequent care provided in the first year; history state costs reflect annual resource use for the ongoing management of complications in subsequent years.[79] Costs were assessed from the perspective of a comprehensive US health care payer and were originally reported in 2012 US dollars (USD); the costs in Table 4.8 reflect inflation to the first half of 2019. Other health care costs related to diabetes monitoring were also included (Table 4.9).

Table 4.8. Cost per T2DM-Related Complication and per Hypoglycemic Event

	Estimate	Lower (-20%)	Upper (+20%)
Incremental Cost in the Year of Event/Diagnosis (per Event)[79,80]			
Heart Failure	$28,021	$22,417	$33,626
Ischemic Heart Disease	$25,247	$20,198	$30,297
Myocardial Infarction	$66,574	$53,259	$79,889
Stroke	$49,677	$39,742	$59,612
Foot Ulcer	$2,532	$2,026	$3,039
Amputation	$10,663	$8,531	$12,796
Hypoglycemia			
Episode Requiring Hospitalization	$19,435	$15,548	$23,322
Episode Requiring ED visit	$1,546	$1,237	$1,856
Episode Requiring Glucagon Injection	$208	$166	$249
Incremental Cost of Living with History of Complication (per year)[79,80]			
Heart Failure*	$2,246	$1,797	$2,695
Ischemic Heart Disease*	$2,246	$1,797	$2,695
Myocardial Infarction*	$2,246	$1,797	$2,695
Stroke	$18,329	$14,663	$21,994
Blindness	$3,376	$2,700	$4,051
Renal Disease	$84,583	$67,666	$101,499

*Annual state costs for cardiovascular complications were obtained from a Medical Expenditure Panel Survey report on heart condition-associated office visits and medications.

Table 4.9. Other Health Care Cost Parameters

	Estimate	Lower (-20%)	Upper (+20%)
Outpatient visit: noninsulin [58]	$550	$440	$659
Outpatient visit: insulin[58]	$601	$481	$722

Model Analysis

The model estimated the average survival, quality-adjusted survival, drug cost, complication cost, and number of T2DM complications for 745 included NHANES patients. Unlike a traditional Markov cohort model with deterministic results, the base-case result for each model outcome is the average of all simulations, in this case 2,500 microsimulations per patient (1,862,500 total simulations); we chose 2,500 microsimulations per patient to ensure statistical convergence. Time spent in each T2DM health state was summed to provide estimates of life expectancy and quality-adjusted life expectancy. Long-term estimates of costs, QALYs, and life-years were discounted at 3% per year. We calculated the incremental results for each intervention versus background treatment alone as the incremental cost per life year and quality-adjusted life year, and also the incremental cost per MACE, CHF, and ESRD avoided.

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges for each input described in the model inputs section above. In order to efficiently operationalize the one-way sensitivity analysis within the framework of the patient-level Monte Carlo microsimulation, we fixed the parameter values for all non-patient-level inputs and then performed 100 UKPDS equation simulations for each of 100 NHANES patients for each parameter's low and high value in order to produce an estimate of uncertainty for each high and low value of each parameter. We also calculated the 95% credible ranges for each mean value for each high and low value of each parameter from the results of the 100 equation by 100 patient simulations.

Probabilistic sensitivity analysis was performed in conjunction with the primary analysis by jointly varying all model parameters over 2,500 individual simulations, then calculating 95% credible range estimates for each model outcome based on the results. Additionally, we performed a threshold analysis by systematically altering the price of oral semaglutide to estimate the maximum prices that would correspond to given willingness to pay (WTP) thresholds versus each comparator.

Scenario Analyses

We intend to include the following scenario analyses in the final report, but have yet to produce the estimates given the substantial computation time required to produce even base-case results within a microsimulation model framework:

- Modified societal perspective that includes components such as productivity impacts or other indirect costs as applicable.
- Shorter model time horizon (5 years)
- Relative changes in long-term MACE and renal outcome effectiveness

We note that estimating the societal burden of this disease, and in the context of a patient-level microsimulation, is rather complex and requires consideration of multiple clinical complications along with the underlying disease.

Model Validation

We used several approaches to validate the model. First, we shared preliminary methods to manufacturers, patient groups, and clinical experts. Based on feedback from these different groups on our methodology, we refined our approach and data inputs used in the model, as relevant. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. Finally, we compared results to other cost-effectiveness models in this therapy area.

4.3 Results

Base-Case Results

All base-case results represent averages over sufficient simulations to achieve statistical convergence; nonetheless, we urge caution when interpreting these findings as they are highly uncertain. The uncertainties are reflected both in statistical variance in the model input parameters and risk equations, as shown in the probabilistic sensitivity analyses, and in the additional uncertainties from the NMA caused by concerns about whether effect modification could result from differences in the underlying CVOTs. Results of probabilistic sensitivity analyses are presented in a subsequent section.

Oral semaglutide (based on the placeholder price) had the highest total costs (lifetime mean = $113,000 versus $86,000 to $102,000) among the five modeled treatment strategies but resulted to the fewest 3-point MACE (18.9% vs. 21.0% to 21.5%). Among the five modeled treatment strategies, oral semaglutide was in the middle of the range of life years gained (3.29 vs. 2.99 to 3.38) and the second most QALYs gained (1.95 vs. 1.68 to 1.89).

Oral semaglutide (based on its placeholder price) was most cost-effective compared to sitagliptin and liraglutide (incremental cost-effectiveness ratios = $80,000/QALY and $100,000/QALY, respectively), followed by the comparison to background treatment alone (incremental cost-effectiveness ratio = $160,000/QALY). Oral semaglutide (based on the placeholder price) was dominated by empagliflozin. The oral semaglutide costs per MACE avoided, in order of lowest to highest, were $530,000 versus liraglutide, $600,000 versus sitagliptin, $940,000 versus empagliflozin, and >$1 million versus background treatment alone.

Table 4.10. Results for the Base Case for Oral Semaglutide Compared to Comparators

Treatment	Add-On Drug Cost	Complication Cost	Total Cost	MACE	CHF	ESRD	Life Years	QALYs
Oral Semaglutide* + background treatment	$21,000	$75,000	$119,000	19.7%	12.7%	45.7%	3.44	1.95
Sitagliptin (Januvia®) + background treatment	$4,000	$76,000	$103,000	22.0%	11.4%	48.8%	3.13	1.76
Empagliflozin (Jardiance®) + background treatment	$7,000	$73,000	$94,000	21.8%	9.4%	44.8%	3.50	1.99
Liraglutide (Victoza®) + background treatment	$18,000	$73,000	$105,000	21.7%	9.8%	45.0%	3.53	1.81
Background treatment alone	--	$76,000	$89,000	22.3%	11.7%	48.5%	3.13	1.77

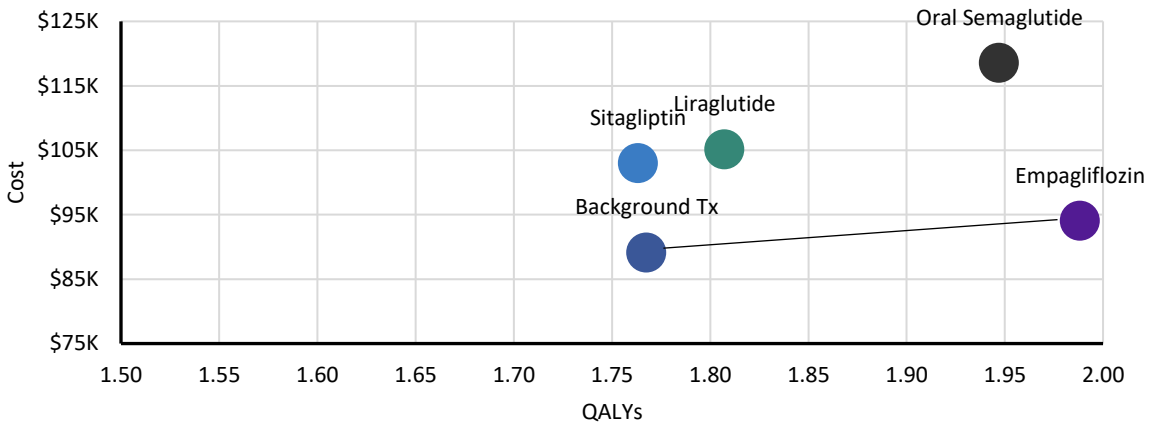
*Using the placeholder price for oral semaglutide

Table 4.11. Incremental Cost-Effectiveness Ratios: Oral Semaglutide versus Each Comparator

Comparator vs. Oral Semaglutide*	Cost per LY Gained	Cost per QALY Gained	Cost per MACE Avoided	Cost per CHF Avoided	Cost per ESRD Avoided
Sitagliptin (Januvia®) + background treatment	$50,000	$80,000	$680,000	Dominated	$500,000
Empagliflozin (Jardiance®) + background treatment	Dominated	Dominated	$1,170,000	Dominated	Dominated
Liraglutide (Victoza®) + background treatment	Dominated	$100,000	$660,000	Dominated	Dominated
Background treatment alone	$90,000	$160,000	$1,100,000	Dominated	$1,020,000

*Using the placeholder price for oral semaglutide

Figure 4.2. Cost-Effectiveness Frontier



*Using the placeholder price for oral semaglutide

Figure 4.2 displays the deterministic results of the simulations for each comparator and reports the lifetime total costs and QALYs for each. Drugs that are farther to the right provide the greatest clinical benefit and drugs higher on the y-axis are more expensive. The line on the graph depicts the cost-effectiveness efficiency frontier. Those therapies that lie to the left of/above the frontier are dominated by therapies that lie on the frontier. Thus, therapies to the left of the frontier, using only the deterministic findings, are considered to not be as cost-effective as those therapies on the frontier.

Sensitivity Analysis Results

To demonstrate effects of individual parameter uncertainty on both costs and health outcomes, we varied each parameter using standard errors (if available) or by ±20% to evaluate changes in incremental cost and incremental QALYs for the comparison of oral semaglutide versus background therapy alone.

Due to the microsimulation model structure, we performed 100 UKPDS equation simulations for each of 100 NHANES patients for each parameter's low and high value. The resulting low (blue) and high (green) bars in the tornado diagrams thus represent the mean values of 10,000 (100x100) simulations each. We also included the 95% credible ranges for each mean value, indicated by the whiskers on the end of each bar. The results were highly uncertain given (1) statistical variance in the model input parameters and risk equations, (2) additional uncertainties from the NMA caused by concerns about whether effect modification could result from differences in the underlying CVOTs, and (3) the relatively limited (compared to the base-case analysis) number of simulations performed for each parameter necessitated by computation time constraints. As with the base-case results, we urge caution when interpreting the findings of the one-way sensitivity analysis.

The parameters with the greatest impact on incremental cost were the costs of T2DM complications (renal disease, amputation, ischemic heart disease, myocardial infarction), hypoglycemia-related costs, and insulin-related costs. We note that the cost of oral semaglutide was not among the top 20 most impactful parameters in the comparison versus background treatment alone, but may be more impactful in comparisons versus the other add-on therapies.

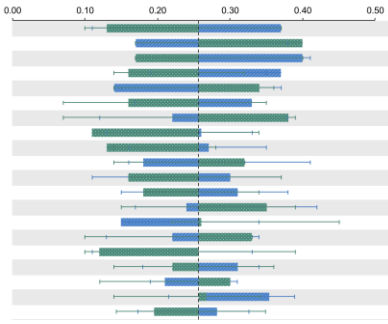
The parameters with the greatest impact on incremental QALYs were the baseline utility, the probability of severe hypoglycemia for patients on insulin, the NMA-derived congestive heart failure hazard ratio, and utility coefficients for T2DM complications.

Figure 4.3. Tornado Diagram(s) for One-Way Sensitivity Analyses of Oral Semaglutide versus Background Therapy Alone

Incremental Cost

Parameter	Low Value	High Value	Low Result	2.5%	97.5%	High Result	2.5%	97.5%	Spread
Cost (event history): Renal Disease	$67,666	$101,499	$37,610	$33,327	$42,049	$51,977	$45,601	$54,006	$14,366
Severe Hypoglycemia (Cycles 2+): Background Treatment Only	0.040	0.060	$34,681	$34,982	$45,361	$48,652	$43,862	$50,852	$13,971
Cost (year of event): Amputation	$8,531	$12,796	$37,648	$37,293	$46,871	$47,985	$42,381	$52,783	$10,336
Cost (event history): Ischemic heart disease	$1,797	$2,695	$50,243	$38,657	$49,796	$41,258	$36,884	$47,698	$8,985
Cost (event history): Myocardial infarction	$1,797	$2,695	$47,317	$37,183	$49,429	$39,812	$38,912	$45,328	$7,505
Cost (year of event): Hypoglycemia Requiring Hospitalization	$15,548	$23,322	$37,770	$37,717	$43,709	$44,232	$34,255	$47,985	$6,463
Cost of Outpatient visit: noninsulin	$440	$659	$47,241	$37,551	$46,824	$41,362	$39,245	$45,243	$5,879
Ppn. Insulin Type: Premix	0.496	0.744	$44,550	$41,446	$50,489	$50,054	$36,191	$50,339	$5,504
Ppn. Insulin Type: Basal	0.256	0.384	$46,616	$37,435	$50,698	$41,164	$40,108	$48,259	$5,453
Cost per Insulin Unit: Premix	$0.11	$0.17	$41,339	$37,896	$46,645	$36,097	$36,616	$50,388	$5,243
Cost of Outpatient visit: insulin	$481	$722	$43,090	$37,183	$48,243	$38,040	$36,993	$48,455	$5,050
Weight change: Background Tx	-0.6 kg	-0.4 kg	$42,877	$39,705	$47,298	$47,470	$38,965	$48,504	$4,593
Discontinuation (Cycle 1): Oral Semaglutide	0.089	0.133	$40,874	$39,816	$46,505	$45,327	$37,763	$45,359	$4,453
Cost (year of event): Foot ulcer	$2,026	$3,039	$44,167	$41,606	$49,325	$48,586	$38,275	$47,859	$4,419
CHF HR: Oral Semaglutide HR vs. Background Tx	0.76	1.40	$41,853	$37,034	$45,696	$37,520	$37,584	$47,930	$4,333
Ppn. Insulin Type: Bolus	0.024	0.036	$38,375	$35,435	$47,780	$42,075	$38,642	$47,835	$3,700
Sev. Hypoglycemia: Oral Semaglutide	0.001	0.002	$40,837	$39,744	$46,295	$44,498	$38,893	$46,558	$3,661
Weight change: Oral Semaglutide	-4.5 kg	-3.0 kg	$43,811	$42,646	$46,292	$40,390	$39,058	$48,600	$3,421
Final insulin dose (IU/kg)	0.450	0.790	$43,185	$39,905	$48,003	$46,431	$38,088	$46,367	$3,246
Cost (year of event): Hypoglycemia Requiring Glucagon Injection	$166	$249	$39,883	$40,148	$47,232	$43,091	$39,179	$46,171	$3,208

Incremental QALYs



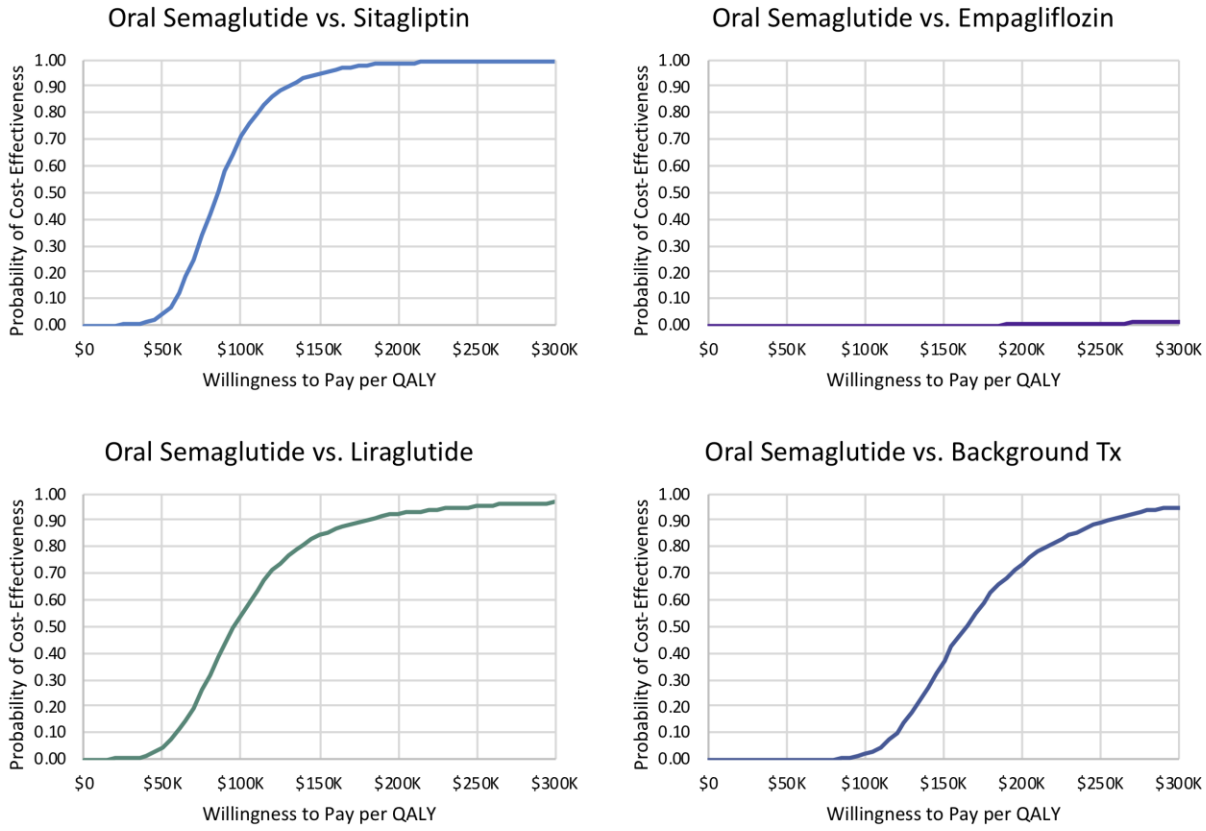
Parameter	Low Value	High Value	Low Result	2.5%	97.5%	High Result	2.5%	97.5%	Spread
Baseline T2DM Utility	0.755	0.845	0.37	0.11	0.37	0.13	0.10	0.37	0.24
Severe Hypoglycemia (Cycles 2+): Insulin	0.168	0.252	0.17	0.18	0.38	0.40	0.17	0.39	0.24
CHF HR: Oral Semaglutide HR vs. Background Tx	0.76	1.40	0.40	0.17	0.41	0.17	0.17	0.40	0.23
Utility coefficient: Myocardial infarction history	-0.023	0.001	0.37	0.19	0.35	0.16	0.14	0.32	0.21
Ppn. Insulin Type: Basal	0.256	0.384	0.14	0.15	0.37	0.34	0.14	0.36	0.20
Utility coefficient: Ischemic heart disease history	-0.026	-0.006	0.33	0.17	0.32	0.16	0.07	0.35	0.16
Utility coefficient: Myocardial infarction event	-0.073	-0.011	0.22	0.12	0.38	0.38	0.07	0.39	0.16
Severe Hypoglycemia (Cycles 2+): Background Treatment Only	0.040	0.060	0.26	0.13	0.33	0.11	0.12	0.34	0.15
Neph HR: Oral Semaglutide HR vs. Background Tx	0.46	0.89	0.27	0.16	0.35	0.13	0.14	0.28	0.14
Utility coefficient: Diabetes duration (per year)	-0.006	-0.005	0.18	0.16	0.41	0.32	0.14	0.32	0.14
Utility coefficient: Others	-0.024	0.004	0.30	0.11	0.37	0.16	0.17	0.37	0.14
Final insulin dose (IU/kg)	0.450	0.790	0.31	0.15	0.38	0.18	0.19	0.34	0.13
Mild/Moderate Hypoglycemia (Cycles 2+): Add-on Treatments	0.264	0.396	0.24	0.17	0.42	0.35	0.15	0.39	0.11
Starting insulin dose (IU/kg)	0.210	0.530	0.15	0.16	0.34	0.26	0.22	0.45	0.11
HbA1c change: Background Tx	-0.282	-0.188	0.22	0.13	0.34	0.33	0.10	0.33	0.11
Utility coefficient: Foot ulcer event	-0.034	-0.014	0.22	0.11	0.33	0.12	0.10	0.39	0.10
Sev. Hypoglycemia: Background Tx	0.000	0.000	0.31	0.18	0.34	0.22	0.14	0.36	0.09
Severe Hypoglycemia (Cycles 2+): Add-on Treatments	0.040	0.060	0.21	0.19	0.31	0.30	0.12	0.29	0.09
MACE HR: Oral Semaglutide HR vs. Background Tx	0.63	0.93	0.35	0.21	0.39	0.27	0.14	0.34	0.09
Utility coefficient: Stroke event	-0.273	-0.135	0.28	0.17	0.33	0.20	0.14	0.35	0.09

Table 4.12. Probabilistic Sensitivity Analysis Results: Oral Semaglutide versus Each Comparator

Comparator	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY	Cost-Effective at $200,000 per QALY	Cost-Effective at $250,000 per QALY
Sitagliptin	4%	71%	95%	99%	99%
Empagliflozin	0%	0%	0%	0%	1%
Liraglutide	4%	54%	84%	92%	95%
Background Treatment Alone	0%	2%	37%	74%	89%

*Using the placeholder price for oral semaglutide
QALY: quality-adjusted life year

Figure 4.4 Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Acceptability Curves for Oral Semaglutide versus Each Comparator



*Using the placeholder price for oral semaglutide
QALY: quality-adjusted life year, Tx: treatment

Scenario Analyses Results: *Forthcoming*

These will be included in the next version of the report.

Threshold Analyses Results

Table 4.13. Threshold Analysis Results: Oral Semaglutide versus Background Treatment Alone

Comparator	Annual Price to Achieve $50,000 per QALY	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY
Background Treatment Alone	$5,397	$5,890	$6,383

*The WAC price for oral semaglutide was not available as of the date of this report.

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs. We will be sharing the model with manufacturers for external verification.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

In our review of the literature, we found no cost-effectiveness model that compared oral semaglutide to other T2DM treatment strategies. Our focus therefore in this section is on review and contrast of methodologies used in the modeling of T2DM treatment strategies. The numerous available strategies and pathways available for the treatment of T2DM have led to the development and publication of several cost-effectiveness analyses in the past few decades.[63-66,69,81-86] Such analyses include both cohort and microsimulation models. For the purposes of this report we have limited the comparison to other published microsimulation models, specifically the UKPDS OM2[59], a model predicting health outcomes in T2DM, and a microsimulation cost utility model by Laiteerapong et al.[58]

The UKPDS OM2 is an update of the original UKPDS Outcomes Model 1 (OM1), also a patient simulation model that predicts health outcomes of patients with T2DM. The UKPDS OM2 re-estimated the original seven risk equations in the UKPDS OM1 over a longer time-horizon plus additional risk equations for other complications such as diabetic ulcer. Additionally, it also included new risk equations for all-cause mortality in T2DM patients. Our model applied the updated UKPDS OM2 risk equations (developed for the UK population) to a US-specific population that was derived from 2013-14 and 2015-16 NHANES survey data on 745 patients that fit the baseline characteristics of patients on background anti-hyperglycemic medications with uncontrolled T2DM.

A key comparison of our model is to the one by Laiteerapong et al. Risks of different levels of hypoglycemia in our model are based on the hypoglycemia risk module developed by Laiteerapong et al. in their microsimulation model. Both models use the baseline UKPDS OM2 risk equations in modeling health outcomes, but for T2DM patients in the U.S. Considering differences between our model and the one by Laiteerapong et al., a key difference is unlike their or any other model, we specifically estimate risk for MACE and renal events using HRs derived from an NMA of key trials in

our population. This HR is applied to the UKPDS OM2-derived risk equations for specific treatment strategies included in our model. To our knowledge, ours is the first and currently only microsimulation model to undertake such a novel approach to predict these long-term events in T2DM. We believe this approach better accounts for treatment-specific effects on critical outcomes such as MACE and renal outcomes in T2DM patients than the approach used by Laiteerapong et al. or others, who used the unmodified risk-equations from the UKPDS OM2. Other differences between the two models include the NHANES population; we used a more recent population compared to theirs which results in slightly different patient characteristics. As mentioned earlier we modeled a new treatment – oral semaglutide, which has not been previously modeled, our treatment costs were different, and we used an adapted approach to applying utility values when individuals had a history of an event.

Limitations

As with all modeling exercises, there are many limitations that should be considered when interpreting these findings. The overarching limitation of this model is the complexity of T2DM, its large number of co-morbidities, and its patient-specific clinical management. This complexity demands a patient-level microsimulation. Yet, it is extremely challenging to expect regression equations to reliably predict any one patient's actual outcomes, therefore we undertook a large number of sensitivity and scenario analyses in order to avoid depending on a single deterministic output.

The patients simulated in the model were drawn from a national survey in the U.S., but they may not be representative of a specific subpopulation of people with T2DM. Therefore, the equation-predicted events and estimated results from the model may not be generalizable beyond the NHANES population. Furthermore, the events predicted in these patients hold uncertainty that is inherent in the risk equations. And these risk equations were not developed specifically from the NHANES patients with which we performed our simulations, thus the equations may not precisely predict each event for the simulated patients.

The CV and renal outcome estimates for our model could only be estimated from indirect treatment comparisons (by NMA) that are potentially susceptible to effect modification. Differences in the populations studied in those trials may contribute bias to the estimated differences in outcomes. We also assumed that the CV benefits observed in the trials that targeted MACE as the primary outcomes remained constant for each patient's lifetime. With a lack of data on longer term follow-up for these events or real-world evidence of adherence and its relationship with such benefits, we were required to make an assumption. We are testing this assumption in a scenario analysis, which will be reported in the final version of the report.

People with T2DM are treated based on clinical guidelines, which have been muted for this modeling exercise. We assumed that all patients discontinuing their initial model treatment

received insulin in order to provide direct head-to-head estimates of value for those initial treatment decisions. However, individual patients would likely experience a cascade of treatments upon discontinuation, which could have different costs and outcomes for that patient than what were modeled. Therefore, the post-treatment estimates of costs and outcomes may be biased.

The utility values for events modeled from the risk equations were drawn from two sources due to a lack of a single comprehensive source of health-related quality of life inputs. It is also important to point out that the two sources used different preference-weighted measures (EQ-5D and HUI3), and these two instruments are known to produce slightly different utility estimates.

Conclusions

We created a patient-level microsimulation in order to compare the value of five different treatment strategies for patients with T2DM. Oral semaglutide as an add-on therapy to background antihyperglycemic treatment produced incremental benefits in MACE avoided, along with relatively more QALYs compared to background antihyperglycemic treatment alone. Oral semaglutide use resulted in better patient outcomes than background treatment alone or sitagliptin, and similar outcomes to liraglutide or empagliflozin with overlapping 95% confidence ranges for QALYs.

With a placeholder price of $6,520 per year oral semaglutide was estimated to be cost-effective at a WTP threshold of $150,000 per QALY gained, versus both sitagliptin and liraglutide. Its incremental cost-utility ratio over the modeled time horizon in the base case versus these other two treatment strategies was close to $100,000 per QALY gained. We calculated that the threshold price versus background treatment alone was $5,900 per year to achieve an incremental cost-effectiveness ratio of $100,000/QALY, or $6,400 per year to achieve an incremental cost-effectiveness ratio of $150,000/QALY. The comparison of incremental value with empagliflozin is uncertain due to the 95% confidence range of incremental QALYs crossing zero.

All of these incremental value estimates are coupled with high levels of uncertainty. This uncertainty is a combination statistical variance from model parameters and additional uncertainty in the NMA results from which MACE benefits for oral semaglutide are derived. Therefore, it is difficult to draw strong conclusions between oral semaglutide and the other add-on treatments.

4.4 Summary and Comment

Oral semaglutide is expected to produce incremental benefit versus alternative T2DM treatments in terms of MACE prevented. However, the complexity of T2DM, its large number of co-morbidities, and its patient-specific clinical management mean that MACE prevention is only part of the treatment puzzle, and other treatments may provide better overall benefit and at lower cost. Based on the current clinical evidence, with limited follow-up, and without knowing the eventual price for oral semaglutide, we are unable to draw conclusions on its cost effectiveness with any

certainty. The ultimate value of oral semaglutide will be determined by the price that is set by the manufacturer and its long-term effectiveness.

5. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of oral semaglutide to liraglutide, empagliflozin, sitagliptin, and ongoing background therapy. We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Council of clinicians, patients, and health services researchers. As part of their deliberations, Council members will judge whether a treatment may substantially impact the considerations listed in Table 5.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Council member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Council member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's value assessment framework. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Council's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

5.1 Potential Other Benefits

The primary "other benefit" to consider with oral semaglutide is the advantage of having an oral GLP-1 receptor agonist. Many patients with T2DM are hesitant to move to treatment with injectable medications, but currently many patients cannot achieve target HbA1c levels with available oral medications alone. Oral semaglutide is likely to allow many patients to remain on oral treatment who would otherwise require escalation of therapy using either an injectable GLP-1 receptor agonist or insulin.

5.2 Contextual Considerations

We did not find important contextual considerations in assessing oral semaglutide.

6. Value-Based Price Benchmarks

Value-based price benchmarks will be included in the revised Evidence Report that will be released on or around 10/31/2019.

7. Potential Budget Impact

7.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of oral semaglutide in adults in the U. with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s). We used oral semaglutide's placeholder list price, placeholder net price, and the three threshold prices in our estimates of budget impact.

7.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using oral semaglutide rather than existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

We believe that if and when approved for use in the US, oral semaglutide can replace antidiabetic drugs (ADDs) in the DPP-4 inhibitor, GLP-1 receptor agonist, and SGLT-2 inhibitor classes, as well as be considered as an add-on therapy to background antihyperglycemic treatment. We thus included two candidate populations in our analysis of potential budget impact for this drug: 1) a prevalent population already on a second ADD – existing treatment with DPP-4 inhibitors, GLP-1s receptor agonists, or SGLT-2 inhibitors – wherein patients switch to oral semaglutide, and 2) an incident population of patients who have inadequate glycemic control with background antihyperglycemics such as metformin, for whom oral semaglutide will be the second ADD.

For the prevalent population, we first estimated the prevalence of T2DM among adults in the US at 8.6%.[87] We then estimated the proportion of T2DM patients with inadequate glycemic control, using real-world evidence (RWE) that was sourced from the US Centricity Electronic Medical Records (CEMR) dataset that comprises over 34 million individual longitudinal electronic medical records.[88] The estimate of 48% patients who added on a second ADD was sourced from a subset of this dataset, comprising approximately 740,000 T2DM patients on metformin with HbA1c ≥7.5%. From the same RWE study, we estimated that among those on a second ADD, the market share of DPP-4 inhibitor, GLP-1 receptor agonist, and SGLT-2 inhibitor use was 20%, 7%, and 7% respectively, in 2016. We then applied the derived estimates to the 2019-2023 estimated US adult population to arrive at an eligible population size of approximately 3.7 million patients or approximately 735,000 patients each year over five years. We assumed in our analysis of potential budget impact among the prevalent population that oral semaglutide as a potential ADD for switching would replace

entirely the market share of drugs in these other classes, represented by sitagliptin (DPP-4 inhibitor), liraglutide (GLP-1 receptor agonist) and empagliflozin (SGLT-2 inhibitor).

For the incident population of T2DM patients with inadequate glycemic control who require a second ADD, we first estimated the incidence of T2DM among adults in the US at 0.7%[89], and then applied the same RWE estimate of 48% to derive the number of patients requiring a second ADD. This resulted in an approximate population size of 844,000 patients each year who would be eligible for treatment with oral semaglutide as an add-on therapy to their background antihyperglycemics.

ICER's methods for estimating potential budget impact are described in detail elsewhere[90] and have been recently updated. The intent of our revised approach to budgetary impact is to document the percentage of patients who could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the U.S. economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

7.3 Results

Table 7.1 illustrates the five-year annualized per-patient potential budget impact of oral semaglutide when used as a switching therapy in place of the DPP-4s, GLP-1s and SGLT-2s. These results are based on its placeholder list price ($10,041 per year), placeholder net price ($6,520 per year), and annual prices to reach cost-effectiveness thresholds of $150,000, $100,000, and $50,000 per QALY versus background antihyperglycemics ($6,383, $5,890, and $5,397, respectively).

Table 7.1. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon – Oral Semaglutide versus Other Second-Line ADDs

	Average Annual Per Patient Budget Impact				
	Placeholder List Price	Placeholder Net price	At Price to Reach $150,000/QALY	At Price to Reach $100,000/QALY	At Price to Reach $50,000/QALY
Oral Semaglutide (Annualized Cost)	$24,800	$22,000	$21,900	$21,500	$21,100
DPP-4 + GLP-1 + SGLT-2 (Annualized Cost)	$18,400				
Oral Semaglutide Budget Impact	$6,400	$3,600	$3,500	$3,100	$2,700

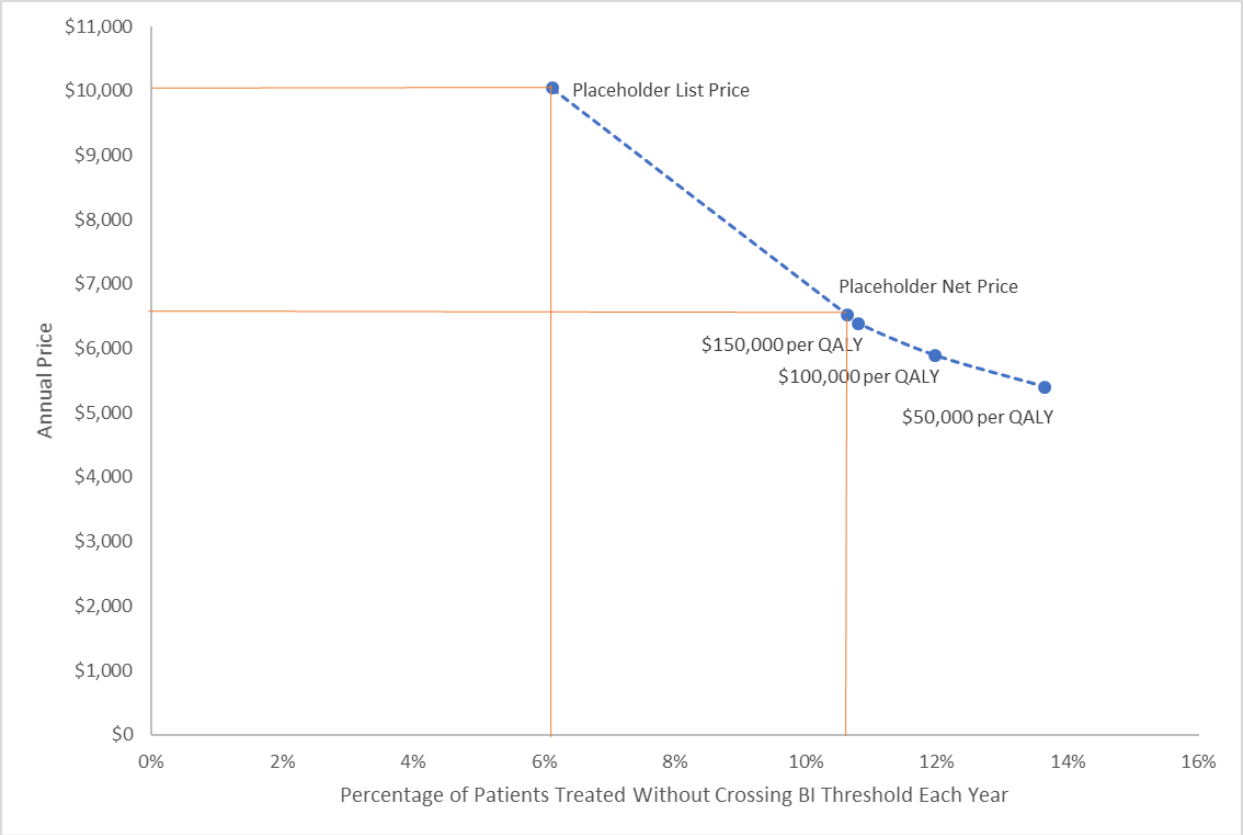
All annualized costs include drug and non-drug health care costs
QALY: quality-adjusted life year

In a prevalent population where oral semaglutide is considered a switching therapy, the average annual potential budgetary impact when using its placeholder list price and placeholder net price

was an additional per-patient cost of approximately $6,400 and $3,600, respectively, versus a market share weighted mix of DPP-4 inhibitors, GLP-1s receptor agonists, or SGLT-2 inhibitors. Its average annual potential budget impact versus this mix of second ADDs at its prices to reach cost-effectiveness thresholds of $50,000 to $150,000 per QALY (vs. background antihyperglycemics alone) ranged from approximately $4,800 per patient to approximately $5,400 per patient.

In this population, as shown in Figure 7.1, approximately 6% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at oral semaglutide's placeholder list price and approximately 11% of patients at its placeholder net price. Between 11% and 14% of patients could be treated without crossing the budget impact threshold at its prices to reach cost-effectiveness thresholds between $150,000 and $50,000 per QALY.

Figure 7.1. Potential Budget Impact Scenarios of Oral Semaglutide as a Switching Therapy at Placeholder List and Net Price



BI: budget impact, QALY: quality-adjusted life year

Table 7.2 illustrates the five-year annualized per-patient budget impact of oral semaglutide when used as an add-on therapy to background antihyperglycemics in patients with inadequate glycemic control, requiring their first add-on (second ADD-naïve) ADD therapy. These results are based on its placeholder list price ($10,041 per year), placeholder net price ($6,520 per year) and annual prices

to reach cost-effectiveness thresholds of $150,000, $100,000, and $50,000 per QALY ($6,383, $5,890 and $5,397, respectively) for oral semaglutide.

Table 7.2. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon: Oral Semaglutide versus Background Antihyperglycemics

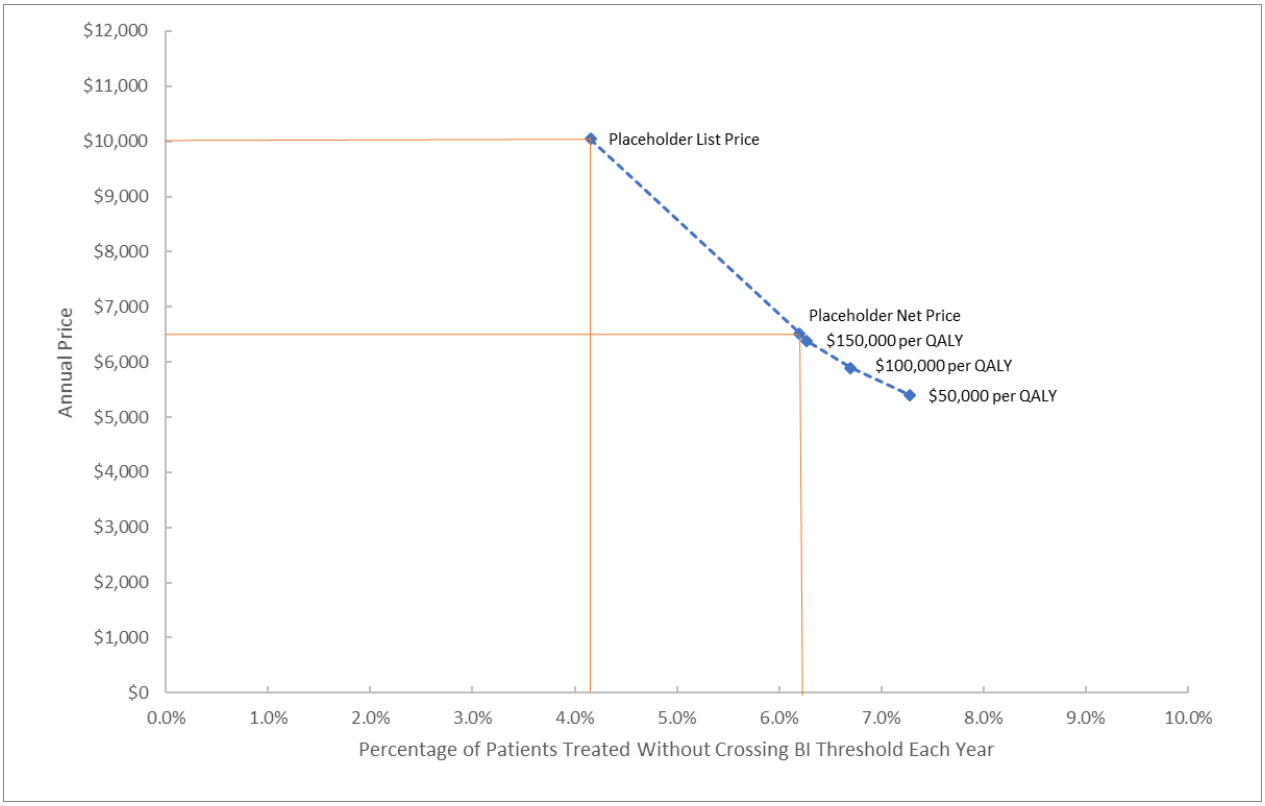
	Average Annual Per Patient Budget Impact				
	Placeholder List Price	Placeholder Net Price	At Price to Reach $150,000/QALY	At Price to Reach $100,000/QALY	At Price to Reach $50,000/QALY
Oral Semaglutide (Annualized Cost)	$24,800	$22,000	$21,900	$21,500	$21,100
Background Antihyperglycemics (Annualized Cost)	$16,500				
Oral Semaglutide Budget Impact	$8,300	$5,500	$5,400	$5,100	$4,600

All annualized costs include drug and non-drug health care costs
QALY: quality-adjusted life year

In a population where oral semaglutide is considered an add-on therapy to background antihyperglycemics, the average annual potential budgetary impact when using its placeholder list price and placeholder net price was an additional per-patient cost of approximately $8,300 and $5,500, respectively. Its average annual potential budget impact in the same population at its prices to reach cost-effectiveness thresholds of $50,000 to $150,000 per QALY ranged from approximately $4,600 per patient to approximately $5,400 per patient.

In this population, as shown in Figure 7.2, a little over 4% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at oral semaglutide's placeholder list price and approximately 6.2% could be treated at its placeholder net price before the budget exceeded this threshold. Between 6.3% and 7.3% of patients could be treated without crossing the budget impact threshold at its prices to reach cost-effectiveness thresholds between $150,000 and $50,000 per QALY.

Figure 7.2. Potential Budget Impact Scenarios of Oral Semaglutide as an Add-On Therapy at Different Acquisition Prices



BI: budget impact, QALY: quality-adjusted life year

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This is the second ICER review of T2DM.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table A2. Search Strategy of MEDLINE and Cochrane Central Register of Controlled Trials (via Ovid)*

	Search Terms
1	exp Diabetes Mellitus, Type 2/
2	(((adult or ketosis-resistant or matur* or late or "non-insulin depend*" or "noninsulin depend*" or slow or stable or "type 2" or "type II" or lipoatrophic) adj3 diabet*) or T2D* or MODY or NIDDM).ti,ab.
3	(semaglutide or "nn 9924" or nn9924).ti,ab.
4	exp Sitagliptin Phosphate/
5	sitagliptin or "mk 0431" or mk0431 or januvia).ti,ab.
6	(empagliflozin or "BI 10773" or BI10773 or jardiance).ti,ab.
7	exp Liraglutide/
8	(liraglutide or "NN 2211" or NN2211 or victoza).ti,ab.
9	3 or 4 or 5 or 6 or 7 or 8
10	1 or 2
11	9 and 10
12	(address or autobiography or bibliography or biography or case reports or clinical trial phase i or comment or conference review or congress or consensus development conference or duplicate publication or dictionary or directory or editorial or guideline or interview or lecture or legal case or legislation or letter or meta analysis or news or newspaper article or note or patient education handout or periodical index or personal narrative or portrait or practice guideline or review or systematic review or video-audio media).pt.
13	conference abstract.pt.
14	limit 13 to yr="1946-2016"
15	11 not (12 or 14)
16	(clinical and trial).ti,ab. or exp 'clinical trials as topic'/ or clinical trial.pt. or random*.ti,ab. or exp 'random allocation'/ or tu.xs
17	15 and 16
18	limit 17 to english language
19	(animals not (human and animals)).sh.
20	18 not 19
21	remove duplicates from 20
*Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials April 2019	

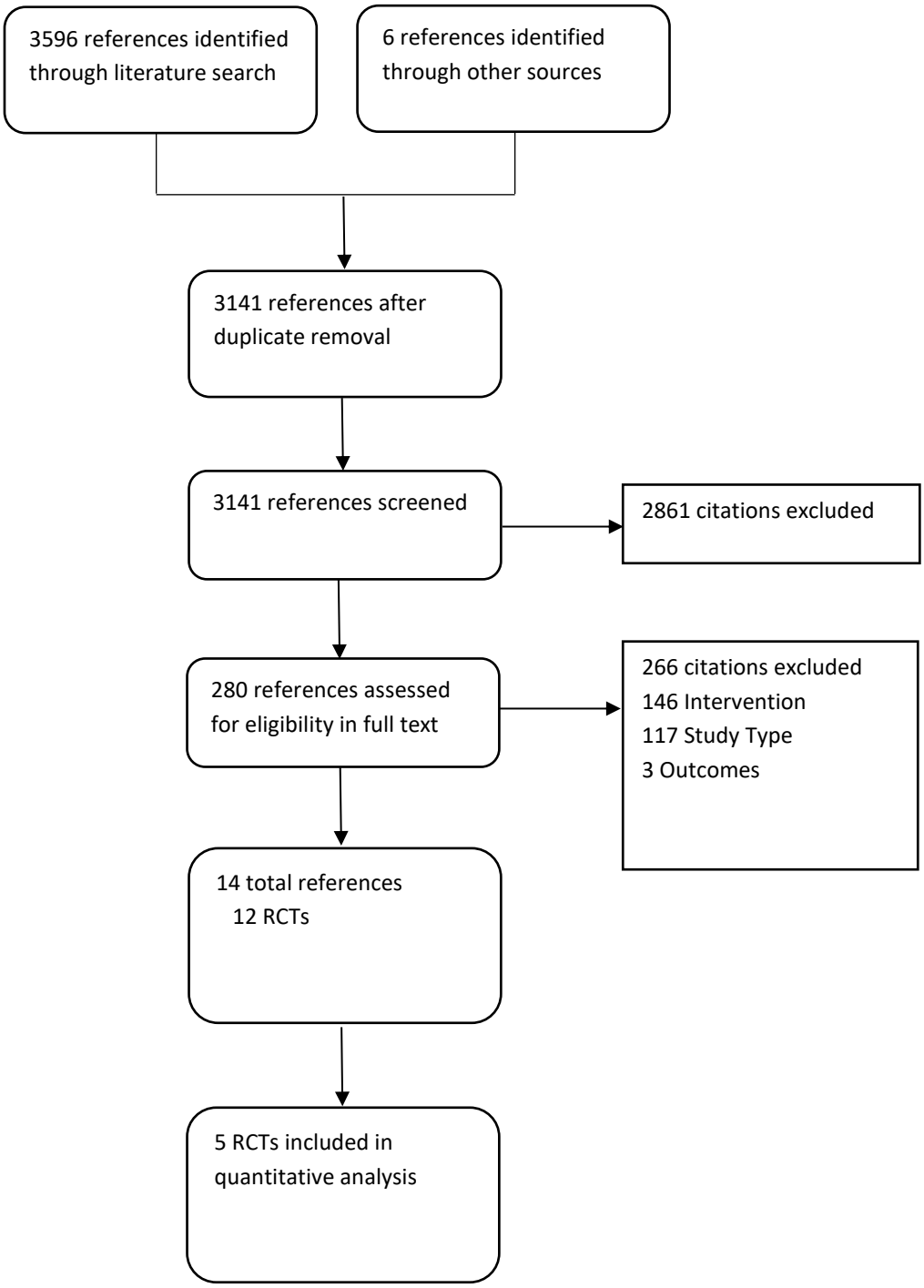
Ran search on June 11, 2019

Table A3. Search Strategy of EMBASE

	Search Terms
1	'non insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus'
2	(((adult OR 'ketosis resistant' OR matur* OR late OR 'non-insulin depend*' OR 'noninsulin depend*' OR slow OR stable OR 'type 2' OR 'type ii' OR lipoatrophic) NEAR/3 diabet*):ti,ab) OR t2d*:ti,ab OR mody:ti,ab OR niddm:ti,ab
3	'semaglutide'/exp
4	semaglutide:ti,ab OR 'nn 9924':ti,ab OR nn9924:ti,ab
5	'sitagliptin'/exp
6	sitagliptin:ti,ab OR 'mk 0431':ti,ab OR mk0431:ti,ab OR januvia:ti,ab
7	'empagliflozin'/exp
8	empagliflozin:ti,ab OR bi10773:ti,ab OR 'bi 10773':ti,ab OR jardiance:ti,ab
9	'liraglutide'/exp
10	liraglutide:ti,ab OR nn2211:ti,ab OR 'nn 2211':ti,ab OR victoza:ti,ab
11	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12	#1 OR #2
13	#11 AND #12
14	#13 NOT ('animal experiment'/de OR 'animal model'/de OR 'case report'/de OR 'human cell'/de OR 'human tissue'/de OR 'in vitro study'/de OR 'meta analysis'/de OR 'meta analysis (topic)'/de OR 'network meta-analysis'/de OR 'nonhuman'/de OR 'phase 1 clinical trial (topic)'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'systematic review'/de OR 'systematic review (topic)'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
15	#14 NOT ('conference abstract'/it AND [1950-2016]/py)
16	('clinical':ti,ab AND 'trial':ti,ab) OR 'clinical trial'/exp OR random* OR 'drug therapy':lnk OR 'clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp
17	#15 AND #16
18	#17 AND [english]/lim
19	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
20	#18 NOT #19
21	#20 NOT [medline]/lim

Ran search on June 11, 2019

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Oral Semaglutide for T2DM



Appendix B. Previous Systematic Reviews and Technology Assessments

We did not identify any prior systematic reviews or any completed or ongoing health technology assessments of oral semaglutide.

We summarized recent systematic reviews of DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists to provide context around how the comparator treatments compare to other agents within the same drug class.

DPP-4 inhibitors

Guo, W. Q., Li, L., Su, Q., Dai, W. R., & Ye, Z. L. Effect of Dipeptidyl Peptidase-4 Inhibitors on Heart Failure: A Network Meta-Analysis. Value in Health. 2017;20(10): 1427-1430.

A network meta-analysis (NMA) of fifty randomized controlled trials (RCTs) evaluated the effectiveness of dipeptidyl peptidase-4 (DPP-4) inhibitors on the risk of heart failure (HF) in patients who have type-2 diabetes mellitus (T2DM). With outcomes being hospital admissions for HF and occurrence of HF, five DPP-4 agents were evaluated: alogliptin, linagliptin, sitagliptin, saxagliptin, and vildagliptin. The agents were compared to each other as well as to other antihyperglycemic agents and placebo. Compared to placebo, results showed that there was no increased risk of HF events for patients treated with vildagliptin (risk ratio [RR] 0.71; 95% CI 0.25-1.68), sitagliptin (RR 0.86; 95% CI 0.43-1.57), and saxagliptin (RR 0.84; 95% CI 0.33-1.610). The agent alogliptin showed significant higher risk of HF (RR 2.13; 95% CI 1.06-6.26) as compared to placebo, and linagliptin showed a trend towards increased risk of HF but was not significant (RR 2.76; 95% CI 0.98-8.31). The results of the NMA favored both vildagliptin (RR 0.33; 95% CI 0.07-0.99) and sitagliptin (RR 0.40; 95% CI 0.11-0.96) when compared to alogliptin in association with a lower risk of HF. The results also favored vidaglltipin (RR 0.25; 95% CI 0.06-0.94), sitagliptin (RR 0.31; 95% CI 0.09-0.95), and saxaglitpin (RR 0.30; 95% CI 0.09-0.97) compared to linagliptin in association with a lower risk of HF. The researchers noted a few limitations of the NMA due to individual study designs. First, in a portion of the trials, DPP-4 inhibitors and other antihyperglycemic drugs were used in conjunction which makes establishing a direct link between DPP-4 inhibitors and HF risk difficult. Additionally, across the fifty trials, varying doses and differences in operationalizing HF potentially increases differences among studies. Lastly, network inconsistency in relation to comparing placebo, alogliptin, and active comparators arose in a small number of analyses.

Elgendy, I. Y., Mahmoud, A. N., Barakat, A. F., Elgendy, A. Y., Saad, M., Abuzaid, A., ... & Bavry, A. A. Cardiovascular Safety of Dipeptidyl-Peptidase IV Inhibitors: a meta-analysis of placebo-controlled randomized trials. American Journal of Cardiovascular Drugs. 2017;17(2), 143-155.

A meta-analysis evaluated DPP-4 inhibitors as compared to a placebo in patients with T2DM with a focus on cardiovascular safety. The analysis included 90 multicenter, placebo-controlled, double-blind randomized control trials with a total of 66,730 patients and a follow-up time ranging from two to 156 weeks. With the main outcome assessed being heart failure, outcomes including all-cause and cardiovascular mortality, myocardial infarction, and ischemic stroke were also assessed. At a mean of 108 weeks, DPP-4 inhibitors were not significantly associated with increased risk of heart failure as compared to the placebo (odds ratio [OR] 1.11; 95% CI 0.99-1.25; P=0.07). Between the DPP-4 inhibitor and placebo groups, the risk of ischemic stroke (OR 0.99; 95% CI 0.85-1.15; P=0.92), myocardial infarction (OR 0.98; 95% CI 0.88-1.09; P=0.69), cardiovascular mortality (OR 1.02; 95% CI 0.92-1.14; P=0.72), and all-cause mortality (OR 1.03; 95% CI 0.94-1.12; P=0.53) was similar. Further, analysis found no difference in treatment effect based on the type of DPP-4 inhibitors (P=0.76). As a class, the safety profile of DPP-4 inhibitors was concluded to be similar to the placebo for patients with T2DM with the exception of one weak evidence for increased risk of heart failure. A few key limitations of the meta-analysis were noted. Firstly, many of the included studies were small and did not address cardiovascular outcomes directly, but all were designed to test safety of the medication. In addition, the follow-up duration period varied among studies, but subgroup analyses were conducted and found that results were similar. Lastly, definitions of heart failure varied across studies but after statistical testing, there was no heterogeneity.

SGLT-2 inhibitors

Toyama T, Neuen BL, Jun M, et al. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and meta-analysis. Diabetes, obesity & metabolism. 2019;21(5):1237-1250.

We identified a systematic review and meta-analysis of SGLT-2 inhibitors assessing CV, renal, and safety outcomes in patients with T2DM and CKD. Twenty-seven studies were identified and included in the analysis with 18 being individual trials, eight being pooled analyses, and one being a regulatory report. Patients with CKD were defined as having an eGFR of less than 60 mL/min/1.73m2. Three medications were assessed (canagliflozin, dapagliflozin, and empagliflozin), and outcomes analyzed included 3-point MACE, CV death, and hospitalized or fatal heart failure. Results showed canagliflozin was the only individual agent that had a significant reduction in 3-point MACE, with the class having an overall significant reduction with a HR of 0.81 (95% CI: 0.70-0.94). For CV death, no agents showed a significant reduction and neither did the class with a HR of 0.88 (95% CI: 0.61-1.16). For hospitalized or fatal heart failure, only canagliflozin showed a significant reduction for the individual agents, while the class had a HR of 0.61 (95% CI: 0.48-0.78). Although no individual agents showed significance for the renal composite outcome (doubling of serum creatinine, ESRD, or renal death), the overall class had a significant reduction with a HR of 0.71 (95% CI: 0.53-0.95). The overall class did not show any significance for UTIs along with the same effect being seen across all individual agents. Dapagliflozin and empagliflozin both showed a significant increase in genital infections as well as the overall class with a HR of 2.86 (95% CI: 2.00-

4.10). The authors note the largest limitation of this analyses is that most of the data was derived from subgroup analyses of three large CVOTs, none of which were not dedicated to assessing renal endpoints.

Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31-39.

We identified a systematic review and meta-analysis of SGLT-2 inhibitors on CV and renal outcomes in patients with established CVD or CV risk factors only. The analysis included three SGLT-2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) and their respective CVOTs (CANVAS Program, DECLARE-TIMI 58, and EMPA-REG OUTCOME). All agents were assessed in patients with established CVD, while only the dapagliflozin and canagliflozin CVOTs provided data for patients with CV risk factors only. For patients with CVD, the SGLT-2 inhibitor class had an overall HR of 0.86 (95% CI: 0.80-0.93) for 3-point MACE. Canagliflozin and empagliflozin showed significant reductions in 3-point MACE while dapagliflozin did not have a significant reduction. Among patients with risk factors only, there were no significant effects on 3-point MACE with the overall class or individual agents. For the renal composite outcome (renal worsening, ESRD, or renal death), for patients with CVD, all of the agents showed a significant reduction while the overall class had a HR of 0.56 (95% CI: 0.47-0.67).

GLP-1 Receptor Agonists

Kristensen SL, Rorth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol. 2019.

We identified a systematic review and meta-analysis of GLP-1 receptor agonists assessing CV, mortality, and renal outcomes from CVOTs. This review consisted of seven agents (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, injectable semaglutide, and oral semaglutide) with their corresponding CVOTs (Harmony Outcomes, REWIND, EXSCEL, LEADER, ELIXA, SUSTAIN-6, and PIONEER 6). The meta-analysis showed the GLP-1 receptor agonists class significantly reduced 3-point MACE with a HR of 0.88 (95% CI 0.82-0.94). Albiglutide, dulaglutide, liraglutide, and injectable semaglutide showed significant reductions for 3-point MACE while the other agents did not. However, the data used in the calculation of 3-point MACE for lixisenatide for this meta-analysis is the HR and corresponding 95% CI for 4-point MACE (CV death, non-fatal MI, non-fatal stroke, and unstable angina). For CV death, only liraglutide and oral semaglutide showed significance, however, the class had a HR of 0.88 (95% CI: 0.81-0.96). For all-cause mortality, only exenatide, liraglutide, and oral semaglutide showed significance while the class overall had a HR of 0.88 (95% CI: 0.83-0.95). For a composite of renal outcomes (development of microalbuminuria, decline in eGFR, progression to ERSD, or death attributable to renal causes), only five of the seven CVOTs reported

the outcomes to calculate this composite (ELIXA, LEAER, SUSTAIN-6, EXSCEL, and REWIND). The class overall had a HR of 0.83 (95% CI: 0.78-0.89) with significant reductions reported for only dulaglutide, liraglutide, and injectable semaglutide. The authors note a limitation to this analysis is the differences in trial design and patient populations among the included CVOTs.

Across Classes

Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus. Circulation. 2019;139(17):2022-2031.

We identified a systematic review and meta-analysis that assessed CV and renal outcomes for GLP-1 receptor agonists and SGLT-2 inhibitors from their respective CVOTs. A total of eight trials were included in this analysis with five assessing GLP-1 receptor agonists (albiglutide, exenatide, liraglutide, lixisenatide, and injectable semaglutide) and three assessing SGLT-2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin). For patients with ASCVD, both GLP-1 receptor agonists and SGLT-2 inhibitors showed similar results with HRs of 0.87 (95% CI: 0.82-0.92) and 0.86 (0.80-0.93) respectively. For the outcome of hospitalization for heart failure, SGLT-2 inhibitors showed a significant reduction with a HR of 0.69 (95% CI: 0.61-0.79) while GLP-1 receptor agonists showed no significant results (HR: 0.93; 95% CI: 0.83-1.04). For a composite renal outcome (new-onset macroalbuminuria, ESRD, and renal death), both classes showed a significant reduction while SGLT-2 inhibitors had a more profound effect with a HR of 0.62 (95% CI: 0.58-0.67) while GLP-1 receptor agonists had a HR of 0.82 (95% CI: 0.75-0.89). However, when removing macroalbuminuria outcome from the renal outcome, GLP-1 receptor agonists lose their significant effect (HR: 0.92; 95% CI: 0.80-1.06) while SGLT-2 inhibitors effect remains similar (HR: 0.55; 95% CI: 0.48-0.64).

Alfayez OM, Al Yami MS, Alshibani M, et al. Network meta-analysis of nine large cardiovascular outcome trials of new antidiabetic drugs. Primary care diabetes. 2019;13(3):204-211.

We identified a systematic review and meta-analysis that assessed CV outcomes for GLP-1 receptor agonists, SGLT-2 inhibitors, and DPP-4 inhibitors from their respective CVOTs. A total of nine trials were included in this analysis with four being of GLP-1 receptor agonists (albiglutide, exenatide, liraglutide, and injectable semaglutide), two being of SGLT-2 inhibitors (canagliflozin and empagliflozin), and three being of DPP-4 inhibitors (alogliptin, saxagliptin, and sitagliptin). The GLP-1 receptor agonists as a class overall had a RR for 3-point MACE of 0.92 (95% CI: 0.87-0.97), a RR for CV death of 0.88 (95% CI: 0.82-0.96), and a RR for hospitalization for heart failure of 0.94 (95% CI: 0.84-1.05). The results from their network meta-analysis showed no significant difference between in-class agents of GLP-1 receptor agonists for any of the CV outcomes. The SGLT-2 inhibitors as a class overall had a RR for 3-point MACE of 0.96 (95% CI: 0.88-1.05), a RR for CV death of 0.87 (95%

CI: 0.76-1.00), and a RR for hospitalization for heart failure of 0.72 (95% CI: 0.60-0.86). The results from their network meta-analysis showed no significant difference between in-class agents of SGLT-2 inhibitors for any of the CV outcomes. The DPP-4 inhibitors as a class overall had a RR for 3-point MACE of 0.99 (95% CI: 0.93-1.05), a RR for CV death of 1.01 (95% CI: 0.91-1.12), and a RR for hospitalization for heart failure of 1.13 (95% CI: 1.00-1.26). The results from their network meta-analysis showed no significant difference between in-class agents of DPP-4 inhibitors for any of the CV outcomes.

Appendix C. Ongoing Studies

Title/ Trial Sponsor	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Oral Semaglutide					

Title/ Trial Sponsor	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
A Heart Disease Study of Semaglutide in Patients With Type 2 Diabetes (SOUL) **Novo Nordisk A/S** NCT03914326	Phase III, randomized, blinded, parallel assignment Enrollment: 9,642	Arm 1: Oral semaglutide (increasing doses 3mg/7mg/14mg) once daily Arm 2: Placebo (one tablet daily) Treatment duration: 3.5 to five years	Inclusion: • Age ≥ 50 • Diagnosed with T2DM • HbA1C 6.5% - 10.0% (both inclusive) • At least one of the following conditions: coronary heart disease, cerebrovascular disease, symptomatic peripheral artery disease, or chronic kidney disease Exclusion: • MI, stroke, hospitalization for unstable angina or transient ischemic attack within 60 days prior to screening • Planned revascularization • Class IV Heart failure (New York Heart Association classification)	Primary: Time to first occurrence of 3-point MACE (CV death, nonfatal MI, nonfatal stroke) Secondary (selected): Time to first composite renal outcome; time to first major adverse limb event (MALE)	July 29, 2024

A Research Study Comparing a New Medicine Oral Semaglutide to Sitagliptin in People With Type 2 Diabetes (PIONEER 12) **Novo Nordisk A/S** NCT04017832	Phase III, randomized, blinded, parallel assignment Enrollment: 1,444	Arm 1: Oral semaglutide 3 mg once daily Arm 2: Oral semaglutide 7 mg once daily Arm 3: Oral semaglutide 14 mg once daily Arm 4: Sitagliptin tablets 100 mg once daily Treatment duration: 26 weeks	Inclusion: • Age ≥ 18 • Diagnosed with T2DM for ≥ 60 days prior to screening • HbA1c between 7.0-10.5% (both inclusive) • Stable daily dose of metformin (≥ 1500 mg or max tolerated dose for patient) for ≥ 60 days prior to screening Exclusion: • MI, stroke, hospitalization for unstable angina or transient ischemic attack within 180 of screening • Class IV heart failure (New York Heart Association classification) • Planned revascularization • Renal impairment • Family (first degree relative) / personal history of MEN 2 or MTC • History or presence of acute or chronic pancreatitis • History of relevant surgical procedures of the stomach (potentially affect absorption of trial product) • Subjects with alanine aminotransferase (ALT) • Uncontrolled and potentially unstable diabetic retinopathy or maculopathy • Presence or history of malignant neoplasms within 5 years prior to screening	Primary: Change in HbA1c Secondary (selected): Change in body weight, fasting plasma glucose, lipid levels, and Short-Form-36 version 2	August 11, 2021

Title/ Trial Sponsor	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Injectable Semaglutide (selected)					
A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease (FLOW) **Novo Nordisk A/S** **NCT03819153**	Phase III, randomized, blinded, parallel assignment Enrollment: 3,160	Arm 1: Injectable semaglutide 1.0 mg once-weekly Arm 2: Placebo Treatment duration: up to five years	Inclusion: • Age ≥ 18 • Diagnosed with T2DM • HbA1c≤10% • Renal impairment (eGFR≥50 and ≤75 mL/min/1.73 m^2 and UACR >300 and <5000 mg/g, or eGFR≥25 and <50 mL/min/1.73 m^2 and UACR >100 and <5000 mg/g) • Treatment with a renin-angiotensin-aldosterone system blocking agent, including an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), unless contraindicated Exclusion: • Congenital or hereditary kidney diseases, autoimmune kidney diseases, or congenital urinary tract malformations • MI, stroke, hospitalization for unstable angina or transient ischemic attack within 60 days prior to screening • Class IV heart failure (New York Heart Association classification) • Planned revascularization • Current or recent chronic or intermittent hemodialysis or peritoneal dialysis • Uncontrolled and potentially unstable diabetic retinopathy or maculopathy	Primary: Time to first composite outcome including persistent eGFR decline ≥50% from baseline, reaching ESRD, death from kidney disease or CV death Secondary (selected): Annual rate of change in eGFR; time to first 3-point MACE	August 19, 2024

A Research Study to Look at How Semaglutide Compared to Placebo Affects Diabetic Eye Disease in People With Type 2 Diabetes (FOCUS) **Novo Nordisk A/S** **NCT03811561**	Phase III, randomized, blinded, parallel assignment Enrollment: 1,500	Arm 1: Injectable semaglutide 1.0 mg once-weekly Arm 2: Placebo Treatment duration: up to five years	Inclusion: • Age ≥ 18 • Diagnosed with T2DM • HbA1c 7.0% to 10% (both inclusive) • Eye inclusion criteria (both eyes must meet all criteria): – Early Treatment Diabetic Retinopathy Study (ETDRS) level of 10-75 (both inclusive) – No ocular or intraocular treatment for diabetic retinopathy or macular oedema within 12 months prior screening, and no anticipated need for treatment within six months after randomization – Best-corrected visual acuity ≥30 letters – No previous treatment with pan-retinal laser photocoagulation Exclusion: • MI, stroke, hospitalization for unstable angina or transient ischemic attack within 60 days of screening • Class IV heart failure (New York Heart Association classification) • Planned revascularization • Renal impairment • Presence or history of malignant neoplasms within 5 years prior to screening • Family (first degree relative) / personal history of MEN 2 or MTC	Primary: Presence of ≥ 3 steps ETDRS subject level progression Secondary (selected): change in visual acuity; occurrence of treatment for diabetic retinopathy or macular oedema	February 5, 2025

Long Term Comparative Effectiveness of Once Weekly Semaglutide Versus Standard of Care in a Real World Adult US Population With Type 2 Diabetes - a Randomized Pragmatic Trial **Novo Nordisk A/S** NCT03596450	Phase IV, randomized, open-label, parallel assignment Enrollment: 2,250	Arm 1: Injectable semaglutide according to labelled dosing, once-weekly Arm 2: Standard of Care Treatment duration: two years	Inclusion: • Age ≥ 18 • Diagnosed with T2DM • Treatment with metformin as monotherapy • Current member of Anthem affiliated commercial health plan • Available and documented HbA1c • Treatment intensification required to achieve glycemic target, determined at discretion of the study physician Exclusion: • Treatment with any other medication for diabetes within 30 days prior to screening	Primary: Proportion of patients with HbA1c<7.0% Secondary (selected): Change in HbA1c, body weight; changes in various quality of life measures including: Diabetes Treatment Satisfaction Questionnaire, Short Form 12-Item Version 2, and Work Productivity and Activity Impairment, General Health Questionnaire; amount of all-cause healthcare resource utilization	November 20, 2020

Title/ Trial Sponsor	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Research Studies Looking at How Semaglutide Works in People With Type 2 Diabetes, as Part of Local Clinical Practice, conducting in various locations: **UNITED KINDGOM** NCT03876015 **NETHERLANDS** NCT03929679 **SPAIN** NCT04067999 **CANADA** NCT03457012 **SWITZERLAND** NCT03631186 **DENMARK/SWEDEN** NCT03648281 **Novo Nordisk A/S**	Prospective cohorts	Arm: Injectable semaglutide dosed at physicians' discretion, once-weekly Treatment duration: 30 weeks	Inclusion: • Age ≥ 18 • Diagnosed with T2DM • Available and documented HbA1c • Decision to initiate treatment with semaglutide was made independently of decision to enter trial Exclusion: • Known hypersensitivity • Mental incapacity, unwillingness, or language barriers precluding adequate understanding or cooperation	Primary: Change in HbA1c Secondary (selected): Change in weight; change in Diabetes Treatment Satisfaction Questionnaire and Short-Form-36	Ranging from November 2019 to January 2021

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs, using the categories "good," "fair," or "poor" (see Appendix Table F2)[91] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

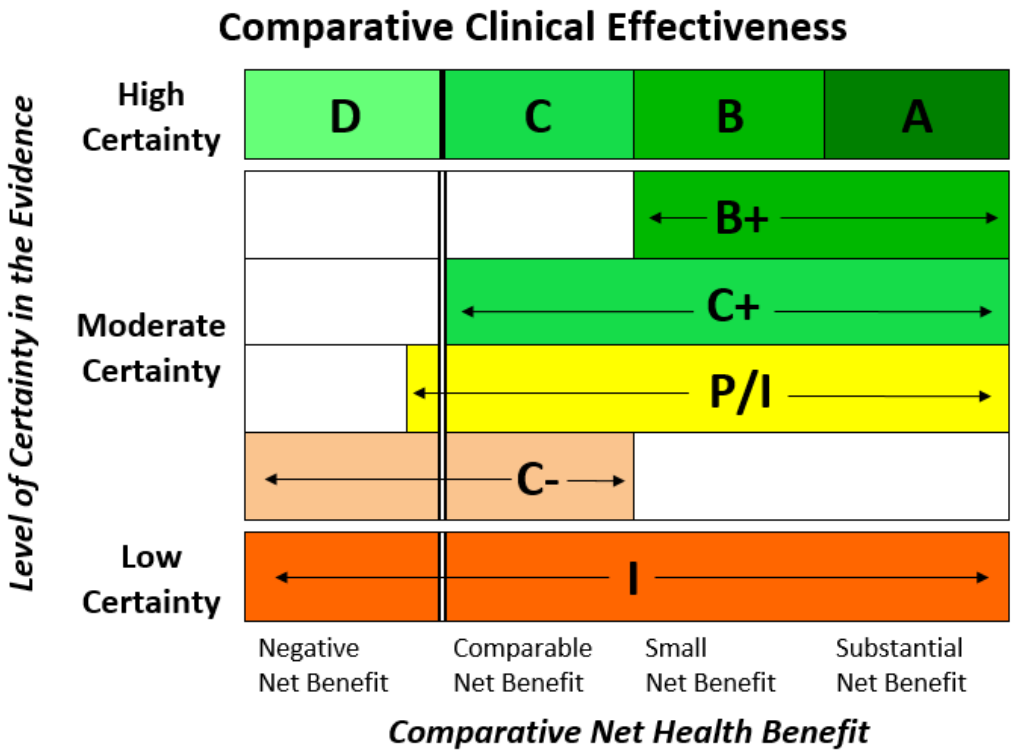
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[38]

Figure D1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable" *- High certainty of a comparable net health benefit*
D = "Negative" *- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

Table D1. Study Quality of Included Trials

	Comparable Groups	Non-Differential Loss to Follow-Up	Use of Blinding	Clear Definition of Interventions	Clean Definition of Outcomes	Appropriate Handling of Missing Data	Overall Quality
PIONEER 1	Yes	Yes	Yes	Yes	Yes	Yes	Good
PIONEER 2*							
PIONEER 3	Yes	Yes	Yes	Yes	Yes	Yes	Good
PIONEER 4	Yes	Yes	Yes	Yes	Yes	Yes	Good
PIONEER 5	Yes	Yes	Yes	Yes	Yes	Yes	Good
PIONEER 7	Yes	Yes	No	Yes	Yes	Yes	Good
PIONEER 8*							
Cardiovascular Outcomes Trials							
PIONEER 6	Yes	Yes	Yes	Yes	Yes	Yes	Good
SUSTAIN 6	Yes	Yes	Yes	Yes	Yes	Yes	Good
LEADER	Yes	Yes	Yes	Yes	Yes	Yes	Good
EMPA-REG OUTCOME	Yes	Yes	Yes	Yes	Yes	Yes	Good
TECOS	Yes	Yes	Yes	Yes	Yes	Yes	Good

*The data for PIONEER 2 and PIONEER 8 were only available in grey literature. Due to this, we did not assign quality rating for the trials. We will assign a quality rating upon release of peer-reviewed publications.

Table D2. Study Design of Included PIONEER Trials

Trial	Interventions	Inclusion Criteria	Phases	Key Outcomes	Rescue Medication Criteria
PIONEER 1 vs. placebo added diet & exercise N=703	1. Oral semagltuide 3 mg (n=175) 2. Oral semagltuide 7 mg (n=175) 3. Oral semagltuide 14 mg (n=175) 4. Placebo (n=178)	• Adults (≥18 y) diagnosed with T2DM for ≥30 days • Treated with stable diet & exercise for ≥30 days • HbA1c of 7.0%-9.5%	26-week blinded	Change in HbA1c at week 26 (primary) Change in body weight at week 26 (secondary)	FPG >240 mg/dL from weeks 8 to 13 or >200 mg/dL from week 14+
PIONEER 2 vs. empagliflozin added to MET N=821	1. Oral semaglutide 14 mg (n=411) 2. Empagliflozin 25 mg (n=410)	• Adults (>18 y) diagnosed with T2DM for ≥90 days • Treated with stable dose of MET for ≥90 days • HbA1c of 7.0%-10.5%	52-week open-label	Change in HbA1c at week 26 (primary) Change in body weight at week 26 (secondary)	Not available
PIONEER 3 vs. sitagliptin added to MET ± SU N=1864	1. Oral semagltuide 3 mg (n=466) 2. Oral semagltuide 7 mg (n=466) 3. Oral semagltuide 14 mg (n=465) 4. Sitagliptin 100 mg (n=467)	• Adults (≥18 y) diagnosed with T2DM for ≥90 days • Treated with stable dose of MET ± SU for ≥90 days • HbA1c of 7.0%-10.5%	78-week, blinded	Change in HbA1c at week 26 (primary) Change in body weight at week 26 (secondary)	FPG >260 mg/dL for weeks 8 to 13, >240 mg/dL for weeks 14 to 25, and >200 mg/dL or HbA1c >8.5% for week 26+
PIONEER 4 vs. liraglutide added to MET ± SGLT-2i N=711	1. Oral semaglutide 14 mg (n=285) 2. Liraglutide 1.8 mg (n=284) 3. Placebo (n=142)	• Adults (≥18 y) diagnosed with T2DM for ≥90 days • Treated with stable dose of MET with or without SGLT-2i for ≥90 days • HbA1c of 7.0%-9.5%	52-week, blinded	Change in HbA1c at week 26 (primary) Change in body weight at week 26 (secondary)	FPG> 240 mg/dL from weeks 8 to 13, >200 mg/dL from week 14+, or HbA1c >8·5% from week 26+
PIONEER 7 vs. sitagliptin added to 1 to 2 oral agents N=504	1. Oral semaglutide [flexible, 3, 7, or 14 mg] (n=253) 2. Sitagliptin 100 mg (n=251)	• Adults (≥18 y) diagnosed with T2DM for ≥90 days • Treated with stable dose 1 to 2 oral agents (MET, SU, TZD, SGLT-2i) for ≥90 days • HbA1c of 7.0%-9.5%	52-week, open-label	Proportion achieving HbA1c<7.0% at week 52 (primary) Change in body weight at week 52 (secondary)	HbA1c of 8·5% from week 32+

Trial	Interventions	Inclusion Criteria	Phases	Key Outcomes	Rescue Medication Criteria
PIONEER 8 vs. placebo added to insulin N=731	1. Oral semaglutide 3 mg (n=184) 2. Oral semaglutide 7 mg (n=182) 3. Oral semaglutide 14 mg (n=181) 4. Placebo (n=184)	• Adults (>18 y) diagnosed with T2DM for ≥90 days • Treated with stable insulin ≥90 days (basal insulin alone, basal + bolus insulin, premixed insulin) • HbA1c of 7.0%-9.5%	52-week, blinded	Change in HbA1c at week 26 (primary) Change in body weight at week 26 (secondary)	Not available
PIONEER 5 vs. placebo added to 1 to 2 oral agents N=324	1. Oral semaglutide 14 mg (n=163) 2. Placebo (n=161)	• Adults (>18 y) diagnosed with T2DM for ≥90 days • Moderate renal impairment (eGFR 30-59 mL/min/1.73m2) • Treated with 1 of the following for ≥90 days: MET, a SU, or both; or basal insulin ± MET • HbA1c of 7.0%-9.5%	26-week, double-blind	Change in HbA1c at week 26 (primary) Change in body weight at week 26 (secondary)	FPG >240 mg/dL in weeks 12 to 16 or >200 mg/dL from week 17+
PIONEER 6 vs. placebo added to standard-of-care treatment N=3183	1. Oral semaglutide 14 mg (n=1591) 2. Placebo (n=1592)	≥50 years old with eCVD or CKD, or ≥60 years old with CV risk factors	Event-driven, double-blind	3-point composite MACE (primary)	Investigators were encouraged to intensify treatment in line with standard of care guidelines

CKD: chronic kidney disease, eCVD: established cardiovascular disease, eGFR: estimated glomerular filtration rate, FPG: fasting plasma glucose, HbA1c: glycated hemoglobin, MACE: major adverse cardiovascular events, MET: metformin, mg: milligram, SU: sulfonylurea, SGLT-2i: sodium-glucose cotransporter inhibitor, T2DM: type 2 diabetes, TZD: thiazolidinediones, y: years

Table D3. Baseline Characteristics of Head-to-Head PIONEER Trials

Trial	PIONEER 2		PIONEER 3				PIONEER 4			PIONEER 7	
Arm	SEM 14 mg	EMP 25 mg	SEM 3 mg	SEM 7 mg	SEM 14 mg	SIT 100 mg	SEM 14 mg	LIR 1.8 mg	PBO	SEM flex	SIT 100 mg
N	411	410	466	466	465	467	285	284	142	253	251
Age, years	57 (10)	58 (10)	58 (10.0)	58 (10.0)	57 (10.0)	58 (10.0)	56 (10)	56 (10)	57 (10)	56.9 (9.7)	58.9 (10.1)
Male	206 (50.1%)	209 (51.0%)	254 (54.5%)	245 (52.7%)	247 (53.1%)	238 (51.0%)	147 (52%)	149 (52%)	74 (52%)	145 (57%)	140 (56%)
White	*Not available*		344 (73.8%)	330 (71.0%)	317 (68.2%)	333 (71.3%)	208 (73%)	212 (75%)	99 (70%)	195 (77%)	186 (74%)
Black or African American			38 (8.2%)	38 (8.2%)	45 (9.7%)	39 (8.4%)	12 (4%)	9 (3%)	8 (6%)	22 (9%)	25 (10%)
Asian			56 (12.0%)	69 (14.8%)	61 (13.1%)	59 (12.6%)	39 (14%)	36 (13%)	19 (13%)	34 (13%)	38 (15%)
Hispanic or Latino			76 (16.3%)	77 (16.6%)	75 (16.1%)	93 (19.9%)	17 (6%)	18 (6%)	5 (4%)	48 (19%)	57 (23%)
HbA1c, %	8.1 (0.9)	8.1 (0.9)	8.3 (1.0)	8.4 (1.0)	8.3 (0.9)	8.3 (0.9)	8.0 (0.7)	8.0 (0.7)	7.9 (0.7)	8.3 (0.6)	8.3 (0.6)
Duration of Diabetes, years	7.2 (5.8)	7.7 (6.3)	8.4 (6.1)	8.3 (5.8)	8.7 (6.1)	8.8 (6.0)	7.8 (5.7)	7.3 (5.3)	7.8 (5.5)	8.6 (6.3)	9.0 (6.2)
Body Weight, kg	91.9 (20.5)	91.3 (20.1)	91.6 (22.0)	91.3 (20.8)	91.2 (21.7)	90.9 (21.0)	92.9 (20.6)	95.5 (21.9)	93.2 (20.0)	88.9 (19.6)	88.4 (20.1)
Body Mass Index, kg/m²	32.9 (6.3)	32.8 (5.9)	32.6 (6.7)	32.6 (6.4)	32.3 (6.3)	32.5 (6.2)	32.5 (5.9)	33.4 (6.7)	32.9 (6.1)	31.5 (6.5)	31.5 (6.1)
Fasting Plasma Glucose, mg/dL	171.5 (41.8)	174.0 (45.2)	174.2 (50.5)	170.3 (42.9)	167.9 (45.1)	171.8 (41.9)	9.27 (2.23)*	9.30 (2.22)*	9.25 (2.27)*	9.8 (2.4)*	9.8 (2.6)*
eGFR, mL/min per 1.73 m²	*Not available*		96 (15)	96 (16)	95 (16)	96 (15)	96 (15)	96 (15)	95 (15)	97.0 (14.4)	95.3 (15.6)
Metformin	411 (100%)	410 (100%)	466 (100%)	465 (100%)	465 (100%)	467 (100%)	285 (100%)	284 (100%)	142 (100%)	248 (98%)	238 (95%)
Sulfonylurea	N/A	N/A	220 (47.2%)	218 (46.9%)	220 (47.3%)	219 (46.9%)	N/A	N/A	N/A	123 (49%)	123 (49%)
SGLT-2 Inhibitor	N/A	N/A	N/A	N/A	N/A	N/A	74 (26%)	73 (26%)	36 (25%)	18 (7%)	35 (14%)
TZD	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	9 (4%)	4 (2%)
Insulin	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

*Data are reported in mmol/L

dL: deciliter, eGFR: estimated glomerular filtration rate, EMP: empagliflozin, flex: flexible, HbA1c: glycated hemoglobin, kg: kilogram, L: liter, LIR: liraglutide, m: meter, mg: milligram, min: minute, mmoL: millimoles, mL: milliliter, N/A: not applicable, PBO: placebo, SEM: semaglutide, SIT: sitagliptin, TZD: thiazolidinediones

Table D4. Baseline Characteristics of Placebo-Controlled PIONEER Trials

Trial	PIONEER 1				PIONEER 5		PIONEER 6		PIONEER 8			
Arm	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO	SEM 14 mg	PBO	SEM 14 mg	PBO	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO
N	175	175	175	178	163	161	1591	1592	184	182	181	184
Age, years	55 (11)	56 (11)	54 (11)	54 (11)	71 (8)	70 (8)	66 (7)	66 (7)	61 (9)	60 (10)	61 (10)	60 (10)
Male	89 (50.9%)	93 (53.1%)	86 (49.1%)	89 (50.0%)	83 (51%)	73 (45%)	1084 (68.1%)	1092 (68.6%)	102 (55.4%)	103 (56.6%)	85 (47%)	105 (57.1%)
White	135 (77.1%)	131 (74.9%)	130 (74.3%)	132 (74.2%)	158 (97%)	152 (94%)	1148 (72.2%)	1152 (72.4%)	*Not available*			
Black or African American	6 (3.4%)	11 (6.3%)	10 (5.7%)	10 (5.6%)	4 (2%)	9 (6%)	89 (5.6%)	103 (6.5%)				
Asian	31 (17.7%)	30 (17.1%)	29 (16.6%)	31 (17.4%)	1 (1%)	0.0	324 (20.4%)	306 (19.2%)				
Hispanic or Latino	52 (29.7%)	31 (17.7%)	46 (26.3%)	51 (28.7%)	7 (4%)	14 (9%)	NR	NR				
HbA1c, %	7.9 (0.7)	8.0 (0.6)	8.0 (0.7)	7.9 (0.7)	8.0 (0.7)	7.9 (0.7)	8.2 (1.6)	8.2 (1.6)	8.2 (0.7)	8.2 (0.7)	8.2 (0.7)	8.2 (0.7)
Duration of Diabetes, yrs	3.8 (5.3)	3.6 (5.1)	3.4 (4.4)	3.4 (4.6)	14.1 (8.6)	13.9 (7.4)	14.7 (8.5)	15.1 (8.5)	*Not available*			
Body Weight, kg	86.9 (21.0)	89.0 (21.8)	88.1 (22.1)	88.6 (23.4)	91.3 (17.8)	90.4 (17.5)	91.0 (21.4)	90.8 (21.0)	85.9 (21.5)	87.1 (23.6)	84.6 (21.0)	86.0 (21.4)
BMI, kg/m²	31.8 (6.3)	31.6 (6.4)	31.7 (6.6)	32.2 (6.9)	32.2 (5.4)	32.6 (5.5)	32.3 (6.6)	32.3 (6.4)	*Not available*			
FPG, mg/dL	158 (42)	162 (42)	158 (39)	160 (39)	9.1 (2.7)*	9.1 (2.8)*	155.0 (58.1)	157.3 (60.8)				
eGFR, mL/min per 1.73 m²	99 (14)	95 (16)	97 (16)	100 (15)	47 (10)	48 (10)	74 (21)	74 (21)				
Metformin	*N/A*				132 (81.0%)	110 (68.3%)	1221 (76.7%)	1242 (78.0%)				
Sulfonylurea					65 (39.9%)	66 (41.0%)	517 (32.5%)	510 (32.0%)				
SGLT-2 Inhibitor					N/A	N/A	165 (10.4%)	140 (8.8%)				
TZD					N/A	N/A	65 (4.1%)	53 (3.3%)				
Insulin					59 (36.2%)	55 (34.2%)	968 (60.8%)	962 (60.4%)	184 (100%)	182 (100%)	181 (100%)	184 (100%)

*Data are reported in mmol/L

dL: deciliter, eGFR: estimated glomerular filtration rate, HbA1c: glycated hemoglobin, kg: kilogram, L: liter, m: meter, mg: milligram, min: minute, mmoL: millimoles, mL: milliliter, N/A: not applicable, NR: not reported, PBO: placebo, SEM: semaglutide, TZD: thiazolidinediones

Table D5. Key Efficacy Outcomes in Head-to-Head PIONEER Trials

Trial	PIONEER 2		PIONEER 3				PIONEER 4			PIONEER 7	
Arm	SEM 14 mg	EMP 25 mg	SEM 3 mg	SEM 7 mg	SEM 14 mg	SIT 100 mg	SEM 14 mg	LIR 1.8 mg	PBO	SEM flex	SIT 100 mg
N at baseline	411	410	466	465	465	467	285	284	142	253	251
Change in HbA1c, %											
Week 26, N	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*278*	*272*	*134*	*NR*	
Mean change	-1.3	-0.9	-0.6	-1	-1.3	-0.8	-1.2 (0.1)	-1.1 (0.1)	-0.2 (0.1)		
ETD (95% CI); p-value	-0.4 (-0.6, -0.3) p<0.0001	reference	0.2 (0.0, 0.3) p=0.008	-0.3 (-0.4 , -0.1) p<0.001	-0.5 (-0.6, -0.4) p<0.001	reference	----	SEM vs. LIR: -0.1 (-0.3, 0) p=0.0645	SEM vs. PBO: -1.1 (-1.2, -0.9) p<0.0001		
Week 52, N	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*275*	*269*	*133*	*253*	*251*
Mean change	-1.3	-0.9	-0.6	-1.0	-1.2	-0.7	-1.2	-0.9	-0.2	-1.3 (0.1)	-0.8 (0.1)
ETD (95% CI); p-value	-0.4 (-0.5, -0.3) p<0.0001	reference	0.0 (-0.1, 0.2); p=0.50	-0.3 (-0.4, -0.1) p<0.001	-0.5 (-0.6, -0.3) p<0.001	reference	----	SEM vs. LIR: -0.3 (-0.5, -0.1); p=0.0002	SEM vs. PBO: -1.0 (-1.2, -0.8); p<0.0001	-0.5 (-0.7, -0.4) p<0.0001	reference
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	
Mean change			-0.6	-0.8	-1.1	-0.7					
ETD (95% CI); p-value			0.0 (-0.1 , 0.2) p=0.61	-0.1 (-0.3 , 0.0) p=0.06	-0.4 (-0.6, -0.3) p<0.001	reference					
Proportion Achieving HbA1c<7.0%											
Week 26, N	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*278*	*272*	*134*	*NR*	
%	66.8	40	27	42	55	32	67.6	61.8	14.2		
OR (95% CI); p-value	3.39 (2.47, 4.65) p<0.0001	reference	ETD: -5 (-11, 1) p=0.07	ETD: 10 (4, 17) p<0.001	ETD: 23 (17, 30) p<0.001	reference	----	SEM vs. LIR: 1.31 (0.91, 1.89) p=0.153	SEM vs. PBO: 17.1 (9.5, 30.77) p<0.0001		
Week 52, N			*NR*	*NR*	*NR*	*NR*	*275*	*269*	*133*	*230*	*238*
%	66.1	43.2	27	38	53	31	60.7	55	15	58	25

Trial	PIONEER 2		PIONEER 3				PIONEER 4			PIONEER 7	
Arm	**SEM 14 mg**	**EMP 25 mg**	**SEM 3 mg**	**SEM 7 mg**	**SEM 14 mg**	**SIT 100 mg**	**SEM 14 mg**	**LIR 1.8 mg**	**PBO**	**SEM flex**	**SIT 100 mg**
OR (95% CI); p-value	2.71 (1.99, 3.69) p<0.0001	reference	ETD: -4 (-10, 2) p=0.15	ETD: 7 (0, 13) p=0.04	ETD: 22 (16, 28) p<0.001	reference	----	SEM vs. LIR: 1.33 (0.93, 1.91) p=0.1193	SEM vs. PBO: 11.36 (6.4, 20.19) p<0.0001	4.40 (2.89, 6.7) p<0.0001	reference
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	
%			27	37	44	29					
OR (95% CI); p-value			ETD: -2 (-8, 4) p=0.48	ETD: 8 (2, 14) p=0.01	ETD: 15 (8, 21) p<0.001	reference					
Proportion Achieving HbA1c≤6.5%											
Week 26, N	*Not available*		*NR*	*NR*	*NR*	*NR*	*278*	*272*	*134*	*NR*	
%			13	26	36	14	48	43	5		
OR (95% CI); p-value			ETD: -1 (-5, 3) p=0.60	ETD: 12 (7, 17) p<0.001	ETD: 22 (16, 27) p<0.001	reference	----	SEM vs. LIR: 1.22 (0.86, 1.74 p=0.2687	SEM vs. PBO: 21.42 (9.41, 48.75) p<0.0001		
Week 52, N			*NR*	*NR*	*NR*	*NR*	*275*	*269*	*133*	*230*	*238*
%			14	22	32	14	43	33	4	33.0	12.2
OR (95% CI); p-value			ETD: -0 (-5, 4) p=0.90	ETD: 8 (3, 13) p<0.001	ETD: 18 (13, 24) p<0.001	reference	----	SEM vs. LIR: 1.63 (1.13, 2.33) p=0.0084	SEM vs. PBO: 21.38 (8.36, 54.63) p<0.0001	3.82 (2.32, 6.3) p<0.0001	reference
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	
%			13	23	29	14					
OR (95% CI); p-value			ETD: -1 (-5, 3) p=0.63	ETD: 9 (4, 14) p<0.001	ETD: 15 (10, 20) p<0.001	reference					
Proportion with HbA1c<7.0% without Hypoglycemia or Weight Gain											
Week 26, N	*Not available*		*NR*	*NR*	*NR*	*NR*	*278*	*271*	*134*	*NR*	
%			20	34	46	20	60.8	53.5	11.2		

Trial	PIONEER 2		PIONEER 3				PIONEER 4			PIONEER 7	
Arm	**SEM 14 mg**	**EMP 25 mg**	**SEM 3 mg**	**SEM 7 mg**	**SEM 14 mg**	**SIT 100 mg**	**SEM 14 mg**	**LIR 1.8 mg**	**PBO**	**SEM flex**	**SIT 100 mg**
OR (95% CI); p-value			ETD: -1 (-5, 4) p=0.80	ETD: 14 (8, 19) p<0.001	ETD: 26 (20, 32) p<0.001	reference	----	SEM vs. LIR: 1.33 (0.93, 1.88) p=0.1141	SEM vs. LIR: 15.31 (8.31, 28.2) p<0.0001		
Week 52, N			*NR*	*NR*	*NR*	*NR*	*275*	*269*	*133*	*230*	*238*
%			20	30	43	20	56.4	48.3	11.3	45.2	14.7
OR (95% CI); p-value			ETD: -0 (-5, 5) p=0.97	ETD: 10 (5, 16) p<0.001	ETD: 23 (17, 29) p<0.001	reference	----	SEM vs. LIR: 1.39 (0.98, 1.97) p=0.0680	SEM vs. LIR: 12.58 (6.79, 23.28) p<0.0001	5.12 (3.21, 8.18) p<0.0001	reference
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	
%			20	31	34	19					
OR (95% CI); p-value			ETD: 1 (-4, 6) p=0.80	ETD: 11 (6, 17) p<0.001	ETD: 15 (9, 20) p<0.001	reference					
Change in Body Weight, kg											
Week 26, N	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*278*	*271*	*134*	*NR*	
Mean change	-3.8	-3.7	-1.2	-2.2	-3.1	-0.6	-4.4 (0.2)	-3.1 (0.2)	-0.5 (0.3)		
ETD (95% CI), p-value	-0.1 (-0.7, 0.5)	reference	-0.6 (-1.1, -0.1) p=0.2	-1.6 (-2.0, -1.1) p<0.001	-2.5 (-3.0, -2.0) p<0.001	reference	----	SEM vs. LIR: -1.2 (-1.9, -0.6) p=0.003	SEM vs. PBO: -3.8 (-4.7, -3.0) p<0.0001		
Week 52, N	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*275*	*269*	*133*	*253*	*251*
Mean change	-3.8	-3.6	-1.6	-2.4	-3.4	-0.8	-4.3	-3	-1	-2.6 (0.3)	-0.7 (0.2)
ETD (95% CI), p-value	-0.2 (-0.9, 0.5)	reference	-0.8 (-1.4, -0.2) p=0.008	-1.7 (-2.3, -1.1) p<0.001	-2.7 (-3.3, -2.1) p<0.001	reference	----	SEM vs. LIR: -1.3 (-2.1, -0.5) p=0.0019	SEM vs. PBO: -3.3 (-4.3, -2.4) p<0.0001	-1.9 (-2.6, -1.2) p<0.0001	reference
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	
Mean change			-1.9	-2.7	-3.2	-1					
ETD (95% CI), p-value			-0.8	-1.7	-2.1	reference					

Trial	PIONEER 2		PIONEER 3				PIONEER 4			PIONEER 7	
Arm	SEM 14 mg	EMP 25 mg	SEM 3 mg	SEM 7 mg	SEM 14 mg	SIT 100 mg	SEM 14 mg	LIR 1.8 mg	PBO	SEM flex	SIT 100 mg
			(-1.5, -0.1) p=0.02	(-2.3, -1.0) p<0.001	(-2.8, -1.5) p<0.001						
Proportion with Weight Loss≥5.0%											
Week 26, N	*Not available*		*NR*	*NR*	*NR*	*NR*	*278*	*271*	*134*	*NR*	
%			13	19	30	10	43.5	27.7	7.5		
OR (95% CI); p-value			ETD: 3 (-1, 7) p=0.15	ETD: 9 (4, 13) p<0.001	ETD: 20 (15, 25); p<0.001	reference	----	SEM vs. LIR: 1.95 (1.36, 2.8); p=0.0003	SEM vs. PBO: 9.4 (4.71, 18.77); p<0.0001		
Week 52, N			*NR*	*NR*	*NR*	*NR*	*275*	*269*	*133*	*233*	*239*
%			17	27	34	12	44.7	24.5	12	27.0	12.1
OR (95% CI); p-value			ETD: 5 (-0, 9) p=0.06	ETD: 15 (10, 20) p<0.001	ETD: 22 (16, 27) p<0.001	reference	----	SEM vs. LIR: 5.64 (3.17, 10.02) p<0.0001	SEM vs. PBO: 2.38 (1.65, 3.43) p<0.0001	2.71 (1.65, 4.45) p<0.0001	reference
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	
%			21	27	33	14					
OR (95% CI); p-value			ETD: 7 (2, 12) p=0.01	ETD: 13 (8, 19) p<0.001	ETD: 19 (13, 24) p<0.001	reference					
Proportion with Weight Loss≥10.0%											
Week 26, N	*Not available*		*NR*	*NR*	*NR*	*NR*	*278*	*271*	*134*	*NR*	
%			1	5	7	2	14	6	0		
OR (95% CI); p-value			ETD: -0 (-2, 1) p=0.70	ETD: 4 (1, 6) p=0.005	ETD: 5 (2, 8) p<0.001	reference	----	SEM vs. LIR: 2.45 (1.35, 4.44) p=0.0032	SEM vs. PBO: 39.88 (2.58, 615.6) p=0.0083		
Week 52, N			*NR*	*NR*	*NR*	*NR*	*275*	*269*	*133*	*233*	*239*
%			4	7	11	3	16	7	3	6.4	2.1

Trial	PIONEER 2		PIONEER 3				PIONEER 4			PIONEER 7	
Arm	**SEM 14 mg**	**EMP 25 mg**	**SEM 3 mg**	**SEM 7 mg**	**SEM 14 mg**	**SIT 100 mg**	**SEM 14 mg**	**LIR 1.8 mg**	**PBO**	**SEM flex**	**SIT 100 mg**
OR (95% CI); p-value			ETD: 1 (-1, 3) p=0.43	ETD: 4 (2, 7) p=0.003	ETD: 8 (5, 12) p<0.001	reference	----	SEM vs. LIR: 2.31 (1.33, 4.01) p=0.0028	SEM vs. PBO: 5.74 (2.14, 15.36) p=0.0005	3.63 (1.28, 10.31) p=0.0156	reference
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	
%			4	10	11	4					
OR (95% CI); p-value			ETD: -0 (-3, 3) p=0.89	ETD: 6 (3, 10) p<0.001	ETD: 7 (3, 10) p<0.001	reference					
Proportion with HbA1c reduction ≥1.0% and Weight Loss≥3.0%											
Week 26, N	*Not available*		NR	NR	NR	NR	278	271	135	*NR*	
%			13	26	37	9	130 (46.8)	93 (34.3)	5 (3.7)		
OR (95% CI); p-value			ETD: 4 (-1, 8) p=0.09	ETD: 17 (12, 22) p<0.001	ETD: 28 (23, 33) p<0.001	reference	----	SEM vs. LIR: 1.65 (1.16, 2.33) p=0.0050	SEM vs. PBO: 22.76 (8.99, 57.65) p<0.0001		
Week 52, N			*NR*	*NR*	*NR*	*NR*	*275*	*269*	*132*	*230*	*238*
%			17	24	36	12	43.6	28.6	6.8	34.8	10.5
OR (95% CI); p-value			ETD: 5 (1, 10) p=0.03	ETD: 12 (7, 17) p<0.001	ETD: 24 (19, 30) p<0.001	reference	----	SEM vs. LIR: 1.94 (1.35, 2.78) p=0.003	SEM vs. PBO: 10.44 (5.08, 21.44) p<0.0001	4.70 (2.82, 7.84) p<0.0001	reference
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	
%			18	26	34	14					
OR (95% CI); p-value			ETD: 4 (-0, 9); p=0.08	ETD: 12 (7, 17); p<0.001	ETD: 20 (14, 25); p<0.001	reference					
Change in Body Mass Index, kg/m^2											
Week 26, N	*Not available*		*NR*	*NR*	*NR*	*NR*	*278*	*271*	*134*	*NR*	
Mean change			-0.4	-0.8	-1.1	-0.2	-1.6 (0.1)	-1.1 (0.1)	-0.2 (0.1)		

Trial	PIONEER 2		PIONEER 3				PIONEER 4			PIONEER 7	
Arm	**SEM 14 mg**	**EMP 25 mg**	**SEM 3 mg**	**SEM 7 mg**	**SEM 14 mg**	**SIT 100 mg**	**SEM 14 mg**	**LIR 1.8 mg**	**PBO**	**SEM flex**	**SIT 100 mg**
ETD (95% CI), p-value			-0.2 (-0.4, -0.0) p=0.02	-0.6 (-0.7, -0.4) p<0.001	-0.9 (-1.1, -0.7) p<0.001	reference	----	SEM vs. LIR: -0.5 (-0.7, -0.2) p=0.0002	SEM vs. PBO: -1.4 (-1.7, -1.1) p<0.0001		
Week 52, N			*NR*	*NR*	*NR*	*NR*	*275*	*269*	*133*	*253*	*251*
Mean change			-0.6	-0.9	-1.2	-0.3	-1.6 (0.1)	-1.1 (0.1)	-0.3 (0.2)	-0.9	-0.3
ETD (95% CI), p-value			-0.3 (-0.5, -0.1) p=0.005	-0.6 (-0.8, -0.4) p<0.001	-1.0 (-1.2, -0.7) p<0.001	reference	----	SEM vs. LIR: -0.5 (-0.8, -0.2) p=0.0006	SEM vs. PBO: -1.2 (-1.6, -0.9) p<0.0001	-0.7 (-0.9, -0.4) p<0.0001	reference
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	
Mean change			-0.7	-1	-1.1	-0.4					
ETD (95% CI), p-value			-0.3 (-0.6, -0.1) p=0.01	-0.6 (-0.8, -0.4) p<0.001	-0.8 (-1.0, -0.5) p<0.001	reference					
Change in Fasting Plasma Glucose, mg/dL or mmol/L (noted)											
Week 26, N	*Not available*		*NR*	*NR*	*NR*	*NR*	*276*	*269*	*133*	*NR*	
Mean change			-13.6 mg/dL	-21.3	-30.5	-15.4	-2 (0.1) mmol/L	-1.87 (0.1)	-0.36 (0.2)		
ETD (95% CI), p-value			1.9 (-3.6, 7.3) p=0.50	-5.9 (-11.4, -0.3) p=0.04	-15.1 (-20.6, -9.7) p<0.001	reference	----	SEM vs. LIR: -0.13 (-0.41, 0.14) p=0.3422	SEM vs. PBO: -1.64 (-1.99, -1.28) p<0.0001		
Week 52, N			*NR*	*NR*	*NR*	*NR*	*273*	*269*	*132*	*252,*	*250*
Mean change			-15.9	-22	-32.6	-18.1	-1.88 (0.1)	-1.47 (0.1)	-0.70 (0.2)	-2.22 mmol/L	-1.44
ETD (95% CI), p-value			2.2 (-3.3, 7.7) p=0.44	-3.9 (-9.7, 1.9) p=0.18	-14.5 (-20.0, -9.1) p<0.001	reference	----	SEM vs. LIR: -0.41 (-0.74, -0.08); p=0.0136	SEM vs. PBO: -1.19 (-1.58, -0.79) p<0.0001	-0.78 (-1.2, -0.37) p=0.0002	reference
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	

Trial	PIONEER 2		PIONEER 3				PIONEER 4			PIONEER 7	
Arm	**SEM 14 mg**	**EMP 25 mg**	**SEM 3 mg**	**SEM 7 mg**	**SEM 14 mg**	**SIT 100 mg**	**SEM 14 mg**	**LIR 1.8 mg**	**PBO**	**SEM flex**	**SIT 100 mg**
Mean change (SE)			-17.1	-18.1	-30.8	-15					
ETD (95% CI), p-value			-2.1 (-8.0, 3.9); p=0.50	-3.1 (-9.3, 3.1); p=0.33	-15.8 (-21.7, -9.9); p<0.001	reference					
Change in Seven-point Self-Measured Whole-Blood Glucose, mg/dL or mmol/L (noted)											
Week 26, N	*Not available*		*NR*	*NR*	*NR*	*NR*	*263*	*257*	*129*	*NR*	
Mean change			-20 mg/dL	-26.8	-29.3	-21.2	-2.2 (0.1) mmol/L	-1.9 (0.1)	-0.8 (0.1)		
ETD (95% CI), p-value			1.2 (-3.7, 6.1) p=0.63	-5.6 (-10.4, -0.7) p=0.03	-8.0 (-13.1, -2.9) p=0.002	reference	----	SEM vs. LIR: -0.3 (-0.6, -0.0) p=0.0294	SEM vs. PBO: -1.4 (-1.8, -1.1) p<0.0001		
Week 52, N			*NR*	*NR*	*NR*	*NR*	*263*	*251*	*126*		
Mean change			-21.7	-26.9	-33.1	-24.7	-2.1 (0.1)	-1.6 (0.1)	-1.0 (0.1)		
ETD (95% CI), p-value			3.0 (-1.8, 7.8) p=0.22	-2.2 (-7.0, 2.6) p=0.37	-8.4 (-13.2, -3.6) p=0.001	reference	----	SEM vs. LIR: -0.5 (-0.8, -0.2) p=0.0008	SEM vs. PBO: -1.1 (-1.5 ,-0.8) p<0.0001		
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	
Mean change			-22.6	-25.3	-30.4	-22.7					
ETD (95% CI), p-value			0.0 (-5.0, 5.1); p=0.99	-2.6 (-7.9, 2.6); p=0.33	-7.7 (-12.7, -2.7); p=0.003	reference					
Change in Systolic Blood Pressure (mmHg)											
Week 26, N	*Not available*		*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	
Mean change			-1	-3	-3	-2	-4	-3	-2		
ETD (95% CI), p-value			1 (-1, 2) p=0.40	-1 (-3, 1) p=0.32	-1 (-3, 1) p=0.25	reference	----	-0 (-2, 2) p=0.6744	-2 (-4, 1) p=0.2178		

Trial	PIONEER 2		PIONEER 3				PIONEER 4			PIONEER 7	
Arm	SEM 14 mg	EMP 25 mg	SEM 3 mg	SEM 7 mg	SEM 14 mg	SIT 100 mg	SEM 14 mg	LIR 1.8 mg	PBO	SEM flex	SIT 100 mg
Week 52, N			*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Mean change			-2	-5	-3	-1	-3	-2	0	-4	-2
ETD (95% CI), p-value			-1 (-3, 0) p=0.15	-4 (-6, -2) p<0.001	-2 (-4, -1) p=0.01	reference	----	-1 (-3, 2) p=0.6243	-3 (-6, -1) p=0.0082	-2 (-4, 1) p=0.1828	reference
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	
Mean change (SE)			-1	-3	-3	0					
ETD (95% CI), p-value			-1 (-3, 1); p=0.33	-3 (-5, -1); p=0.001	-2 (-4, -0); p=0.02	reference					
Change in Diastolic Blood Pressure (mmHg)											
Week 26, N	*Not available*		*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	
Mean change			-1	-1	-1	0	-1	-1	0		
ETD (95% CI), p-value			-1 (-2, 1) p=0.31	-0 (-1, 1) p=0.69	-0 (-1, 1) p=0.63	reference	----	-1 (-2, 1) p=0.3391	1 (-2, 1) p=0.3426		
Week 52, N			*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Mean change			-2	-1	-2	-1	-1	-1	1	-1	-1
ETD (95% CI), p-value			-1 (-2, -0) p=0.03	-0 (-1, 1) p=0.53	-1 (-2, 0) p=0.28	reference	----	0 (-1, 1) p=0.6722	-2 (-3, -0) p=0.097	-0 (-1, 2) p=0.7157	reference
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	
Mean change			-1	-1	-1	-1					
ETD (95% CI), p-value			-0 (-2, 1) p=0.56	-0 (-2, 1) p=0.63	-0 (-1, 1) p=0.64	reference					
Total Cholesterol-- Ratio to Baseline											
Week 26, N	*Not available*		*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	
Ratio to baseline			1	0.98	0.97	1	0.96	0.97	1		
ETR (95% CI), p-value			1.00 (0.97, 1.02) p=0.67	0.98 (0.96, 1.00) p=0.05	0.97 (0.94, 0.99) p=0.001	reference	----	0.99 (0.96, 1.02) p=0.3949	0.96 (0.93, 1.00) p=0.0415		
Week 52, N			*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*226*	*234*

Trial	PIONEER 2		PIONEER 3				PIONEER 4			PIONEER 7	
Arm	SEM 14 mg	EMP 25 mg	SEM 3 mg	SEM 7 mg	SEM 14 mg	SIT 100 mg	SEM 14 mg	LIR 1.8 mg	PBO	SEM flex	SIT 100 mg
Ratio to baseline			1	1	0.99	1.01	0.98	0.98	1.02	0.96	1
ETR (95% CI), p-value			0.99 (0.97, 1.02) p=0.62	0.99 (0.97, 1.02) p=0.52	0.98 (0.96, 1.00) p=0.06	reference	----	1.00 (0.97, 1.03) p=0.9778	0.96 (0.92, 0.99) p=0.0162	0.96 (0.93, 0.99) p=0.0111	reference
Week 78, N			*NR*	*NR*	*NR*	*NR*					
Ratio to baseline	*N/A*		1	0.99	0.99	1	*N/A*			*N/A*	
ETR (95% CI), p-value			0.99 (0.97, 1.02) p=0.67	0.99 (0.96, 1.01) p=0.37	0.99 (0.96, 1.01) p=0.28	reference					
LDL-C-- Ratio to Baseline											
Week 26, N			*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	
Ratio to baseline			1.02	0.99	0.98	1.02	0.96	0.97	0.99		
ETR (95% CI), p-value			0.99 (0.96, 1.03) p=0.74	0.96 (0.93, 1.00) p=0.04	0.95 (0.92, 0.99) p=0.008	reference	----	0.98 (0.93, 1.04) p=0.5184	0.96 (0.91, 1.03) p=0.2668		
Week 52, N	*Not available*		*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*226*	*233*
Ratio to baseline			1.01	1	1	1.03	0.99	1	1.06	0.97	1.03
ETR (95% CI), p-value			0.99 (0.95, 1.02) p=0.47	0.98 (0.94, 1.01) p=0.20	0.97 (0.94, 1.00) p=0.09	reference	----	0.99 (0.95, 1.05) p=0.8413	0.94 (0.88, 1.00) p=0.0430	0.94 (0.89, 0.99) p=0.0259	reference
Week 78, N			*NR*	*NR*	*NR*	*NR*					
Ratio to baseline	*N/A*		1.02	1	1	1.03	*N/A*			*N/A*	
ETR (95% CI), p-value			1.00 (0.96,	0.98 (0.94, 1.02) p=0.23	0.98 (0.94,	reference					

Trial	PIONEER 2		PIONEER 3				PIONEER 4			PIONEER 7	
Arm	SEM 14 mg	EMP 25 mg	SEM 3 mg	SEM 7 mg	SEM 14 mg	SIT 100 mg	SEM 14 mg	LIR 1.8 mg	PBO	SEM flex	SIT 100 mg
			1.04) p=0.99		1.02) p=0.31						
HDL-C-- Ratio to Baseline											
Week 26, N	*Not available*		*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	
Ratio to baseline			0.97	0.99	0.98	0.99	1.02	1.02	1.03		
ETR (95% CI), p-value			0.98 (0.96, 1.00) p=0.05	1.00 (0.98, 1.02) p=0.98	0.99 (0.97, 1.01) p=0.46	reference	----	1.01 (0.98, 1.03) p=0.6678	1.00 (0.97, 1.02); p=0.7697		
Week 52, N			*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*226*	*233*
Ratio to baseline			0.99	1.01	1.01	1	1.02	1	1.01	1	1.01
ETR (95% CI), p-value			0.99 (0.97, 1.01) p=0.40	1.01 (0.99, 1.03) p=0.27	1.01 (1.00, 1.03) p=0.13	reference	----	1.02 (1.00, 1.04) p=0.0779	1.01 (0.99, 1.04) p=0.3500	0.99 (0.97, 1.02) p=0.6181	reference
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	
Ratio to baseline			0.97	0.99	1	0.99					
ETR (95% CI), p-value			0.98 (0.96, 1.00) p=0.09	1.00 (0.98, 1.02) p=0.85	1.01 (0.99, 1.03) p=0.32	reference					
Triglycerides-- Ratio to Baseline											
Week 26, N	*Not available*		*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	
Ratio to baseline			0.99	0.96	0.92	0.97	0.89	0.91	0.99		
ETR (95% CI), p-value			1.02 (0.97, 1.06) p=0.52	0.99 (0.94, 1.04) p=0.63	0.95 (0.91, 0.99) p=0.03	reference	----	0.98 (0.92, 1.04) p=0.4969	0.90 (0.84, 0.97) p=0.0063		
Week 52, N			*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*226*	*233*

Trial	PIONEER 2		PIONEER 3				PIONEER 4			PIONEER 7	
Arm	**SEM 14 mg**	**EMP 25 mg**	**SEM 3 mg**	**SEM 7 mg**	**SEM 14 mg**	**SIT 100 mg**	**SEM 14 mg**	**LIR 1.8 mg**	**PBO**	**SEM flex**	**SIT 100 mg**
Ratio to baseline			1	0.98	0.93	0.99	0.87	0.9	0.96	0.89	0.91
ETR (95% CI), p-value			1.01 (0.96, 1.06) p=0.72	0.99 (0.94, 1.04) p=0.64	0.94 (0.90, 0.99) p=0.01	reference	----	0.96 (0.90, 1.03) p=0.2379	0.90 (0.83, 0.98) p=0.0137	0.97 (0.91, 1.04) p=0.4301	reference
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	
Ratio to baseline			0.96	0.95	0.92	0.94					
ETR (95% CI), p-value			1.01 (0.96, 1.07) p=0.60	1.01 (0.96, 1.06) p=0.79	0.97 (0.92, 1.03) p=0.32	reference					
eGFR-- Ratio to Baseline											
Week 26, N	*Not available*		*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	—	
Geometric mean (CV)			0.99 (10.9)	0.98 (10.0)	0.98 (10.3)	0.97 (9.5)	0.99 (10.3)	0.99 (11.4)	1.00 (7.9)		
Week 52, N			*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*		
Geometric mean (CV)			0.99 (12.5)	0.98 (11.2)	0.98 (12.0)	0.98 (11.6)	0.99 (11.1)	1.00 (11.9)	1.01 (7.5)		
Week 78, N	*N/A*		*NR*	*NR*	*NR*	*NR*	*N/A*			*N/A*	
Geometric mean (CV)			0.99 (14.6)	0.98 (10.7)	0.98 (12.7)	0.98 (10.8)					
Proportion on Rescue Medication											
Week 26, N	*411*	*410*	*466*	*465*	*465*	*467*	*285*	*284*	*142*	*NR*	
%	*Not available*		5.4	2.4	1.1	2.8	3.5	3.2	7.7		
Week 52, N			*466*	*465*	*465*	*467*	*285*	*284*	*142*	*253*	*251*
%			26.0	15.7	6.7	20.1	7.0	6.3	30.3	3.2	15.9
Week 78, N	*N/A*		*466*	*465*	*465*	*467*	*N/A*			*N/A*	
%			34.3	22.2	10.1	27.6					
Overall, N	*411*	*410*	*466*	*465*	*465*	*467*	*285*	*284*	*142*	*253*	*251*
	24.6	21.5	47.9	35.4	28	39.4	21.8	18.6	41.5	20	24

Trial	PIONEER 2		PIONEER 3				PIONEER 4			PIONEER 7	
Arm	SEM 14 mg	EMP 25 mg	SEM 3 mg	SEM 7 mg	SEM 14 mg	SIT 100 mg	SEM 14 mg	LIR 1.8 mg	PBO	SEM flex	SIT 100 mg
Proportion on Additional Glucose-Lowering Medication											
Week 26, N	*Not available*		*466*	*465*	*465*	*467*	*285*	*284*	*142*	*NR*	
%			7.1	4.3	3.2	4.3	7.0	5.6	8.5		
Week 52, N			*466*	*465*	*465*	*467*	*285*	*284*	*142*	*253*	*251*
%			29.4	18.5	11.0	23.8	13.7	10.2	32.4	8.7	18.7
Week 78, N	*N/A*		*466*	*465*	*465*	*467*	*N/A*			*N/A*	
%			38.4	25.6	16.1	31.7					
All-Cause Discontinuation of Trial Product											
End of trial, N	*411*	*410*	*466*	*466*	*465*	*467*	*285*	*284*	*142*	*253*	*251*
%	17.5	11.0	16.7	15.0	19.1	13.1	15.4	12.7	12.0	16.6	9.2
All-Cause Discontinuation of Study											
End of trial, N	*411*	*410*	*466*	*466*	*465*	*467*	*285*	*284*	*142*	*253*	*251*
%	2.7	5.6	7.1	6.4	5.8	3.4	2.8	3.5	5.6	4.7	2.8

95% CI: 95% confidence interval, CV: coefficient of variation, dL: deciliter, eGFR: estimated glomerular filtration rate, EMP: empagliflozin, ETD: estimated treatment difference, ETR: estimated treatment ratio, flex: flexible, HbA1c: glycated hemoglobin, HDL-C: high-density lipoprotein cholesterol, kg: kilogram, L: liter, LDL-C: low-density lipoprotein cholesterol, LIR: liraglutide, mg: milligram, mmHg: millimeters of mercury, mmoL: millimoles, mL: milliliter, N/A: not applicable, NR: not reported, OR: odds ratio, PBO: placebo, SEM: semaglutide, SIT: sitagliptin

Table D6. Key Efficacy Outcomes in Placebo-Controlled PIONEER Trials*

Trial	PIONEER 1				PIONEER 5		PIONEER 8			
Arm	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO	SEM 14 mg	PBO	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO
N at baseline	175	175	175	178	163	161	184	182	181	184
Change in HbA1c, %										
Week 26, N	*167*	*160*	*160*	*168*	*163*	*161*	*NR*	*NR*	*NR*	*NR*
Mean change	-0.9	-1.2	-1.4	-0.3	-1.0 (0.1)	-0.2 (0.1)	-0.6	-0.9	-1.3	-0.1
ETD (95% CI); p-value	-0.6 (-0.8, -0.4) p<0.001	-0.9 (-1.1, -0.6) p<0.001	-1.1 (-1.3, -0.9) p<0.001	reference	-0.8 (-1.0, -0.6) p<0.0001	reference	-0.5 (-0.7, -0.3) p<0.001	-0.9 (-1.1, -0.7) p<0.001	-1.2 (-1.4, -1.0) p<0.001	reference
Week 52, N	*N/A*				*N/A*		*NR*	*NR*	*NR*	*NR*
Mean change (SE)							-0.6	-0.8	-1.2	-0.2
ETD (95% CI); p-value							-0.4 (-0.6, -0.2) p<0.001	-0.6 (-0.8, -0.4) p<0.001	-0.9 (-1.1, -0.7) p<0.001	reference
Proportion Achieving HbA1c<7.0%										
Week 26, N	*167*	*160*	*160*	*168*	*154*	*155*	*Not available*			
%	55.1	68.8	76.9	31	57.8	22.6				
OR (95% CI); p-value	3.09 (1.91, 4.99) p<0.001	5.79 (3.50, 9.59) p<0.001	8.36 (4.86, 14.41) p<0.001	reference	5.50 (3.20, 9.44) p<0.0001					
Week 52, N	*N/A*				*N/A*					
%										
OR (95% CI); p-value										
Proportion Achieving HbA1c≤6.5%										
Week 26, N	*167*	*160*	*160*	*168*	*154*	*155*	*Not available*			
%	35.9	47.5	63.8	17.9	39	7.7				
OR (95% CI); p-value	2.83 (1.66, 4.83) p<0.001	5.10 (2.97, 8.76) p<0.001	9.06 (5.20, 15.78) p<0.001	reference	9.45 (4.54, 19.65) p<0.0001	reference				
Week 52, N	*N/A*				*N/A*					
%										

Trial	PIONEER 1				PIONEER 5		PIONEER 8			
Arm	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO	SEM 14 mg	PBO	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO
OR (95% CI); p-value										
Proportion with HbA1c<7.0% without Hypoglycemia or Weight Gain										
Week 26, N	*NR*	*NR*	*NR*	*NR*	*154*	*155*	*Not available*			
%	37.1	56.9	68.8	23.2	51	17				
OR (95% CI); p-value	1.98 (1.21, 3.24) p=0.007	4.49 (2.74, 7.36) p<0.001	7.13 (4.28, 11.89) p<0.001	reference	5.74 (3.25, 10.16) p<0.0001	reference				
Week 52, N	*N/A*				*N/A*					
%										
OR (95% CI); p-value										
Change in Body Weight, kg										
Week 26, N	*168*	*160*	*160*	*168*	*162*	*161*	*NR*	*NR*	*NR*	*NR*
Mean change	-1.5	-2.3	-3.7	-1.4	-3.4 (0.3)	-0.9 (0.3)	-1.4	-2.4	-3.7	-0.4
ETD (95% CI), p-value	-0.1 (-0.9, 0.8) p=0.87	-0.9 (-1.9, 0.1) p=0.09	-2.3 (-3.1, -1.5) p<0.001	reference	-2.5 (-3.2, -1.8) p<0.0001	reference	-0.9 (-1.8, -0.0) p<0.05	-2.0 (-3.0, -1.0) p<0.001	-3.3 (-4.2, -2.3) p<0.001	reference
Week 52, N	*N/A*				*N/A*		*NR*	*NR*	*NR*	*NR*
Mean change							-0.8	-2	-3.7	0.5
ETD (95% CI), p-value							-1.3 (-2.4, -0.3) p<0.05	-2.5 (-3.6, -1.4) p<0.001	-4.3 (-5.3, -3.2) p<0.001	reference
Proportion with Weight Loss≥5.0%										
Week 26, N	*168*	*160*	*160*	*168*	*154*	*155*	*Not available*			
%	19.6	26.9	41.3	14.9	35.7	9.7				
OR (95% CI); p-value	1.30 (0.73, 2.33) p=0.37	2.05 (1.16, 3.63) p=0.01	3.74 (2.18, 6.41) p<0.001	reference	5.4 (2.9, 10.3) p<0.0001	reference				
Week 52, N	*N/A*				*N/A*					
%										
OR (95% CI); p-value										

Trial	PIONEER 1				PIONEER 5		PIONEER 8			
Arm	**SEM 3 mg**	**SEM 7 mg**	**SEM 14 mg**	**PBO**	**SEM 14 mg**	**PBO**	SEM **3 mg**	**SEM 7 mg**	**SEM 14 mg**	**PBO**
Proportion with Weight Loss≥10.0%										
Week 26, N	*168*	*160*	*160*	*168*	*154*	*155*	*Not available*			
%	2.4	8.1	14.4	1.2	8.4	0				
OR (95% CI); p-value	1.88 (0.34, 10.44) p=0.47	7.74 (1.68, 35.72) p=0.009	12.92 (2.98, 56.07) p<0.001	reference	28.5 (2.3, 346.5) p=0.0086	reference				
Week 52, N	*N/A*				*N/A*					
%										
OR (95% CI); p-value										
Proportion with HbA1c reduction ≥1.0% and Weight Loss≥3.0%										
Week 26, N	*NR*	*NR*	*NR*	*NR*	*154*	*155*	*Not available*			
%	18	36.9	50.6	10.7	39	7.7				
OR (95% CI); p-value	1.71 (0.90, 3.26) p=0.10	4.51 (2.47, 8.22) p<0.001	7.96 (4.40, 14.42) p<0.001	reference	7.96 (3.99, 15.91) p<0.0001	reference				
Week 52, N	*N/A*				*N/A*					
%										
OR (95% CI); p-value										
Change in Body Mass Index, kg/m^2										
Week 26, N	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*Not available*			
Mean change	-0.5	-0.8	-1.4	-0.5	-1.2	-0.3				
ETD (95% CI), p-value	-0.1 (-0.3, 0.2) p=0.74	-0.3 (-0.7, -0.0) p=0.05	-0.9 (-1.2, -0.6) p<0.001	reference	-0.9 (-1.2, -0.7) p<0.0001	reference				
Week 52, N	N/A				N/A					
Mean change										
ETD (95% CI), p-value										
Change in Fasting Plasma Glucose, mg/dL or mmol/L (noted)										

Trial	PIONEER 1				PIONEER 5		PIONEER 8			
Arm	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO	SEM 14 mg	PBO	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO
Week 26, N	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*Not available*			
Mean change	-16.2 mg/dL	-27.9	-32.9	-3.2	-1.5 mmol/L	-0.4				
ETD (95% CI), p-value	-12.9 (-21.4, -4.5) p=0.003	-24.6 (-35.1, -14.2) p<0.001	-29.6 (-38.3, -21.0) p<0.001	reference	-1.2 (-1.7, -0.7) p<0.0001	reference				
Week 52, N	*N/A*				*N/A*					
Mean change										
ETD (95% CI), p-value										
Change in Seven-point Self-Measured Whole-Blood Glucose, mg/dL or mmol/L (noted)										
Week 26, N	*NR*	*NR*	*NR*	*NR*	*NR*		*Not available*			
Mean change	-30.1 mg/dL	-35.5	-40.1	-7.5						
ETD (95% CI), p-value	-22.7 (-31.0, -14.4) p<0.001	-28.1 (-37.4, -18.7) p<0.001	-32.6 (-41.8, -23.5) p<0.001	reference						
Week 52, N	*N/A*				*N/A*					
Mean change										
ETD (95% CI), p-value										
Change in Systolic Blood Pressure (mmHg)										
Week 26, N	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*Not available*			
Mean change	-3	-3	-5	-3	-7	0				
ETD (95% CI), p-value	-1 (-4 , 2) p=0.55	-1 (-4 , 2) p=0.68	-2 (-5 , 0) p=0.10	reference	-7 (-9 -4) p<0.0001	reference				
Week 52, N	*N/A*				*N/A*					
Mean change										
ETD (95% CI), p-value										
Change in Diastolic Blood Pressure (mmHg)										

Trial	PIONEER 1				PIONEER 5		PIONEER 8			
Arm	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO	SEM 14 mg	PBO	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO
Week 26, N	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*Not available*			
Mean change (SE)	-1	-1	-1	-1	-2	1				
ETD (95% CI), p-value	0 (-2 , 2) p=0.91	0 (-2 , 2) p=0.91	-0 (-2 , 1) p=0.68	reference	-3 (-5, -1) p=0.0018	reference				
Week 52, N	*N/A*				*N/A*					
Mean change (SE)										
ETD (95% CI), p-value										
Total Cholesterol-- Ratio to Baseline										
Week 26, N	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*Not available*			
Ratio to baseline	0.98	0.99	0.95	1	0.96	1				
ETR (95% CI), p-value	0.99 (0.95, 1.02) p=0.48	1.00 (0.95, 1.04) p=0.85	0.95 (0.92 , 0.99); p=0.02	reference	0.96 (0.92, 1.00) p=0.0790	reference				
Week 52, N	*N/A*				*N/A*					
Ratio to baseline										
ETR (95% CI), p-value										
LDL-C-- Ratio to Baseline										
Week 26, N	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*Not available*			
Ratio to baseline	0.95	0.98	0.93	0.99	0.97	0.99				
ETR (95% CI), p-value	0.97 (0.91 , 1.03) p=0.25	0.99 (0.92, 1.06) p=0.74	0.94 (0.89 , 1.00) p=0.05	reference	0.98 (0.91, 1.05) p=0.4954	reference				
Week 52, N	*N/A*				*N/A*					
Ratio to baseline										
ETR (95% CI), p-value										
HDL-C-- Ratio to Baseline										
Week 26, N	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*Not available*			
Ratio to baseline	1.03	1.05	1.02	1.03	1.02	1.02				
ETR (95% CI),	1.00	1.03	1.00	reference	1.01	reference				

Trial	PIONEER 1				PIONEER 5		PIONEER 8			
Arm	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO	SEM 14 mg	PBO	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO
p-value	(0.97 , 1.03) p=0.83	(0.99, 1.06) p=0.10	(0.97 , 1.03) p=0.88		(0.97, 1.04) p= 0.7391					
Week 52, N	*N/A*				*N/A*					
Ratio to baseline										
ETR (95% CI), p-value										
Triglycerides-- Ratio to Baseline										
Week 26, N	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*Not available*			
Ratio to baseline	1.01	0.92	0.9	0.99	0.86	0.96				
ETR (95% CI), p-value	1.02 (0.94 , 1.10) p=0.71	0.93 (0.84, 1.02) p=0.13	0.90 (0.83 , 0.99) p=0.02	reference	0.89 (0.83, 0.97) p=0.0044	reference				
Week 52, N	*N/A*				*N/A*					
Ratio to baseline										
ETR (95% CI), p-value										
eGFR-- Ratio to Baseline										
Week 26, N	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*Not available*			
Geometric mean (CV)	0.99 (10.7)	1.00 (9.6)	1.00 (8.2)	1.00 (8.9)	median (range): 1.02 0.27-1.96	median (range): 1.0 (0.68-2.17)				
Week 52, N	*N/A*				*N/A*					
Geometric mean (CV)										
Proportion on Rescue Medication										
Week 26, N	*175*	*175*	*175*	*178*	*NR*	*NR*	*Not available*			
%	13 (7.4)	4 (2.3)	2 (1.1)	27 (15.2)	7 (4.3)	16 (9.9)				
Week 52, N	*N/A*				*N/A*					
%										
Overall, N	*167*	*160*	*160*	*168*	*163*	*161*	*NR*	*NR*	*NR*	*NR*
%	7.4	2.3	1.1	15.2	7 (4.3)	16 (9.9)	27.2	16.5	15.5	31
Proportion on Additional Glucose-Lowering Medication										

Trial	PIONEER 1				PIONEER 5		PIONEER 8			
Arm	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO	SEM 14 mg	PBO	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO
Week 26, N	*175*	*175*	*175*	*178*	*NR*	*NR*	*Not available*			
%	16 (9.1)	8 (4.6)	7 (4.0)	35 (19.7)	12 (7.4)	21 (13.0)				
Week 52, N	*N/A*				*N/A*					
%										
All-Cause Discontinuation of Trial Product										
End of trial, N	*175*	*175*	*175*	*178*	*163*	*161*	*184*	*182*	*181*	*184*
%	6.9	10.3	13.7	10.7	18.4	12.4	13	18.7	20.4	12
All-Cause Discontinuation of Study										
End of trial, N	*175*	*175*	*175*	*178*	*163*	*161*	*184*	*182*	*181*	*184*
%	3.4	8.0	6.9	4.5	3.1	3.1	5.4	4.9	3.3	4.9

*PIONEER 6 results are presented alongside other included CVOTS.

95% CI: 95% confidence interval, CV: coefficient of variation, dL: deciliter, eGFR: estimated glomerular filtration rate, ETD: estimated treatment difference, ETR: estimated treatment ratio, HbA1c: glycated hemoglobin, HDL-C: high-density lipoprotein cholesterol, kg: kilogram, L: liter, LDL-C: low-density lipoprotein cholesterol, mg: milligram, mmHg: millimeters of mercury, mmoL: millimoles, mL: milliliter, N/A: not applicable, NR: not reported, OR: odds ratio, PBO: placebo, SEM: semaglutide

Table D7. Key Safety Parameters in PIONEER Trials*

Trial	PIONEER 1				PIONEER 2		PIONEER 3				PIONEER 4			PIONEER 5		PIONEER 7	
Arm	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO	SEM 14 mg	EMP 25 mg	SEM 3 mg	SEM 7 mg	SEM 14 mg	SIT 100 mg	SEM 14 mg	LIR 1.8 mg	PBO	SEM 14 mg	PBO	SEM flex	SIT 100 mg
N	175	175	175	175	410	409	466	464	465	466	285	284	142	163	161	253	250
Week	26	26	26	26	52	52	78	78	78	78	52	52	52	26	26	52	52
Any AE	57.7	53.1	56.6	55.6	70.5	69.2	79.4	78.2	76.9	83.3	80	74	67	74	65	78	69
SAE	2.9	1.7	1.1	4.5	6.6	9	13.7	10.1	9.5	12.4	11	8	11	10	11	9	10
Death	0	0	0	0	0	0.2	1.1	0.6	0.2	0.6	1.1	1.4	0.7	1	1	0	0.4
Mild AE	50.9	48	46.3	45.5	59	58.7	69.3	68.5	69	73	67	63	61	65	55	66	58
Moderate AE	22.9	16.6	19.4	26.4	34.1	28.9	39.9	36.9	42.8	42.3	42	36	23	37	26	41	30
Severe AE	4.6	0.6	1.7	2.8	5.9	5.6	10.1	8	8.6	11.4	8	8	5	6	9	6	7
AE leading to d/c	2.3	4	7.4	2.2	10.7	4.4	5.6	5.8	11.6	5.2	11	9	4	15	5	9	3
GI AE leading to d/c	1.7	2.3	5.1	0.6	8	0.7	2.4	3.4	6.9	2.6	8	6	2	12	2	6	1
Hypo-glycemia*	2.9	1.1	0.6	0.6	1.7	2	4.9	5.2	7.7	8.4	1	2	2	6	2	5.5	5.6
Severe hypo-glycemia	0	0.6	0	0	0.2	0.2	0	0	0.2	0.9	0	0	0	0	0	0	0
Nausea	8	5.1	16	5.6	19.8	2.4	7.3	13.4	15.1	6.9	20	18	4	19	7	21	2
Diarrhea	8.6	5.1	5.1	2.2	9.3	3.2	9.7	11.4	12.3	7.9	15	11	8	10	4	9	3
Nasopharyn-gitis	5.7	6.3	1.7	3.4			11.4	10.6	10.1	10.1	14	13	11			10	5
Vomiting	2.9	4.6	6.9	2.2	7.3	1.7	2.8	6	9	4.1	9	5	2	12	1	6	1
Headache	3.4	5.7	5.1	5.1			6.2	6.5	8	7.7	9	6	6	6	5	10	6
Decreased appetite	1.1	1.7	5.1	0.6	5.1	0.5	1.7	3	6.9	3	6	7	0	7	0		
Upper respiratory tract infection	—	—	—	—	—	—	7.7	7.5	5.6	6.9	7.7	—	—	—	—	—	—
Hypertension	—	—	—	—	—	—	6.4	5.2	5.6	6.2	6.4	—	—	—	—	—	—

Trial	PIONEER 1				PIONEER 2		PIONEER 3				PIONEER 4			PIONEER 5		PIONEER 7	
Arm	SEM 3 mg	SEM 7 mg	SEM 14 mg	PBO	SEM 14 mg	EMP 25 mg	SEM 3 mg	SEM 7 mg	SEM 14 mg	SIT 100 mg	SEM 14 mg	LIR 1.8 mg	PBO	SEM 14 mg	PBO	SEM flex	SIT 100 mg
Back pain	—	—	—	—	—	—	5.2	5.4	5.4	6.2	4	6	4	1	6		
Urinary tract infection	—	—	—	—	—	—	6.4	4.5	4.9	5.6	0.4	0.4	0	—	—	—	—
Constipation	—	—	—	—	—	—	—	—	—	—	—	—	—	12	4	—	—
Dyspepsia	—	—	—	—	—	—	—	—	—	—	—	—	—	10	1	—	—
Arthralgia	—	—	—	—	—	—	4.7	3	4.5	6.4	—	—	—	—	—	—	—
Influenza	5.1	2.9	2.3	1.1	2	5.1	6.4	5.4	3.9	6.4	—	—	—	—	—	—	—
Diabetic retinopathy	0.6	3.4	1.1	1.7			5.8	5.2	3.4	5.8	2.8	1.1	1.4	1.2	1.2	1.2	1.6

*PIONEER 6 results are presented alongside other included CVOTs. There is limited data currently available for PIONEER 8; all available data has been presented in the report.
AE: adverse event, d/c: discontinuation, EMP: empagliflozin, flex: flexible, GI: gastrointestinal, LIR: liraglutide, mg: milligram, PBO: placebo, SAE: serious adverse event, SEM: semaglutide, SIT: sitagliptin

Table D8. Study Design, Baseline Characteristics, and Key Efficacy Outcomes of Included CVOTs

	PIONEER 6 Oral semaglutide vs. placebo	SUSTAIN 6 Injectable semaglutide vs. placebo	LEADER Liraglutide vs. placebo	EMPA-REG OUTCOME Empagliflozin vs. placebo	TECOS Sitagliptin vs. placebo
Inclusion Criteria					
HbA1c	≥7.0%	≥7.0%	≥7.0%	≥7.0%	6.5-8.0%
Cardiovascular risk	≥50 years old with eCVD or CKD, or ≥60 years old with CV risk factors	≥50 years old with eCVD or CKD, or ≥60 years old with CV risk factors	≥50 years old with eCVD or CKD, or ≥60 years old with CV risk factors	≥18 years old with eCVD	≥50 years old with eCVD
Exclusion Criteria					
Recent MACE	MI, stroke, hospitalization for unstable angina, or TIA within 60 days	Acute coronary or cerebrovascular event within 14 days	Acute coronary or cerebrovascular event within 14 days	ACS, stroke, or TIA within 60 days	None listed
Renal function	Severe (eGFR<30)	None	None	Severe (eGFR<30)	Severe (eGFR<30)
Heart failure	NYHA class 4 heart failure	NYHA class 4 heart failure	NYHA class 4 heart failure	None listed	None listed
Design					
Number enrolled	3183	3297	9340	7020	14671
Interventions	Oral semaglutide 14 mg (n=1591) Placebo (n=1592)	Injectable semaglutide 0.5 mg (n=826) Injectable semaglutide 1.0 mg (n=822) Placebo 0.5 mg (n=824) Placebo 1.0 mg (n=825)	Liraglutide 1.8 mg (n=4668) Placebo (n=4672)	Empagliflozin 25 mg (n=2342) Empagliflozin 10 mg (n=2345) Placebo (n=2333)	Sitagliptin 100 mg* (n=7332) Placebo (n=7339)
Phases	Randomized double-blind phase	Randomized double-blind phase	2-week placebo-run in (adherence) Randomized double-blind phase	2-week placebo-run in (adherence) Randomized double-blind phase	Randomized double-blind phase
Follow-up, median	1.3 years	2.1 years	3.8 years	3.1 years	3.0 years
Key Baseline Characteristics					
Age, mean	66 years	65 years	64 years	63 years	66 years

	PIONEER 6 Oral semaglutide vs. placebo	SUSTAIN 6 Injectable semaglutide vs. placebo	LEADER Liraglutide vs. placebo	EMPA-REG OUTCOME Empagliflozin vs. placebo	TECOS Sitagliptin vs. placebo
HbA1c, mean	8.2%	8.7%	8.7%	8.1%	7.2%
Duration of diabetes, mean	14.9 years	13.9 years	12.8 years	>10 years: 57.1%	11.6 years
BMI, mean	32.3 kg/m^2	32.8 kg/m^2	32.5 kg/m^2	30.6 kg/m^2	30.2 kg/m^2
Caucasian	72.3%	83.0%	NR	72.4%	67.9%
Asian	19.8%	8.3%	NR	21.6%	22.3%
Black/African American	6.0%	6.7%	NR	5.1%	3.0%
Other	1.9%	2.0%	NR	0.9%	6.8%
Cardiovascular Risk					
Established CVD	84.7% (CVD or CKD)	83.0% (CVD or CKD)	81.3% (CVD or CKD)	99.2% (CVD)	100% (CVD)
CV risk factors only	15.3%	N/A	18.6%	N/A	N/A
Prior MI	36.1%	32.5%	30.7%	46.7%	42.6%
Prior stroke or TIA	15.9%	Ischemic Stroke: 11.6% Hemorrhagic Stroke: 3.3%	16.1%	23.1%	NR
Renal impairment	eGFR 30-59: 28.2%	eGFR 30-59: 25.2% eGFR <30: 3.2%	eGFR 30-59: 20.7% eGFR <30: 2.4%	eGFR 30-59: 25.9%	eGFR <50: 9.4%
Heart failure	12.2% (class 2–3)	23.6%	18% (any); 14% (stage 2-3)	~10% (cardiac failure)	18% (any); 2.5% (stage 3+)
Background Medications					
Metformin	77.4%	73.2%	76.5%	74.0%	81.6%
Insulin	60.6%	58.0%	44.6%	48.2%	23.2%
Sulfonylurea	32.3%	42.8%	50.7%	42.8%	45.3%
Antihypertensive	93.9%	93.5%	92.4%	94.9%	ACE or ARB: 78.8% Beta blocker: 63.5%
Lipid-lowering drug	85.2%	76.5%	75.8%	81.0%	Statin: 79.9% Ezetimibe: 5.2%
Antithrombotic/antiplatelet	79.4%	76.3%	67.7%	Not reported	Aspirin: 78.5%
Cardiovascular Outcomes					

	PIONEER 6 Oral semaglutide vs. placebo	SUSTAIN 6 Injectable semaglutide vs. placebo	LEADER Liraglutide vs. placebo	EMPA-REG OUTCOME Empagliflozin vs. placebo	TECOS Sitagliptin vs. placebo
CV death, nonfatal MI, or nonfatal stroke[†] **HR (95% CI)**	Semaglutide: 3.8% Placebo: 4.8% 0.79 (0.57-1.11)	Semaglutide: 6.6% Placebo: 8.9% 0.74 (0.58-0.95)	Liraglutide: 13.0% Placebo: 14.9% 0.87 (0.78-0.97)	Empagliflozin§: 10.5% Placebo: 12.1% 0.86 (0.74-0.99)	Sitagliptin: 10.2% Placebo: 10.2% 0.99 (0.89-1.10)
All-cause death **HR (95% CI)**	Semaglutide: 1.4% Placebo: 2.8% 0.51 (0.31-0.84)	Semaglutide: 3.8% Placebo: 3.6% 1.05 (0.74-1.50)	Liraglutide: 8.2% Placebo: 9.6% 0.85 (0.74-0.97)	Empagliflozin: 5.7% Placebo: 8.3% 0.68 (0.57-0.82)	Sitagliptin: 7.5% Placebo: 7.3% 1.01 (0.90-1.14)
CV death **HR (95% CI)**	Semaglutide: 0.9% Placebo: 1.9% 0.49 (0.27-0.92)	Semaglutide: 2.7% Placebo: 2.8% 0.98 (0.65-1.48)	Liraglutide: 4.7% Placebo: 6.0% 0.78 (0.66-0.93)	Empagliflozin: 3.7% Placebo: 5.9% 0.62 (0.49-0.77)	Sitagliptin 5.2% Placebo: 5.0% 1.03 (0.89-1.19)
Nonfatal stroke **HR (95% CI)**	Semaglutide: 0.8% Placebo: 1.0% 0.74 (0.35-1.57)	Semaglutide: 1.6% Placebo: 2.7% 0.61 (0.38-0.99)	Liraglutide: 3.4% Placebo: 3.8% 0.89 (0.72-1.11)	Empagliflozin: 3.2% Placebo: 2.6% 1.24 (0.92-1.67)	Sitagliptin 2.0%[#] Placebo: 2.2% NR
Nonfatal MI **HR (95% CI)**	Semaglutide: 2.3% Placebo: 1.9% 1.18 (0.73-1.90)	Semaglutide: 2.9% Placebo: 3.9% 0.74 (0.51-1.08)	Liraglutide: 6.0% Placebo: 6.8% 0.88 (0.75-1.03)	Empagliflozin: 4.5% Placebo: 5.2% 0.87 (0.70-1.09)	Sitagliptin 3.9%[#] Placebo: 4.0% NR
Hospitalization for unstable angina **HR (95% CI)**	Semaglutide: 0.7% Placebo: 0.4% 1.56 (0.60-4.01)	Semaglutide: 1.3% Placebo: 1.6% 0.82 (0.47-1.44)	Liraglutide: 2.6% Placebo: 2.7% 0.98 (0.76-1.26)	Empagliflozin: 2.8% Placebo: 2.8% 0.99 (0.74-1.34)	Sitagliptin: 1.6% Placebo: 1.8% 0.90 (0.70-1.16)
Hospitalization for heart failure **HR (95% CI)**	Semaglutide: 1.3% Placebo: 1.5% 0.86 (0.48-1.55)	Semaglutide: 3.6% Placebo: 3.3% 1.11 (0.77-1.61)	Liraglutide: 4.7% Placebo: 5.3% 0.87 (0.73-1.05)	Empagliflozin: 2.7% Placebo: 4.1% 0.65 (0.50-0.85)	Sitagliptin: 3.1%‡ Placebo: 3.1% 1.00 (0.83-1.20)
Microvascular Outcomes					
Diabetic retinopathy **HR (95% CI)**	*AEs related to diabetic retinopathy* Semaglutide: 7.1% Placebo: 6.3%	Semaglutide: 3.0% Placebo: 1.8% 1.76 (1.11-2.78)	Liraglutide: 2.3% Placebo: 2.0% 1.15 (0.87-1.52)	Empagliflozin: 1.6% Placebo: 2.1% 0.78 (0.54-1.12)	*AEs related to diabetic retinopathy* Sitagliptin: 2.8% Placebo: 2.2%
Nephropathy **HR (95% CI)**	Not reported	Semaglutide: 3.8% Placebo: 6.1% 0.64 (0.46-0.88)	Liraglutide: 5.7% Placebo: 7.2% 0.78 (0.67-0.92)	Empagliflozin: 12.7% Placebo: 18.8% 0.61 (0.53-0.70)	Not reported

*50 mg if eGFR ≥30 and <50; †Primary outcome in PIONEER 6, LEADER, and EMPA-REG OUTCOME. The primary outcome in TECOS was a composite of CV death, nonfatal MI, nonfatal stroke; or hospitalization for unstable angina; ‡Results are adjusted for a history of heart failure at baseline; #Only reported as the number of patients with event contributing to the secondary composite endpoint (CV death, nonfatal MI, nonfatal stroke).

95% CI: 95% confidence interval, ACE: angiotensin-converting enzyme inhibitors, ARB: angiotensin II receptor blockers, CKD: chronic kidney disease, CV: cardiovascular, eCVD: established cardiovascular disease, eGFR: estimated glomerular filtration rate, HbA1c: glycated hemoglobin, HR: hazard ratio, MACE: major adverse cardiovascular events, MI: myocardial infarction, mg: milligram, NYHA: New York Heart Association, TIA: transient ischemic attack

Table D9. Key Safety Parameters in Cardiovascular Outcomes Trials

	PIONEER 6		SUSTIAN 6		LEADER		EMPA-REG OUCTOME		TECOS	
	SEM 14 mg	PBO	SEM 0.5/1.0 mg	PBO	LIR 1.8 mg	PBO	EMP 10/25 mg	PBO	SIT 100 mg	PBO
N	1591	1592	1650	1647	4668	4672	4687	2333	7332	7339
Any AE	NR	NR	89.4	90.0	62.3	60.8	90.2	91.7	NR	NR
GI AE	NR	NR	51.5	35.4	NR	NR	NR	NR	NR	NR
SAE	18.9	22.5	34.3	38.0	49.7	50.4	38.2	42.3	NR	NR
AE leading to d/c	11.6	6.5	13.0	6.7	9.5	7.3	17.3	19.4	NR	NR
GI AE leading to d/c	6.8	1.6	7.5	1.1	NR	NR	NR	NR	NR	NR
SAE leading to d/c	2.6	3	NR	NR	4.1	5.2	NR	NR	NR	NR
Acute kidney injury	2	2.3	NR	NR	NR	NR	1	1.6	NR	NR
Acute renal failure	NR	NR	4.0	4.2	NR	NR	5.2	6.6	1.4	1.5
Acute pancreatitis	0.1	0.2	0.6	0.8	0.4	0.5	NR	NR	0.3	0.2
Severe hypoglycemia	1.4	0.8	NR	NR	2.4	3.3	1.3	1.5	2.2	1.9
Severe or symptomatic hypoglycemia	NR	NR	22.4	21.2	NR	NR	27.8	27.9	NR	NR
Malignant neoplasms	2.6	3	4.0	4.2	6.3	6.0	NR	NR	NR	NR
Thyroid neoplasms	0.1	0	0.1	0.1	0.0	<0.1	NR	NR	NR	NR
UTI- overall	NR						18.0	18.1	NR	
UTI- male							10.5	9.4		
UTI- female							36.4	40.6		
Complicated UTI							1.7	1.8		
Genital infection overall							6.4	1.8		
Genital infection- male							5	1.5		
Genital Infection- female							10	2.6		

AE: adverse event, d/c: discontinuation, EMP: empagliflozin, GI: gastrointestinal, LIR: liraglutide, PBO: placebo, SAE: serious adverse event, SEM: semaglutide, SIT: sitagliptin, UTI: urinary tract infection

NMA Supplemental Information

Table D10. Data Inputs for Meta-Analysis of PIONEER 6 and SUSTAIN 6

Trial	Treatment	3-Point MACE		HHF	
		Hazard Ratio	95% CI	Hazard Ratio	95% CI
PIONEER 6	Semaglutide	0.79	0.57-1.11	0.86	0.48-1.55
	Placebo	—	—	—	—
SUSTAIN 6	Semaglutide	0.74	0.58-0.95	1.11	0.77-1.61
	Placebo	—	—	—	—

95% CI: 95% confidence interval; HHF: hospitalization for heart failure; MACE: major adverse cardiovascular event

Table D11. Results from Meta-Analysis of PIONEER 6 and SUSTAIN 6

Treatment	3-Point MACE		HHF	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Semaglutide	0.76	0.62-0.92	1.03	0.76-1.41
Placebo	—	—	—	—

95% CI: 95% confidence interval; HHF: hospitalization for heart failure; major adverse cardiovascular event

Table D12. Data Inputs for NMA of 3-point MACE

Trial	Treatment	Hazard Ratio	95% CI
PIONEER 6/SUSTAIN 6	Semaglutide	0.76	0.62-0.92
	Placebo	—	—
TECOS	Sitagliptin	0.99	0.89-1.1
	Placebo	—	—
EMPA-REG OUTCOME	Empagliflozin	0.86	0.74-0.99
	Placebo	—	—
LEADER	Liraglutide	0.87	0.78-0.97
	Placebo	—	—

95% CI: 95% confidence interval; major adverse cardiovascular event

Table D13. League Table of Hazard Ratios for 3-point MACE

Semaglutide	1.13 (0.89, 1.44)	1.14 (0.91, 1.43)	**1.3 (1.04, 1.63)**	**1.32 (1.08, 1.6)**
0.88 (0.69, 1.13)	Empagliflozin	1.01 (0.84, 1.21)	1.15 (0.96, 1.38)	**1.16 (1.01, 1.34)**
0.87 (0.7, 1.09)	0.99 (0.82, 1.18)	Liraglutide	1.14 (0.98, 1.32)	**1.15 (1.03, 1.28)**
0.77 (0.61, 0.96)	0.87 (0.73, 1.04)	0.88 (0.75, 1.02)	Sitagliptin	1.01 (0.91, 1.12)
0.76 (0.63, 0.93)	**0.86 (0.74, 0.99)**	**0.87 (0.78, 0.97)**	0.99 (0.89, 1.1)	Placebo

Data are hazard ratio (95% credible interval). Estimates in bold signify that the 95% credible interval does not contain one.

Table D14. Data Inputs for NMA of Hospitalization for Heart Failure

Trial	Treatment	Hazard Ratio	95% CI
PIONEER 6/SUSTAIN 6	Semaglutide	1.03	0.76-1.41
	Placebo	—	—
TECOS	Sitagliptin	1	0.83-1.2
	Placebo	—	—
EMPA-REG OUTCOME	Empagliflozin	0.65	0.5-0.85
	Placebo	—	—
LEADER	Liraglutide	0.87	0.73-1.05
	Placebo	—	—

95% CI: 95% confidence interval

Table D15. League Table of Hazard Ratios for Hospitalization for Heart Failure

Semaglutide	**0.63 (0.42, 0.95)**	0.84 (0.59, 1.21)	0.97 (0.68, 1.4)	0.97 (0.71, 1.32)
1.59 (1.05, 2.38)	**Empagliflozin**	1.34 (0.97, 1.85)	**1.54 (1.11, 2.13)**	**1.54 (1.18, 2.01)**
1.18 (0.83, 1.7)	0.75 (0.54, 1.03)	**Liraglutide**	1.15 (0.89, 1.49)	1.15 (0.96, 1.38)
1.03 (0.72, 1.48)	**0.65 (0.47, 0.9)**	0.87 (0.67, 1.13)	**Sitagliptin**	1 (0.83, 1.2)
1.03 (0.76, 1.4)	**0.65 (0.5, 0.85)**	0.87 (0.72, 1.04)	1 (0.83, 1.2)	**Placebo**

Data are hazard ratio (95% credible interval). Estimates in bold signify that the 95% credible interval does not contain one.

Table D16. Data Inputs for NMA of Nephropathy

Trial	Treatment	Hazard Ratio	95% CI
SUSTAIN 6	Semaglutide	0.64	0.46-0.88
	Placebo	—	—
EMPA-REG OUTCOME	Empagliflozin	0.61	0.53-0.69
	Placebo	—	—
LEADER	Liraglutide	0.78	0.67-0.92
	Placebo	—	—

95% CI: 95% confidence interval

Table D17. Results for NMA of Nephropathy

Empagliflozin	1.28 (1.04, 1.57)	**1.64 (1.44, 1.87)**	1.05 (0.74, 1.49)
0.78 (0.64, 0.96)	**Liraglutide**	**1.28 (1.09, 1.5)**	0.82 (0.57, 1.18)
0.61 (0.53, 0.7)	**0.78 (0.67, 0.91)**	**Placebo**	**0.64 (0.46, 0.89)**
0.95 (0.67, 1.35)	1.22 (0.85, 1.75)	**1.56 (1.13, 2.16)**	**Semaglutide**

Data are hazard ratio (95% credible interval). Estimates in bold signify that the 95% credible interval does not contain one.

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☑	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-related costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al.[92]

Figure E1. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds

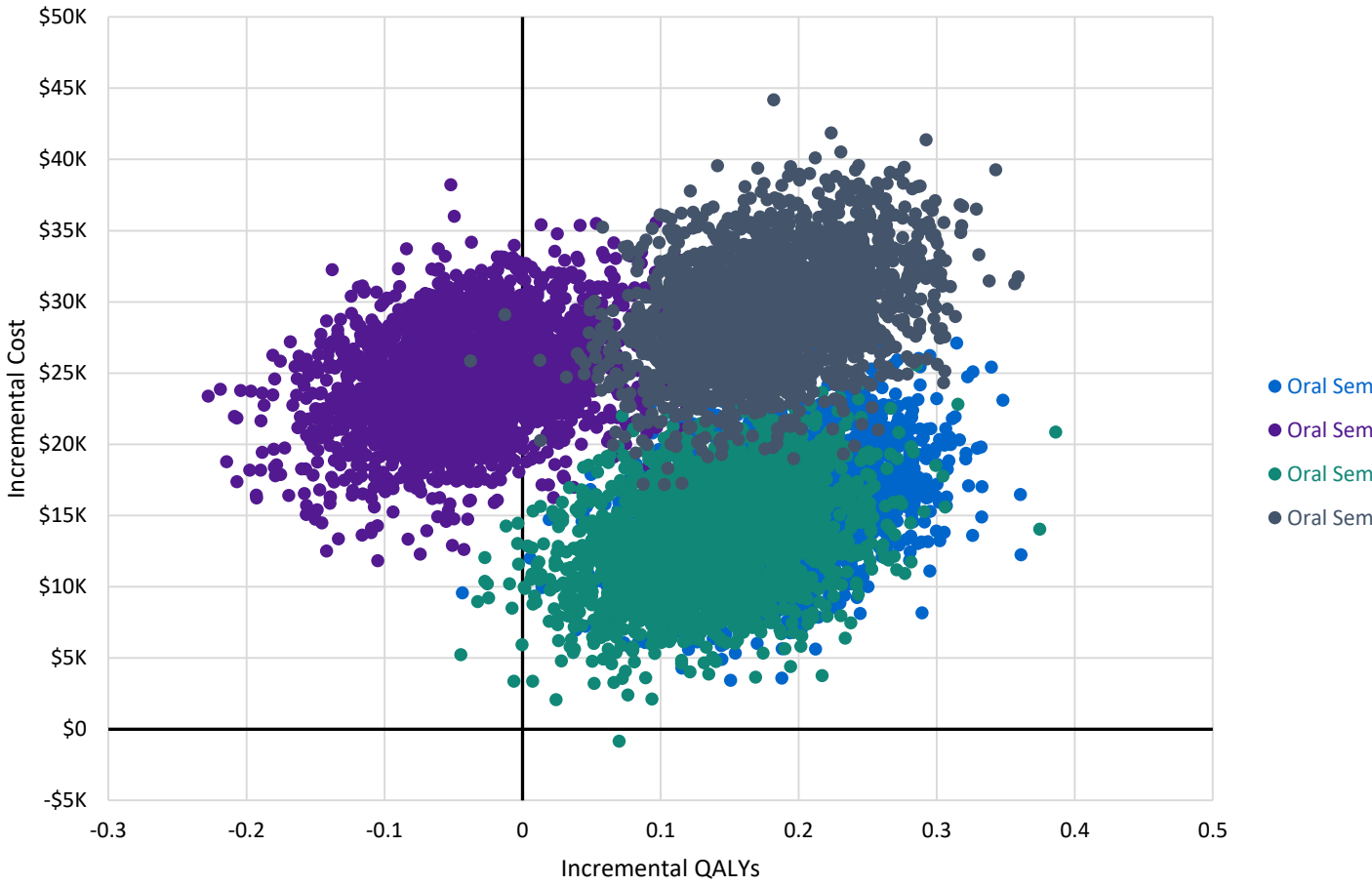


Table E2. Detailed Results by Individual Regimen

	Oral Semaglutide		Sitagliptin		Empagliflozin		Liraglutide		Background Tx	
	Mean	95% CR	Mean	95% CR	Mean	95% CR	Mean	95% CR	Mean	95% CR
Total Cost	$118,526	($112,836 - $124,219)	$102,937	($97,850 - $108,211)	$93,996	($89,133 - $99,045)	$105,092	($99,939 - $110,192)	$89,098	($84,269 - $94,171)
Add-on Agent	$21,226	($20,210 - $22,295)	$4,003	($3,845 - $4,162)	$7,144	($6,804 - $7,491)	$17,971	($17,040 - $18,901)	$0	($ - $)
Background Tx	$3,191	($3,047 - $3,335)	$2,899	($2,774 - $3,030)	$3,245	($3,096 - $3,399)	$3,270	($3,113 - $3,424)	$2,900	($2,770 - $3,031)
Insulin	$1,908	($1,671 - $2,155)	$1,733	($1,518 - $1,951)	$166	($73 - $290)	$350	($206 - $523)	$122	($44 - $230)
Healthcare	$2,190	($2,076 - $2,304)	$1,964	($1,865 - $2,071)	$2,189	($2,072 - $2,310)	$2,209	($2,090 - $2,335)	$1,922	($1,821 - $2,024)
CHF	$3,795	($3,213 - $4,432)	$3,459	($2,852 - $4,075)	$2,861	($2,321 - $3,398)	$2,966	($2,433 - $3,512)	$3,520	($2,947 - $4,121)
IHD	$1,303	($984 - $1,641)	$1,179	($872 - $1,500)	$1,301	($989 - $1,660)	$1,250	($958 - $1,587)	$1,175	($889 - $1,500)
MI	$6,782	($5,576 - $8,080)	$7,575	($6,288 - $8,854)	$7,366	($6,113 - $8,639)	$7,360	($6,115 - $8,644)	$7,710	($6,411 - $9,059)
Stroke	$8,044	($6,761 - $9,397)	$8,204	($6,926 - $9,584)	$8,439	($7,099 - $9,898)	$8,397	($7,017 - $9,880)	$8,304	($6,928 - $9,627)
Blindness	$63	($25 - $116)	$58	($20 - $106)	$62	($22 - $115)	$62	($21 - $114)	$58	($20 - $110)
Foot Ulcer	$61	($36 - $89)	$60	($35 - $88)	$62	($37 - $89)	$62	($37 - $90)	$61	($36 - $87)
Amputation	$357	($226 - $507)	$329	($207 - $466)	$316	($196 - $459)	$317	($196 - $453)	$300	($182 - $429)
Renal Disease	$54,328	($49,710 - $58,807)	$55,582	($51,241 - $60,151)	$52,998	($48,737 - $57,547)	$53,054	($48,814 - $57,432)	$55,197	($50,910 - $59,578)
Hypoglycemia	$15,277	($13,923 - $16,683)	$15,892	($14,500 - $17,339)	$7,847	($7,056 - $8,661)	$7,825	($7,041 - $8,672)	$7,830	($7,008 - $8,688)
Survival										
QALYs	1.95	(1.87 - 2.03)	1.76	(1.69 - 1.84)	1.99	(1.90 - 2.08)	1.81	(1.73 - 1.89)	1.77	(1.69 - 1.84)
Life Years	3.44	(3.29 - 3.59)	3.13	(2.99 - 3.27)	3.50	(3.34 - 3.66)	3.53	(3.36 - 3.69)	3.13	(2.99 - 3.27)

Complications										
CHF	12.7%	(10.6% - 15.0%)	11.4%	(9.3% - 13.6%)	9.4%	(7.4% - 11.4%)	9.8%	(7.8% - 11.8%)	11.7%	(9.7% - 13.9%)
IHD	3.6%	(2.3% - 5.0%)	3.2%	(2.0% - 4.6%)	3.7%	(2.4% - 5.1%)	3.8%	(2.5% - 5.2%)	3.2%	(2.0% - 4.4%)
1st MI	9.9%	(8.1% - 11.8%)	11.1%	(9.1% - 13.0%)	10.9%	(8.9% - 12.9%)	10.9%	(9.0% - 12.9%)	11.3%	(9.3% - 13.3%)
Subs. MI	0.7%	(0.1% - 1.3%)	0.8%	(0.3% - 1.5%)	0.7%	(0.3% - 1.3%)	0.7%	(0.1% - 1.3%)	0.8%	(0.3% - 1.5%)
1st Stroke	6.7%	(5.0% - 8.5%)	7.6%	(5.9% - 9.5%)	7.6%	(5.8% - 9.6%)	7.6%	(5.8% - 9.5%)	7.8%	(6.0% - 9.7%)
Subs. Stroke	2.4%	(1.3% - 3.5%)	2.5%	(1.5% - 3.6%)	2.5%	(1.5% - 3.6%)	2.5%	(1.5% - 3.6%)	2.5%	(1.5% - 3.6%)
Blindness	2.1%	(1.2% - 3.1%)	2.0%	(1.1% - 3.0%)	2.0%	(1.1% - 3.1%)	2.0%	(1.1% - 3.1%)	2.0%	(1.1% - 3.1%)
Foot Ulcer	2.9%	(1.7% - 4.0%)	2.7%	(1.6% - 4.0%)	2.8%	(1.7% - 4.2%)	2.9%	(1.7% - 4.2%)	2.7%	(1.6% - 3.9%)
1st Amp, No Ulc	3.3%	(2.0% - 4.6%)	2.9%	(1.9% - 4.2%)	2.9%	(1.7% - 4.2%)	2.9%	(1.7% - 4.2%)	2.6%	(1.6% - 3.8%)
1st Amp, Ulcer	0.4%	(0.0% - 0.9%)	0.4%	(0.0% - 0.8%)	0.4%	(0.0% - 0.9%)	0.4%	(0.0% - 0.9%)	0.4%	(0.0% - 0.8%)
Subs. Amp	0.6%	(0.1% - 1.3%)	0.5%	(0.0% - 1.1%)	0.3%	(0.0% - 0.8%)	0.3%	(0.0% - 0.8%)	0.3%	(0.0% - 0.8%)
Renal Disease	45.7%	(43.0% - 48.3%)	48.8%	(46.0% - 51.4%)	44.8%	(42.1% - 47.5%)	45.0%	(42.3% - 47.7%)	48.5%	(45.8% - 51.3%)

Table E3. Detailed Incremental Results: Oral Semaglutide vs. Comparators

	Oral Semaglutide vs. Sitagliptin		Oral Semaglutide vs. Empagliflozin		Oral Semaglutide vs. Liraglutide		Oral Semaglutide vs. Background Tx	
	Mean	95% CR	Mean	95% CR	Mean	95% CR	Mean	95% CR
ICER (QALYs)	$84,785	($45,566 - $174,251)	-$596,923	(-$6,752,160 - $4,654,315)	$95,955	($42,460 - $309,597)	$163,899	($102,961 - $345,079)
ICER (Life Years)	$49,556	($26,876 - $105,480)	-$415,659	(-$2,815,046 - $3,528,348)	-$157,381	(-$1,966,731 - $1,504,924)	$93,812	($58,916 - $209,429)
Total Cost	$15,590	($8,171 - $22,664)	$24,530	($17,370 - $31,665)	$13,434	($6,438 - $20,686)	$29,428	($21,997 - $36,903)
Add-on Agent	$17,223	($16,184 - $18,272)	$14,082	($13,053 - $15,126)	$3,256	($1,998 - $4,522)	$21,226	($20,210 - $22,295)
Background Tx	$292	($119 - $467)	-$55	(-$237 - $126)	-$79	(-$267 - $102)	$291	($119 - $474)
Insulin	$175	(-$127 - $488)	$1,742	($1,479 - $2,007)	$1,558	($1,274 - $1,840)	$1,786	($1,528 - $2,054)
Healthcare	$226	($88 - $366)	$1	(-$144 - $154)	-$19	(-$173 - $130)	$268	($132 - $415)
CHF	$336	(-$468 - $1,201)	$934	($166 - $1,736)	$829	($34 - $1,664)	$275	(-$546 - $1,125)
IHD	$124	(-$319 - $582)	$2	(-$460 - $455)	$53	(-$414 - $493)	$128	(-$310 - $564)
MI	-$793	(-$2,587 - $966)	-$583	(-$2,327 - $1,117)	-$578	(-$2,346 - $1,164)	-$928	(-$2,623 - $850)
Stroke	-$160	(-$1,943 - $1,605)	-$395	(-$2,243 - $1,386)	-$353	(-$2,233 - $1,466)	-$260	(-$2,063 - $1,517)
Blindness	$6	(-$54 - $70)	$1	(-$64 - $66)	$2	(-$62 - $68)	$6	(-$58 - $68)
Foot Ulcer	$1	(-$35 - $38)	-$1	(-$36 - $35)	-$1	(-$38 - $35)	$0	(-$35 - $38)
Amputation	$29	(-$159 - $210)	$41	(-$143 - $226)	$41	(-$141 - $225)	$57	(-$123 - $237)
Renal Disease	-$1,254	(-$7,060 - $4,955)	$1,330	(-$4,759 - $7,207)	$1,274	(-$4,432 - $7,037)	-$869	(-$6,776 - $5,406)
Hypoglycemia	-$615	(-$2,232 - $996)	$7,430	($6,001 - $8,901)	$7,452	($5,968 - $8,929)	$7,448	($5,949 - $8,947)
Survival								
QALYs	0.18	(0.08 - 0.29)	-0.04	(-0.15 - 0.07)	0.14	(0.03 - 0.24)	0.18	(0.08 - 0.29)

Life Years	0.31	(0.13 - 0.51)	-0.06	(-0.25 - 0.14)	-0.09	(-0.29 - 0.11)	0.31	(0.13 - 0.51)
Complications								
CHF	1.3%	(-1.7% - 4.4%)	3.3%	(0.4% - 6.3%)	2.9%	(-0.1% - 5.9%)	1.0%	(-2.0% - 4.2%)
IHD	0.4%	(-1.3% - 2.1%)	-0.1%	(-1.9% - 1.7%)	-0.1%	(-2.1% - 1.6%)	0.4%	(-1.3% - 2.1%)
1st MI	-1.2%	(-3.8% - 1.5%)	-1.0%	(-3.6% - 1.7%)	-1.0%	(-3.6% - 1.6%)	-1.4%	(-4.0% - 1.3%)
Subs. MI	-0.1%	(-0.9% - 0.8%)	-0.1%	(-0.8% - 0.8%)	-0.1%	(-0.9% - 0.8%)	-0.1%	(-0.9% - 0.8%)
1st Stroke	-0.9%	(-3.4% - 1.3%)	-1.0%	(-3.4% - 1.6%)	-0.9%	(-3.4% - 1.5%)	-1.1%	(-3.6% - 1.3%)
Subs. Stroke	-0.1%	(-1.5% - 1.3%)	-0.1%	(-1.5% - 1.3%)	-0.1%	(-1.5% - 1.3%)	-0.1%	(-1.5% - 1.2%)
Blindness	0.1%	(-1.3% - 1.5%)	0.1%	(-1.3% - 1.5%)	0.1%	(-1.2% - 1.5%)	0.1%	(-1.3% - 1.5%)
Foot Ulcer	0.1%	(-1.6% - 1.8%)	0.0%	(-1.6% - 1.6%)	0.0%	(-1.7% - 1.6%)	0.1%	(-1.5% - 1.8%)
1st Amp, No Ulc	0.3%	(-1.3% - 2.0%)	0.4%	(-1.2% - 2.0%)	0.4%	(-1.3% - 2.0%)	0.6%	(-0.9% - 2.3%)
1st Amp, Ulcer	0.0%	(-0.5% - 0.7%)	0.0%	(-0.7% - 0.7%)	0.0%	(-0.7% - 0.7%)	0.1%	(-0.5% - 0.7%)
Subs. Amp	0.1%	(-0.7% - 0.9%)	0.2%	(-0.5% - 1.1%)	0.2%	(-0.4% - 1.1%)	0.3%	(-0.4% - 1.1%)
Renal Disease	-3.1%	(-6.6% - 0.3%)	0.9%	(-2.6% - 4.3%)	0.7%	(-2.8% - 4.2%)	-2.9%	(-6.4% - 0.4%)
Cost per Event Avoided								
MACE	2.30E+18	(-$7,150,357 - $7,326,215)	-1.00E+18	(-$10,874,744 - $9,631,953)	3.50E+18	(-$5,859,563 - $6,504,555)	2.51E+18	(-$6,464,511 - $10,275,807)
Renal Disease	$613,874	(-$1,671,049 - $3,883,063)	-$705,489	(-$10,953,147 - $12,650,979)	-$309,661	(-$7,866,547 - $7,956,745)	$1,229,367	(-$4,920,405 - $7,877,581)
Cong. Heart Failure	-$784,284	(-$8,800,630 - $7,065,648)	-$930,882	(-$3,616,912 - -$352,473)	-$564,125	(-$2,568,421 - $703,785)	-$819,234	(-$19,425,516 - $20,148,863)
Threshold Price/QALY								

$50,000/QALY	$6,170	($5,786 - $6,573)	$5,059	($4,700 - $5,455)	$6,169	($5,771 - $6,578)	$5,397	($5,027 - $5,791)
$100,000/QALY	$6,676	($6,105 - $7,234)	$4,946	($4,356 - $5,539)	$6,553	($5,959 - $7,144)	$5,890	($5,333 - $6,471)
$150,000/QALY	$7,181	($6,396 - $7,969)	$4,832	($3,970 - $5,709)	$6,938	($6,078 - $7,788)	$6,383	($5,581 - $7,203)