Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value

Final Evidence Report

December 9, 2019

Prepared for

ICER Staff and Consultants	University of Washington School of Pharmacy Modeling Group
David M. Rind, MD, MSc Chief Medical Officer ICER **Katherine Fazioli, BS** Research Lead ICER **Eric Borrelli, PharmD, MBA** Evidence Synthesis Intern ICER **Rick Chapman, PhD, MS** Director of Health Economics ICER **Varun M. Kumar, MBBS, MPH, MSc (Former)** Associate Director of Health Economics ICER **Pamela Bradt, MD, MPH** Chief Scientific Officer ICER **Steven D. Pearson, MD, MSc** President ICER	**Greg Guzauskas, MSPH, PhD** Research Scientist The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute, Department of Pharmacy University of Washington **Ryan N. Hansen, PharmD, PhD** Assistant Professor The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute, Department of Pharmacy University of Washington

None of the above authors disclosed any conflicts of interest.

DATE OF PUBLICATION: December 9, 2019

How to cite this document: Rind D, Guzauskas G, Fazioli K, Hansen R, Kumar V, Chapman R, Borrelli E, Bradt P, Pearson S. Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value. Institute for Clinical and Economic Review, December 9, 2019. https://icer-review.org/material/diabetes-final-evidence-report-and-meeting-summary/

David Rind served as the lead author for this report. Katherine Fazioli was responsible for the oversight of the systematic review and authorship of the comparative clinical effectiveness section. Rick Chapman and Varun Kumar were responsible for oversight of the cost-effectiveness analyses and Rick Chapman developed the budget impact model. Eric Borrelli assisted with the systematic review and authored the section on coverage policies and clinical guidelines. Greg Guzauskas and Ryan Hansen developed the cost-effectiveness model and authored the corresponding sections of

the report. Pamela Bradt, Rick Chapman, and Steven Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Sumeyye Samur, Catherine Koola, Michelle Poulin, Serina Herron-Smith, and Avery McKenna for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Laura and John Arnold Foundation. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 19% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include Merck and Boehringer Ingelheim. For a complete list of funders and for more information on ICER's support, please visit http://www.icer-review.org/about/support/.

About New England CEPAC

The New England Comparative Effectiveness Public Advisory Council (New England CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. The New England CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The New England CEPAC Council is an independent committee of medical evidence experts from across New England, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about the New England CEPAC is available at https://icer-review.org/programs/new-england-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially impact the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patient populations and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials and provider prescribing patterns may differ in real-world practice settings.

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/

Expert Reviewers

Samar Hafida, MD
Staff Endocrinologist
Joslin Diabetes Center

No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Joanna Mitri, MD, MS
Staff Endocrinologist
Joslin Diabetes Center

Dr. Mitri receives research, consulting, and speaking support from the National Dairy Council. She has also received support from the National Institutes of Health, Kowa, and the Juvenile Diabetes Research Foundation, along with under $6,000 for a one-time consultation with Novo Nordisk.

Elizabeth J. Murphy, MD, DPhil
Chief, Division of Endocrinology and Metabolism
San Francisco General Hospital, University of California, San Francisco

No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table of Contents

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
ARB	Angiotensin receptor blockers
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
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
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
PRO	Patient-reported outcome

QALY	Quality-adjusted life year
RCT	Randomized control trial
SAE	Serious 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

Executive Summary

Background

In the United States (US), approximately 30 million individuals have diabetes mellitus, of whom 95% have Type 2 diabetes mellitus (T2DM).[1] 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 2012, the estimated annual cost of diagnosed diabetes in the US was 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. In addition to lifestyle changes, many individuals with T2DM will require antihyperglycemic medications to achieve and sustain glycemic control.[2,5] 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.[2,5] If lifestyle changes and metformin do not achieve a desired glycemic target, another glucose-lowering drug may be added.[2,5] 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).[2,5]

A new oral form of the GLP-1 receptor agonist semaglutide (Rybelsus®, Novo Nordisk) was approved for the treatment of adults with T2DM in September 2019; an injectable form of semaglutide that is administered subcutaneously once weekly has been available in the US since 2017.[6] The manufacturer also filed for FDA approval of oral semaglutide for a second indication to reduce major CV events in adults with T2DM and established CV disease and a decision is expected by January 2020.[7] Oral semaglutide is the first oral formulation of a GLP-1 receptor agonist to be approved in the US.

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.

Comparative Clinical Effectiveness

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). 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., glycated hemoglobin [HbA1c]) and key measures of benefit (e.g., cardiovascular [CV] outcomes), as well as potential harms.

Our literature search identified 14 references relating to 12 unique randomized controlled trials (RCTs) that met the full inclusion criteria. 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 network meta-analyses (NMAs). 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.

Data on oral semaglutide came primarily from eight randomized trials[8-15] that were part of the manufacturer's phase III PIONEER program shown in Table ES1. 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 cardiovascular outcomes trials (CVOTs) of our comparator therapies.[16-18] In addition, we included evidence from the CVOT of injectable semaglutide (SUSTAIN 6).[19] Table ES2 presents the study design and key baseline characteristics of the included CVOTs.

Table ES1. 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=822)	1. Oral semaglutide 14 mg 2. Empagliflozin 25 mg	• Treated with metformin • HbA1c of 7.0%-10.5%	Age: 58 years HbA1c: 8.1% T2DM Duration: 7.4 years	52-week open-label	Change in HbA1c at 26 weeks
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 26 weeks
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 26 weeks
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 52 weeks
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 26 weeks
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 26 weeks
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 26 weeks

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

*All agents were administered once daily

†Nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death

‡Results are not currently available from the extension phase

Table ES2. Key Characteristics of Included CVOTs

	PIONEER 6 (N=3183)	SUSTAIN 6 (N=3297)	LEADER (N=9340)	EMPA-REG OUTCOME (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 semaglutide 14 mg 2. Placebo	1. Inj semaglutide 0.5 mg 2. Inj semaglutide 1.0 mg 3. Placebo	1. Liraglutide 1.8 mg 2. Placebo	1. Empagliflozin 25 mg 2. Empagliflozin 10 mg 3. Placebo	1. Sitagliptin 100 mg* 2. Placebo
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, CV: cardiovascular, CVD: cardiovascular disease, CVOTs: cardiovascular outcomes trials, 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

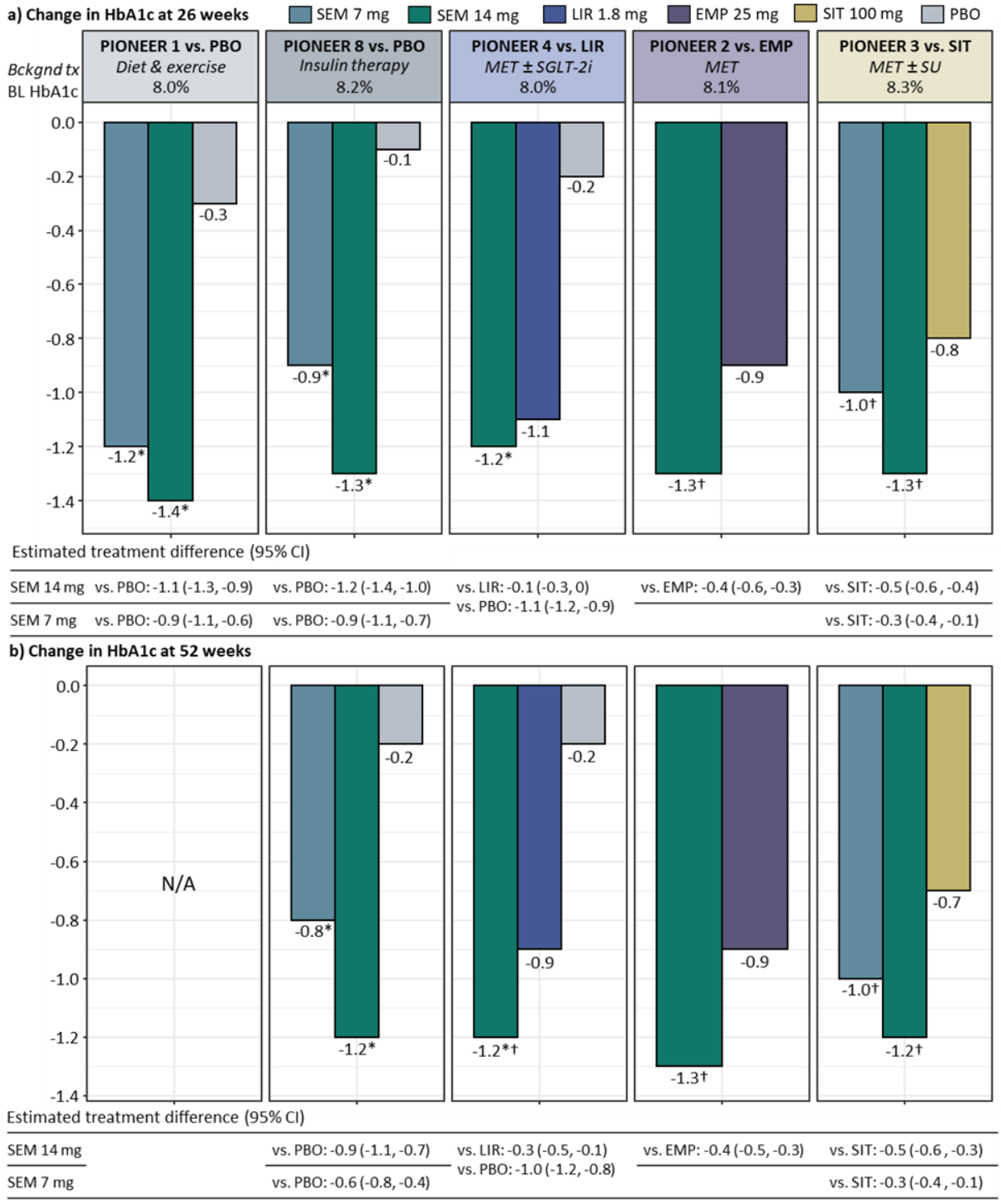
Clinical Benefits

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, a measure of average blood glucose control, 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 and results are shown in Figure ES1. Changes in body weight are shown in Figure ES2.

Figure ES1. Change in HbA1c (Absolute Change in Percentage) at 26 and 52 Weeks

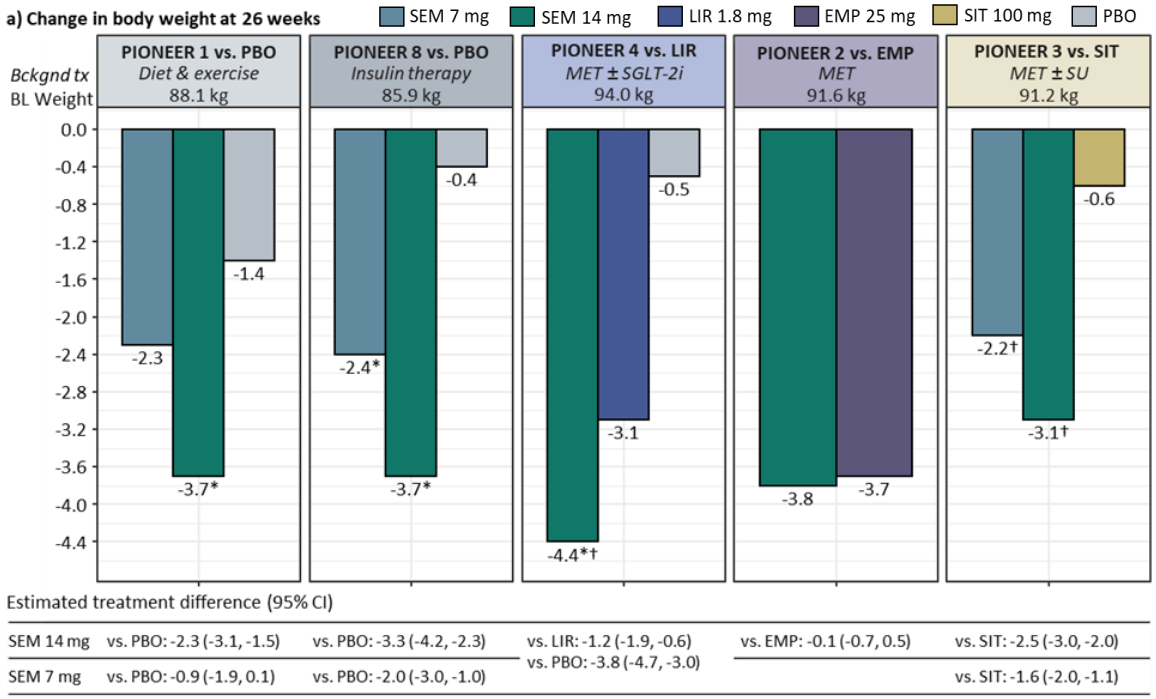


95% CI: 95% confidence interval, BL: baseline, bckgnd: background, EMP: empagliflozin; LIR: liraglutide, MET: metformin, N/A: not applicable, PBO: placebo SEM: semaglutide, SGLT-2i: sodium-glucose cotransporter 2 inhibitor, SIT: sitagliptin; SU: sulfonylurea, tx: treatment

*p<0.001 vs placebo

†p<0.001 vs active comparator

Figure ES2. Change from Baseline in Body Weight (kg) at 26 and 52 Weeks



95% CI: 95% confidence interval, bckgnd: background, BL: baseline, EMP: empagliflozin; LIR: liraglutide, MET: metformin, N/A: not applicable, PBO: placebo SEM: semaglutide, SGLT-2i: sodium-glucose cotransporter 2 inhibitor, SIT: sitagliptin; SU: sulfonylurea, tx: treatment

*p<0.001 vs placebo

†p<0.001 vs active comparator

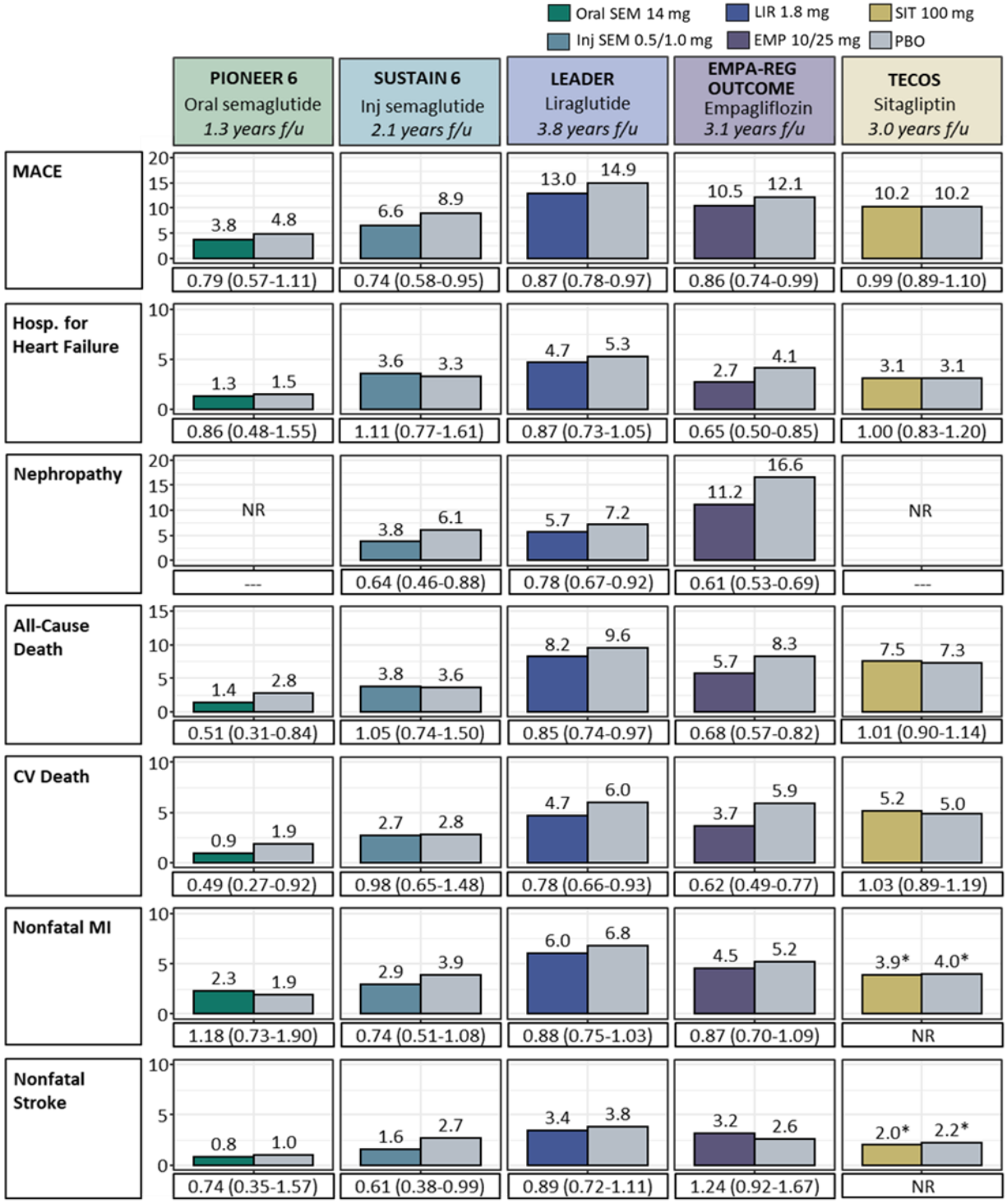
‡p=0.0019 vs active comparator

Key Measures of Benefit

The rates of major adverse cardiovascular events (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. In the NMA, empagliflozin, but not semaglutide, reduced the risk of hospitalization for heart failure.

PIONEER 6 was shorter and smaller than the CVOTs of the other agents. Results of these trials are shown in Figure ES3. Results of the NMA for MACE are shown in Table ES3. In the NMA, empagliflozin decreased the risk of hospitalization for heart failure by 35%, while semaglutide had no effect on this risk (Table ES4).

Figure ES3. Rates and Hazard Ratios (95% CI) for Key Outcomes in Included CVOTs



95% CI: 95% confidence interval, CV: cardiovascular, CVOTs: cardiovascular outcomes trials, EMP: empagliflozin, Hosp.: hospitalization, HR: hazard ratio, LIR: liraglutide, MACE: major adverse cardiovascular event, MI: myocardial infarction, NR: not reported, PBO: placebo, SEM: semaglutide, SIT: sitagliptin

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

Table ES3. 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 ES4. 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.

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 as shown in Table ES5. Rates of discontinuation of therapies are shown in Table ES6.

Table ES5. 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	0	0	1.7
Severe AE	0.6	1.7	2.8	5.9	5.6	8.0	8.6	11.4	8	8	5	6	7	NR	NR	NR
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	6.6	10.5	0.5
Hypoglycemia*	1.1	0.6	0.6	1.7	2.0	5.2	7.7	8.4	1	2	2	5.5	5.6	26.0	26.5	29.3
Severe Hypoglycemia	0.6	0	0	0.2	0.2	0	0.2	0.9	0	0	0	0	0	0.6	1.1	0.5
Nausea	5.1	16	5.6	19.8	2.4	13.4	15.1	6.9	20	18	4	21	2	16.6	23.2	7.1
Diarrhea	5.1	5.1	2.2	9.3	3.2	11.4	12.3	7.9	15	11	8	9	3	12.2	14.9	6.0
Vomiting	4.6	6.9	2.2	7.3	1.7	6.0	9.0	4.1	9	5	2	6	1	7.7	9.9	3.8
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	—	—	9.9	12.7	1.1
Urinary Tract Infection	—	—	—	—	—	4.5	4.9	5.6	—	—	—	—	—	2.8	5.5	3.8
Diabetic Retinopathy	3.4	1.1	1.7	—	—	5.2	3.4	5.8	2.8	1.1	1.4	1.2	1.6	4.4	5.0	4.3

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

*Severe or blood-glucose confirmed symptomatic

Table ES6. 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
Placebo-Controlled Trials						
PIONEER 1 26-week RCT Diet & exercise	Oral semaglutide 7 mg	NR	*N/A*	2.3	10.3	8.0
	Oral semaglutide 14 mg	NR	*N/A*	1.1	13.7	6.9
	Placebo	NR	*N/A*	15.2	10.7	4.5
PIONEER 8 52-week RCT Insulin therapy	Oral semaglutide 7 mg	1.1	18.1	36.8	18.7	4.9
	Oral semaglutide 14 mg	2.2	17.1	36.5	20.4	3.3
	Placebo	4.9	36.4	45.7	12.0	4.9
Head-to-Head Trials						
PIONEER 2 52-week RCT MET	Oral semaglutide 14 mg	1.9	7.5	24.8	17.7	2.9
	Empagliflozin 25 mg	1.2	10.7	21.5	11.0	5.6
PIONEER 3 78-week RCT MET ± SU	Oral semaglutide 7 mg	2.4	15.7	35.4	15.0	6.4
	Oral 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	Oral 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	Oral semaglutide flexible	NR	3.2	19.8	16.6	4.7
	Sitagliptin 100 mg	NR	15.9	24.3	9.2	2.8

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

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.

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,[20] 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, are 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 and requires a period of dose adjustment/titration over 60 days, both of 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).[19] The FDA labels for both oral and injectable semaglutide state, "Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy."[21,22]

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.

Summary and Comment

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 ES7. 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")

Long-Term Cost Effectiveness

Model 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 ongoing antihyperglycemic treatment. The model estimates outcomes that include life years (LYs) gained, quality-adjusted life years (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, including a modified societal perspective.

Population

The population of interest for this review was adults with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s). We utilized a representative population of patients from the U.S., drawing patient-level data from the National Health and Nutrition Examination Survey (NHANES) program, which surveys approximately 5,000 people across the U.S. each year in two-year survey populations.[23] The survey population consists of people from counties across the U.S. A cohort of U.S. adults with self-reported diabetes and HbA1c ≥7 from NHANES 2013-14 and 2015-16 surveys (n=362) served as the population for our microsimulations.

Key Assumptions

Key model assumptions are listed in Table ES8, along with the rationale for each.

Table ES8. 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. We modeled gradual declines in oral semaglutide efficacy for MACE and renal outcomes in scenario analyses.

HbA1c: Glycated hemoglobin, MACE: major adverse cardiovascular event, T2DM: type 2 diabetes mellitus

Model Structure and Event Equations

We modeled diabetes-related complications and mortality based on risk equations from the UKPDS OM2.[24] 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.[24-27] 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).[24] 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 mutually exclusive mortality risk equations 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).[24]

In addition to the UKPDS equations, we applied pooled estimates of treatment discontinuation due to adverse events in cycle 1. Patients discontinuing their primary modeled treatment were assumed to transition to insulin therapy, 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 once their HbA1c reached 8.5 or above; sitagliptin patients were assumed to discontinue treatment and transition to insulin once their HbA1c reached 8.5 or above. After cycle 1, HbA1c and weight change for patients pre- and post-insulin were modeled using a different set of equations,[28] which then influenced the UKPDS OM2 complication risk equations for those patients.

We also modeled mild, moderate, and severe hypoglycemia in cycles 2+ based on the previous UKPDS OM2 adaptation from Laiteerapong et al.[29] Lastly, we utilized age-based cumulative incidence estimates of peripheral vascular disease and atrial fibrillation from the U.S. population,[30,31] and (for atrial fibrillation) relative risk estimates based on patients' HbA1c [32] to simulate these UKPDS-required patient characteristics prior to each microsimulation.

Drug Costs

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.[33] 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 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 October 2019) to arrive at an estimated net price per unit (Table ES9). For oral semaglutide we applied the average discount from WAC for *injectable* semaglutide to arrive at an estimated net price.

The cost for background therapy was estimated from the average WAC prices for available metformin and sulfonylurea oral dosage forms, as a weighted average of patients receiving metformin monotherapy (57%), sulfonylurea monotherapy (26%), or combination metformin and sulfonylurea (17%). These weights were calculated from the distribution of use of these medications in the NHANES patient population.

Table ES9. Drug Cost Inputs

Drug	WAC per Bottle/Pen[34]	Discount From WAC[33]	Net Price per Bottle/Pen/ Insulin Unit	Net Price per Month	Net Price per Year‡
Oral Semaglutide(Rybelsus®), 30-Tablet Bottle*	$772.43	35.1%	$501.31	$508.62	$6,103.45
Sitagliptin (Januvia®), 30-Tablet Bottle	$451.20	72.6%	$123.62	$125.42	$1,505.07
Empagliflozin (Jardiance®), 30-Tablet Bottle	$492.85	65.2%	$171.51	$174.01	$2,088.13
Liraglutide (Victoza®), 18 mg/3mL Pen†	$307.26	28.6%	$219.38	$667.74	$8,012.85
Metformin					$194
Sulfonylureas					$86
Insulin					
Basal			$0.22		Varies by patient weight
Bolus			$0.28		
Premix			$0.14		

mL: milliliters, WAC: wholesale acquisition cost

*WAC price published September 20, 2019; for net price, we assumed the same discount from WAC as that for injectable semaglutide.

†Prices for liraglutide are per 3 ml pen, and the annual price calculation assumes a 1.8 mg (0.3ml)/day dosage.

‡1 year = 365.25 days or 12 months or 52 weeks (note that rounding of the Net Price Per Month column results in slight discrepancies between the Per Month and Per Year columns).

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 lifetime mean total cost for patients treated with oral semaglutide was $295,000 (Table ES10) and costs for the other comparators ranged from $250,000 (background treatment alone) to $305,000 (liraglutide). Oral semaglutide resulted in the fewest MACE, including the fewest cardiovascular deaths. Among the five modeled treatment strategies, oral semaglutide had the highest life years gained (8.18 vs. 7.55 [background treatment alone] and 8.07 [empagliflozin]) and the highest QALYs gained (4.03 vs. 3.63 [background treatment alone] and 3.97 [empagliflozin]).

Table ES10. Results for the Base Case for Oral Semaglutide and Comparators

Treatment	Add-On Drug Cost	Complication Cost	Total Cost	MACE	CHF	ESRD	LYs	QALYs
Oral Semaglutide + background treatment*	$46,000	$208,000	$295,000	59.9%	29.4%	13.0%	8.18	4.03
Sitagliptin (Januvia®) + background treatment	$5,000	$209,000	$254,000	65.8%	27.6%	14.8%	7.66	3.73
Empagliflozin (Jardiance®) + background treatment	$16,000	$204,000	$263,000	63.4%	22.8%	12.4%	8.07	3.97
Liraglutide (Victoza®) + background treatment	$60,000	$203,000	$305,000	62.2%	23.5%	12.4%	8.06	3.72
Background treatment alone	--	$208,000	$250,000	67.2%	27.7%	14.6%	7.55	3.63

CHF: congestive heart failure, ESRD: end-stage renal disease, MACE: major adverse cardiovascular event, QALY: quality-adjusted life years

*Results use an assumed annual net price of $6103 for oral semaglutide.

Oral semaglutide was cost-saving compared to liraglutide, and when compared with background treatment alone (incremental cost-effectiveness ratio = $110,000/QALY) and sitagliptin (incremental cost-effectiveness ratio = $140,000/QALY) was between $100,000 and $150,000/QALY. The incremental cost-effectiveness ratio for oral semaglutide compared with empagliflozin was approximately $480,000/QALY.

Table ES11. Incremental Cost-Effectiveness Ratios: Oral Semaglutide versus Each Comparator

Comparator vs. Oral Semaglutide*	Cost per LY Gained	Cost per MACE Avoided	Cost per QALY Gained
Sitagliptin (Januvia®) + background treatment	$80,000	$700,000	$140,000
Empagliflozin (Jardiance®) + background treatment	$290,000	$920,000	$480,000
Liraglutide (Victoza®) + background treatment	Cost-Saving	Cost-Saving	Cost-Saving
Background treatment alone	$70,000	$630,000	$110,000

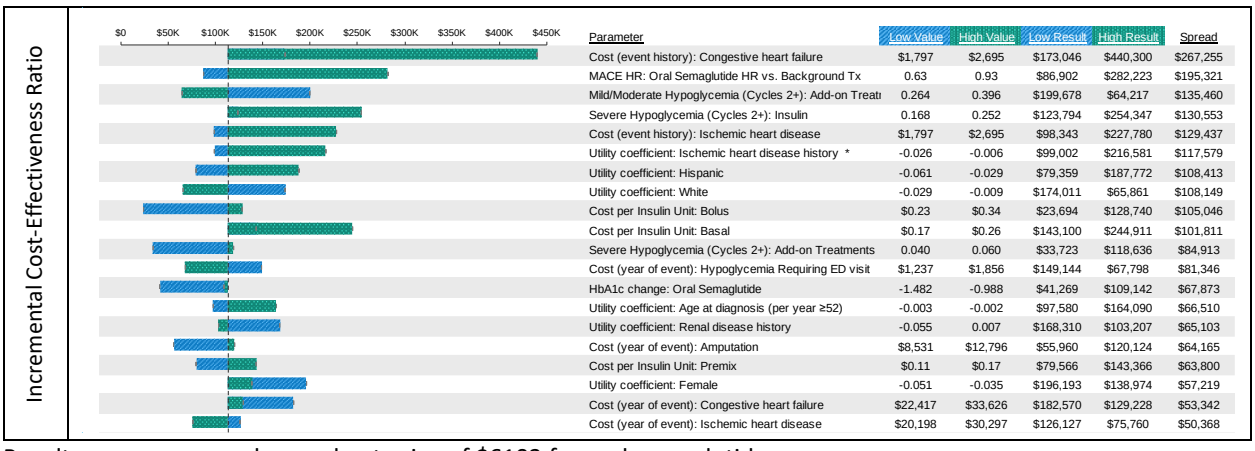
CHF: congestive heart failure, ESRD: end-stage renal disease, LY: life years, MACE: major adverse cardiovascular event, QALY: quality-adjusted life years

*Results use an assumed annual net price of $6103 for oral semaglutide.

Sensitivity Analyses

The parameters with the greatest impact on incremental cost-effectiveness ratios were the cost of CHF, the MACE hazard ratio for oral semaglutide versus background therapy alone, hypoglycemia-related parameters once patients transition to insulin therapy, the cost of IHD, and utility coefficients for IHD and patient demographics. 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 was more impactful in comparisons versus the other add-on therapies.

Figure ES4. Tornado Diagram for One-Way Sensitivity Analysis of Oral Semaglutide versus Background Therapy Alone



Parameter	Low Value	High Value	Low Result	High Result	Spread
Cost (event history): Congestive heart failure	$1,797	$2,695	$173,046	$440,300	$267,255
MACE HR: Oral Semaglutide HR vs. Background Tx	0.63	0.93	$86,902	$282,223	$195,321
Mild/Moderate Hypoglycemia (Cycles 2+): Add-on Treatı	0.264	0.396	$199,678	$64,217	$135,460
Severe Hypoglycemia (Cycles 2+): Insulin	0.168	0.252	$123,794	$254,347	$130,553
Cost (event history): Ischemic heart disease	$1,797	$2,695	$98,343	$227,780	$129,437
Utility coefficient: Ischemic heart disease history *	-0.026	-0.006	$99,002	$216,581	$117,579
Utility coefficient: Hispanic	-0.061	-0.029	$79,359	$187,772	$108,413
Utility coefficient: White	-0.029	-0.009	$174,011	$65,861	$108,149
Cost per Insulin Unit: Bolus	$0.23	$0.34	$23,694	$128,740	$105,046
Cost per Insulin Unit: Basal	$0.17	$0.26	$143,100	$244,911	$101,811
Severe Hypoglycemia (Cycles 2+): Add-on Treatments	0.040	0.060	$33,723	$118,636	$84,913
Cost (year of event): Hypoglycemia Requiring ED visit	$1,237	$1,856	$149,144	$67,798	$81,346
HbA1c change: Oral Semaglutide	-1.482	-0.988	$41,269	$109,142	$67,873
Utility coefficient: Age at diagnosis (per year ≥52)	-0.003	-0.002	$97,580	$164,090	$66,510
Utility coefficient: Renal disease history	-0.055	0.007	$168,310	$103,207	$65,103
Cost (year of event): Amputation	$8,531	$12,796	$55,960	$120,124	$64,165
Cost per Insulin Unit: Premix	$0.11	$0.17	$79,566	$143,366	$63,800
Utility coefficient: Female	-0.051	-0.035	$196,193	$138,974	$57,219
Cost (year of event): Congestive heart failure	$22,417	$33,626	$182,570	$129,228	$53,342
Cost (year of event): Ischemic heart disease	$20,198	$30,297	$126,127	$75,760	$50,368

Results use an assumed annual net price of $6103 for oral semaglutide.

Based on our probabilistic sensitivity analysis that used 2,500 individual simulations for each individual patient, oral semaglutide was predicted to be cost-effective compared to liraglutide

across the range of thresholds, and to have more than 50% chance of being cost-effective against sitagliptin or background treatment alone at a threshold of $150,000 per QALY or higher. However, even at a threshold of $250,000 per QALY, oral semaglutide had only a 27% chance of being cost-effective compared to empagliflozin.

Table ES12. 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	2%	19%	59%	82%	91%
Empagliflozin	2%	3%	8%	18%	27%
Liraglutide	96%	100%	100%	100%	100%
Background Treatment Alone	3%	34%	83%	96%	99%

QALY: quality-adjusted life year

Results use an assumed annual net price of $6103 for oral semaglutide.

Threshold Analyses

We estimated the annual price of oral semaglutide needed to achieve cost per QALY and cost per LY thresholds of $50,000, $100,000, and $150,000, compared to background treatment alone.

Table ES13. Resulting Prices for Oral Semaglutide to Reach Cost per QALY Thresholds Compared to Background Treatment Alone

Outcome	Annual Price to Achieve $50,000 Threshold	Annual Price to Achieve $100,000 Threshold	Annual Price to Achieve $150,000 Threshold
Cost Per QALY Gained	$5,569	$5,983	$6,396
Cost Per LY Gained	$5,807	$6,428	$7,110

LY: life year; QALY: quality-adjusted life year

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 also shared the model with each of the manufacturers involved in this review.

Summary and Comment

All incremental value estimates were coupled with high levels of uncertainty. This uncertainty is a combination of 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 definite conclusions for results comparing oral semaglutide and the other add-on treatments.

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 comorbidities, 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 at lower cost for some patients. Based on the current clinical evidence, with limited follow-up, it is difficult to draw conclusions on its cost effectiveness with a high level of certainty and the ultimate value of oral semaglutide will be determined by its long-term effectiveness and its actual net price.

At its estimated net price, oral semaglutide is likely to meet usual cost-effectiveness thresholds compared with background therapy but is unlikely to meet these thresholds compared with empagliflozin.

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. These elements are listed in the table below.

Potential Other Benefits

Table ES14. Potential Other Benefits

Other Benefits	Description
This intervention offers reduced complexity that will significantly improve patient outcomes.	First oral GLP-1 receptor agonist; may allow better treatment of patients who refuse injectable therapies for T2DM. However, dose titration and requirements for administration on an empty stomach are more burdensome than for comparator oral therapies.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	NA
This intervention will significantly reduce caregiver or broader family burden.	NA
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.	NA
This intervention will have a significant impact on improving return to work and/or overall productivity.	NA
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	NA

NA: not applicable, T2DM: type 2 diabetes mellitus

Contextual Considerations

Table ES15. Potential Contextual Considerations

Contextual Consideration	Description
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.	NA
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	NA
This intervention is the first to offer any improvement for patients with this condition.	NA
Compared to the comparators, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	NA
Compared to the comparators, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	NA
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	NA

NA: not applicable

Value-Based Benchmark Prices

Annual value-based price benchmarks (VBPBs) of oral semaglutide are presented in Table ES16. For oral semaglutide, price discounts of approximately 32% to 36% from the list price (WAC) would be required to reach the $100,000 to $150,000 per QALY threshold prices, respectively.

Table ES16. Value-Based Price Benchmarks for Oral Semaglutide

	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Change from WAC to Reach Threshold Prices
Per QALY Gained	$9,404	$5,983	$6,396	-32% to -36%
Per LY Gained	$9,404	$6,428	$7,110	-24% to -32%

LY: life year, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

We are including results for price per LY gained to ensure that policymakers are aware of the complementary information these results can provide to the cost per QALY findings. The annual price at which oral semaglutide meets the $100,000 to $150,000 per LY range for use in these patients is $6,428 to $7,110. The cost per LY price range is somewhat higher than the cost per QALY range because incremental LYs gained are estimated to be higher than the incremental QALYs gained in this case.

Potential Budget Impact

Methods

We used undiscounted results from the same model employed for the cost-effectiveness analyses to estimate the total potential budgetary impact over five years of oral semaglutide in adults in the US with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s). We used oral semaglutide's list price (WAC), assumed net price, and the three threshold prices to estimate the percentage of patients who could be treated at each of these prices without crossing a budget impact threshold of $819 million per year.

We 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-1 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 used estimates of the prevalence of T2DM among adults in the US[35] and the proportion of T2DM patients with inadequate glycemic control who added on a second treatment 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 this prevalent population switching to oral semaglutide would displace market share of drugs from the DPP-4 inhibitor (sitagliptin), GLP-1 receptor agonist (liraglutide), and SGLT-2 inhibitor classes (empagliflozin).

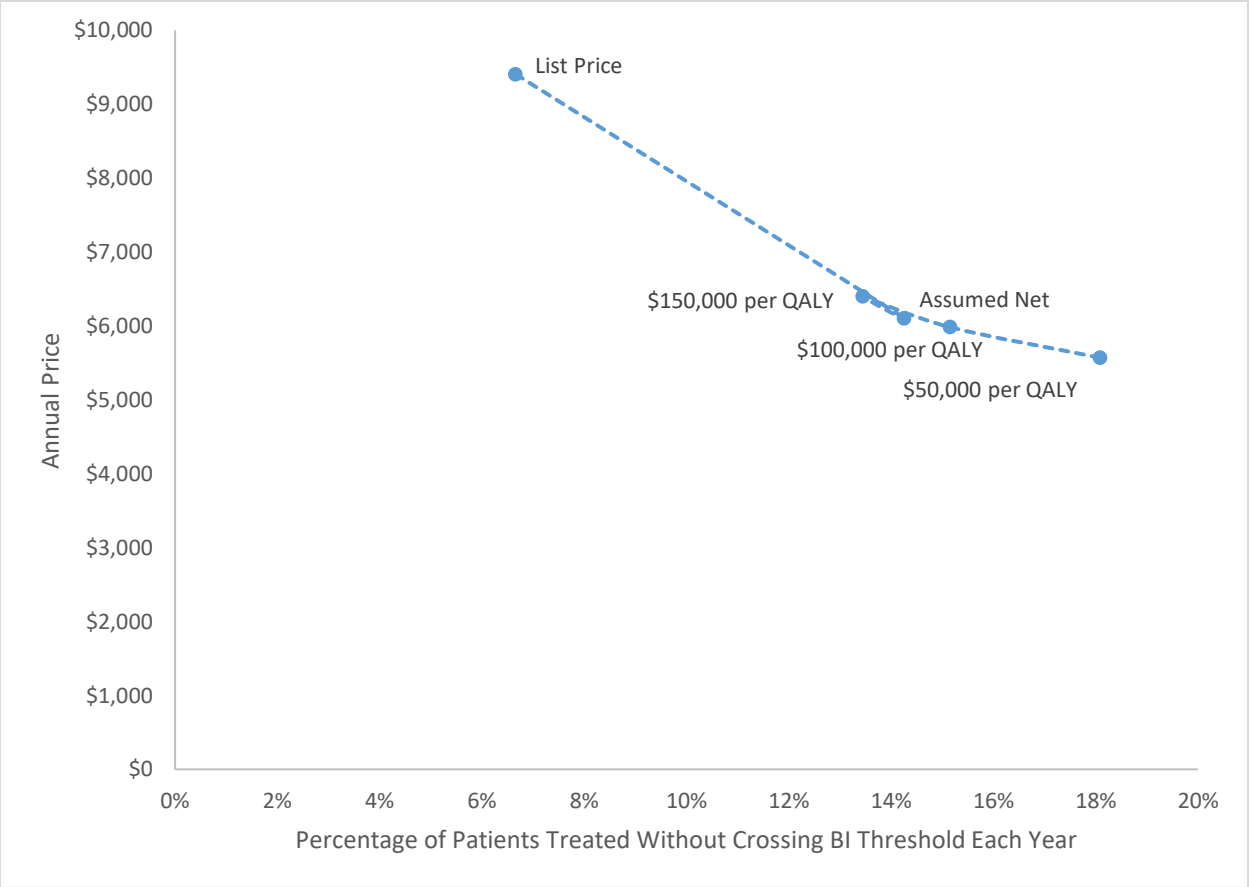
For the incident population of T2DM patients with inadequate glycemic control who require a second ADD, we used estimates of the incidence of T2DM among adults in the US[36] and the number of patients requiring a second ADD to calculate an approximate population size of 844,000 patients each year who would be eligible for treatment with oral semaglutide as an add-on therapy to their background antihyperglycemics.

Results

In the prevalent population assumed to switch to oral semaglutide, approximately 7% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819

million at oral semaglutide's list price and approximately 14% of patients at its assumed net price (Figure ES5). Between 13% and 18% 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.

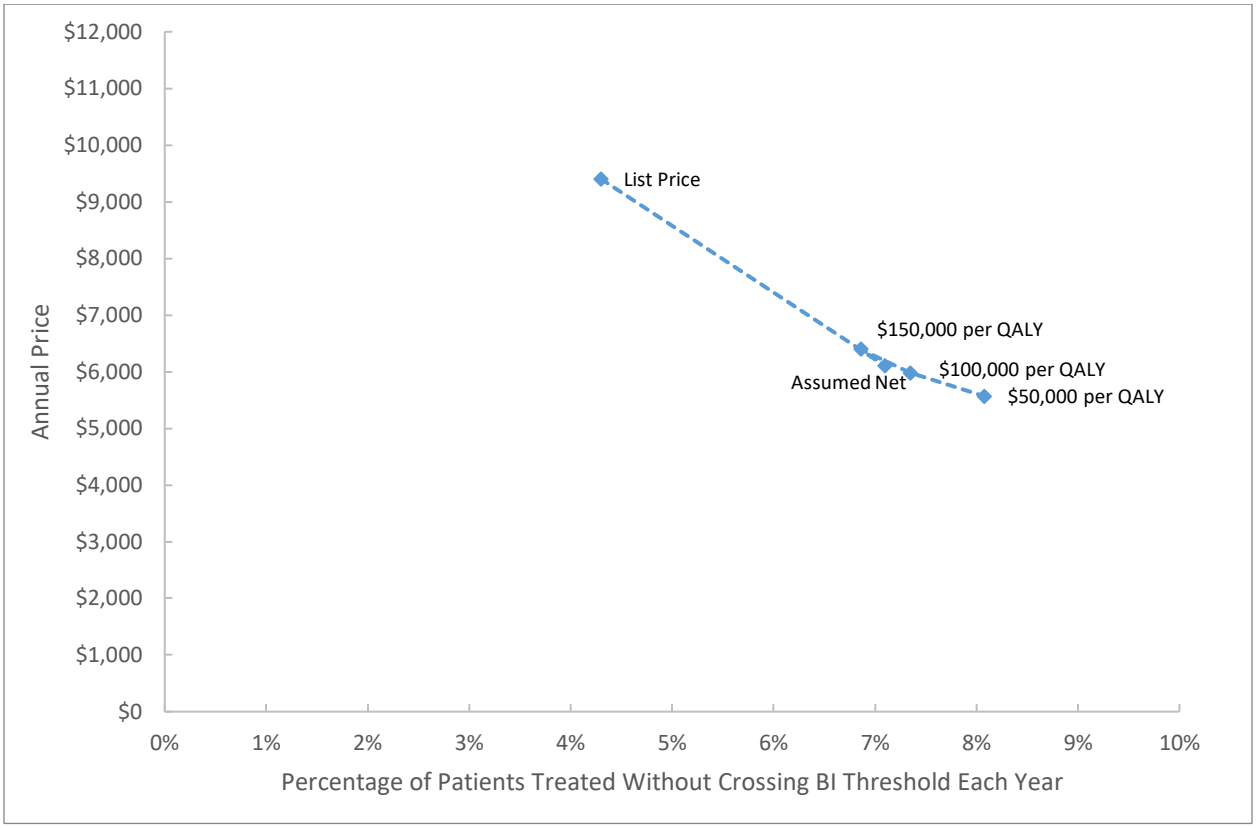
Figure ES5. Potential Budget Impact Scenarios of Oral Semaglutide as a Switching Therapy at Placeholder List and Net Price



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

In the population where oral semaglutide is considered an add-on therapy to background antihyperglycemics, 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 list price and approximately 7.1% could be treated at its assumed net price before the budget exceeded this threshold (Figure ES6). Between 6.9% and 8.1% 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 ES6. Potential Budget Impact Scenarios of Oral Semaglutide as an Add-On Therapy at Different Acquisition Prices



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

Access and Affordability Alert

As discussed above, at oral semaglutide's estimated net price, despite meeting common lifetime cost-effectiveness thresholds versus background therapy alone, only approximately 7% to 14% of eligible US patients could be treated in a given year before exceeding ICER's potential budget impact threshold of $819 million. At the public meeting, clinical experts stated their belief that, because primary care providers are often uncomfortable prescribing injectable GLP-1 receptor agonists, oral semaglutide would be an attractive alternative for up to 50% of the eligible patient population. Given that the clinical goal for uptake would exceed the potential budget impact threshold at the national level, ICER is issuing an access and affordability alert. Currently, this alert is based on the assumed net price, and it should be noted that the findings are subject to change if and when the actual net price becomes available. The purpose of an ICER affordability and access alert is to signal stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health care system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs that threaten sustainable access to high-value care for all patients.

New England CEPAC Votes

The New England CEPAC Panel deliberated on key questions raised by ICER's report at a public meeting on November 14, 2019. The results of these votes are presented below, and additional information on the deliberation surrounding the votes can be found in the full report.

1. Is the evidence adequate to demonstrate that adding **oral semaglutide** (Rybelsus®) to ongoing background therapy provides a positive net health benefit?

Yes: 12 votes	No: 0 votes

2. Is the evidence adequate to demonstrate that the net health benefit of adding **oral semaglutide** is superior to that provided by adding **sitagliptin** (Januvia®)?

Yes: 12 votes	No: 0 votes

3. Is the evidence adequate to demonstrate that the net health benefit of adding **oral semaglutide** is superior to that provided by adding **liraglutide** (Victoza®)?

Yes: 1 vote	No: 11 votes

4. Is the evidence adequate to distinguish the net health benefit of adding **oral semaglutide** from that provided by adding **empagliflozin** (Jardiance®)?

Yes: 1 vote	No: 11 votes

If yes:

4a. Which treatment provides greater net health benefit?

a. Oral semaglutide
b. Empagliflozin

No vote taken

5. For patients currently receiving ongoing background therapy, does adding treatment with **oral semaglutide** offer one or more of the following potential "other benefits or disadvantages." (select all that apply)[a]

This intervention offers reduced complexity compared to liraglutide that will significantly improve patient outcomes.	***9/12***
There are other important benefits or disadvantages that should have an important role in judgements of the value of this intervention.	6/12

6. Are any of the following contextual considerations important in assessing the long-term value for money of **oral semaglutide**? (select all that apply)

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.	5/12
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	***7/12***
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	5/12
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	5/12
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	0/12

7. Given the available evidence on comparative effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **oral semaglutide** versus **ongoing background therapy alone** at current pricing?

Low: 4 votes	***Intermediate: 6 votes***	High: 2 votes

[a] *Votes will be taken on an abbreviated list of potential other benefits and contextual considerations. Although ICER's value framework identifies a broader list, the omitted options were determined not to apply to the treatment in question.*

Key Policy Implications

Following its deliberation on the evidence, the New England CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on the use of oral semaglutide for T2DM to policy and practice. The policy roundtable members included one patient advocate, two clinical experts, two payers, and three representatives from pharmaceutical manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in the full report.

Manufacturers

- Manufacturers with new agents for diabetes mellitus should seize the opportunity to come to market with a lower list price to benefit patients.
- To provide high quality head-to-head evidence on the comparative effectiveness of emerging treatment options for patients with diabetes, manufacturers should look to the example set by the PIONEER trials of oral semaglutide.

Payers

- Prior authorization criteria for antihyperglycemic products should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for submitting prior authorization material should be clear and efficient for providers. Options for specific elements of coverage criteria within insurance coverage policy are discussed in Section 8.3.

Clinicians

- As the treatment options for T2DM continue to evolve, primary care providers should make themselves aware of the 2019 ADA Guidelines on treatment of T2DM to ensure that all treating clinicians know how to identify the varying risks and benefits of different agents for particular subpopulations.
- Clinicians should not "threaten" patients with treatment with insulin if they "fail" other therapies.

Researchers

- Given the high rate of gastrointestinal side effects with oral semaglutide, real world evidence on adherence should be studied and reported.

- It will be important to understand the relative benefits of GLP-1 RAs and SGLT-2i's on patient important outcomes such as cardiovascular events; these can likely best be assessed in head-to-head pragmatic clinical trials.
- Trials of combination therapies, particularly of GLP-1 RAs and SGLT-2i's, should be performed.

1. Introduction

1.1 Background

Background

In the United States (US), approximately 30 million individuals have diabetes mellitus, of whom 95% have Type 2 diabetes mellitus (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 US, including hospitalizations for major cardiovascular disease (CVD) and lower-extremity amputation.[1] In 2012, the estimated annual cost of diagnosed diabetes in the US was 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).[37] 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).[37] Levels of HbA1c are generally used as "glycemic targets" in patients with T2DM, with somewhat less intense control being accepted for 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.[37] In addition to lifestyle changes, many individuals with T2DM will require antihyperglycemic

medications to achieve and sustain glycemic control.[2,5] 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.[2,5] If lifestyle changes and metformin do not achieve a desired glycemic target, another glucose-lowering drug may be added.[2,5] 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).[2,5]

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.[38] These recommendations generally require the conduct of large randomized trials of these new agents in patients at high risk for CV events.[39,40] Since then, several cardiovascular outcome trials (CVOTs) have been conducted, and this evidence has allowed for greater certainty in considering the relative benefits and risks of each therapy.[39] 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. [5]

A new oral form of the GLP-1 receptor agonist semaglutide (Rybelsus®, Novo Nordisk) was approved for the treatment of adults with T2DM in September 2019; an injectable form of semaglutide that is administered subcutaneously once weekly has been available in the US since 2017.[6] The manufacturer also filed for FDA approval of oral semaglutide for a second indication to reduce major CV events in adults with T2DM and established CV disease and a decision is expected by January 2020.[7] Oral semaglutide is the first oral formulation of a GLP-1 receptor agonist to be approved in the US.

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).[41] 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.[5] In some trials, treatment with DPP-4 inhibitors has increased the risk of hospitalization for heart failure.[42]

SGLT-2 Inhibitors

SGLT-2 is a protein in the proximal tubules of the kidney responsible for reabsorbing filtered glucose.[43] 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.[5]

GLP-1 Receptor Agonists

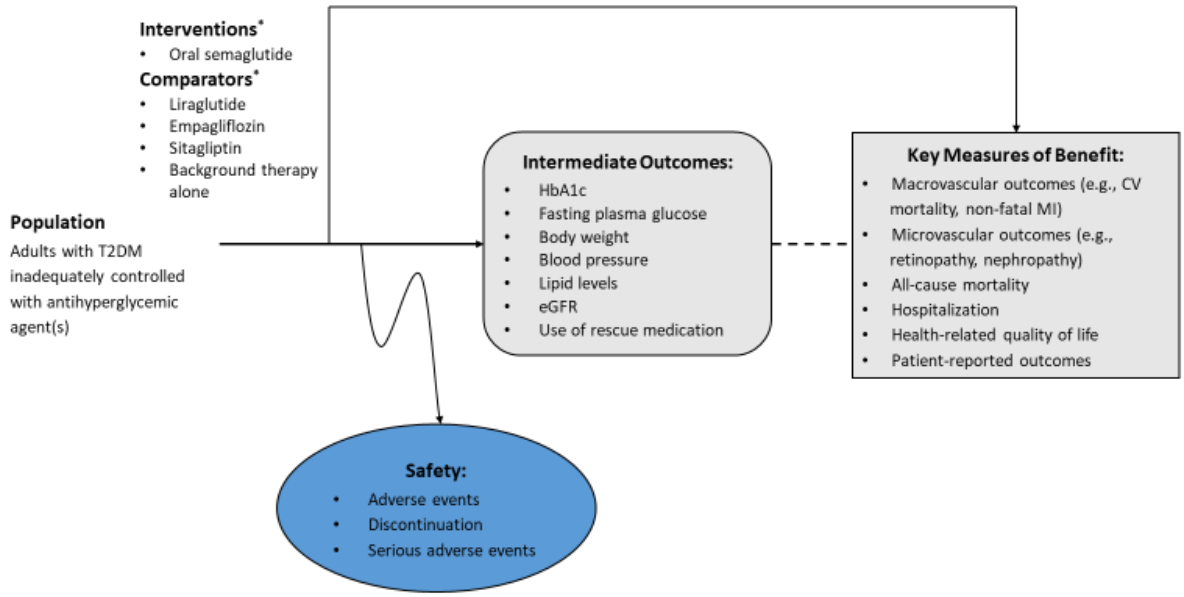
GLP-1 is released by cells in the gastrointestinal tract and stimulates pancreatic release of insulin in response to glucose; it also slows gastric emptying and reduces glucagon levels.[44] Injectable GLP-1 receptor agonists are administered weekly, daily, or twice daily. GLP-1 receptor agonists substantially lower blood glucose levels and result in weight loss and appear to have favorable effects on CV disease and kidney disease.[5] 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.[45]

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.[46]

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.

Although we defined our population as patients inadequately controlled on antihyperglycemic agent(s), we did include evidence from one trial that evaluated oral semaglutide in patients inadequately controlled on diet and exercise alone.

Interventions

Our intervention of interest for this review was oral semaglutide (Rybelsus®, Novo Nordisk) 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).[47] Except for the last criterion, diagnosis requires two abnormal test results. [48]

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.[48]

Fasting Plasma Glucose (FPG): The level of glucose in a patient's blood after having no caloric intake for at least eight hours.[47]

3-Point Major Adverse Cardiovascular Events (MACE): A composite outcome consisting of non-fatal stroke, non-fatal myocardial infarction, and CV death.[49]

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).[50]

Diabetes Treatment Satisfaction Questionnaire: A diabetes specific eight-item instrument assessing patient's satisfaction with their diabetes treatment.[51]

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.[52]

Control of Eating Questionnaire: A 21-item instrument that assesses food cravings from the previous seven days.[53]

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 were captured in the economic model. Rather, we sought services used in the current management of T2DM beyond the potential offsets that arise from a new intervention. ICER encouraged 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. We provided as an example that 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.[54] We received no additional suggestions.

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, most coverage policies assessed had not yet been updated to include oral semaglutide following its FDA approval in September 2019. Only BCMBSMA had oral semaglutide listed in its formulary with the same designation as injectable semaglutide (not covered). We instead reviewed the coverage policies for injectable semaglutide (Ozempic®, Novo Nordisk), 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.[55] 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).[56-60] Liraglutide is not covered on BCBSMA's plan, however, there were other GLP-1 receptor agonists that were covered as preferred agents.[61] 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).[56-61] 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).[56-61] 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).[56-60] Injectable semaglutide is not covered on BCBSMA's plan, however, other GLP-1 receptor agonists were covered as preferred agents.[61] 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 most policies assessed have not been updated to include oral semaglutide following its FDA approval in September 2019.

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)[5]

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).[62] 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%.[37] 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)[63]

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.[63] 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.[64,65] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[66] 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 https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/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.[67]

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-D10) 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 trials (CVOTs) 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.[68] 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.[69] 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 3,724 potentially relevant references (see Appendix Figure A1), of which 14 references[8-19,70,71] 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 eight publications[63,65-71] 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)[63,65-71] were multinational RCTs comparing oral semaglutide to sitagliptin, empagliflozin, liraglutide, and placebo. Two of the PIONEER trials (PIONEER 9 and 10) were conducted exclusively in Japanese patients and are not considered key trials in our review. Briefly, PIONEER 9 compared oral semaglutide to placebo and liraglutide 0.9 mg (a lower dose than recommended by the FDA); oral semaglutide 14 mg was shown to reduce HbA1c more than liraglutide 0.9 mg and placebo.[72] PIONEER 10 compared oral semaglutide to dulaglutide 0.75 mg, and the primary endpoint was the rate of adverse events; oral semaglutide 14 mg and dulaglutide 0.75 mg had similar rates of adverse events, most of which were gastrointestinal adverse events.[73]

Table 3.1 presents the study design and key baseline characteristics of the key 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).[13] 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;[14] PIONEER 3 compared oral semaglutide 3, 7, and 14 mg to sitagliptin 100 mg added to metformin ± a sulfonylurea (47%);[8] PIONEER 4 compared oral semaglutide 14 mg to liraglutide 1.8 mg and placebo added to metformin ± an SGLT-2 inhibitor (26%);[12] and PIONEER 7 compared oral semaglutide flexible dose to sitagliptin 100 mg added to one to two oral antihyperglycemic agents (primarily metformin ± a sulfonylurea).[11] 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.[10] 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.[9] 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 patients inadequately controlled on diet and exercise.[13] 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 ± metformin (67%); 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.[15] 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 with no more than four ounces of water and to wait at least 30 minutes before eating or taking other oral medications. 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. The FDA label recommends oral semaglutide should be started at 3 mg and then escalated to 7 mg after four weeks; after another four weeks, the dose may be increased to 14 mg if additional glycemic control is needed.[21] 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=822)	1. Oral semaglutide 14 mg 2. Empagliflozin 25 mg	• Treated with metformin • HbA1c of 7.0%-10.5%	Age: 58 years HbA1c: 8.1% T2DM Duration: 7.4 years	52-week open-label	Change in HbA1c at 26 weeks
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 26 weeks
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 26 weeks
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 52 weeks
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 26 weeks
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 26 weeks
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 26 weeks

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

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

‡Results are not currently available from the extension phase

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.[16-18] In addition, we included evidence from the CVOT of injectable semaglutide (SUSTAIN 6).[19] 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.[9] 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.[19] 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.[18] 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.[16] 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.[17] 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 8.1% 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 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.

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 trials while all others were blinded (Appendix D).

Table 3.2. Key Characteristics of Included CVOTs

	PIONEER 6 (N=3183)	SUSTAIN 6 (N=3297)	LEADER (N=9340)	EMPA-REG OUTCOME (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 semaglutide 14 mg 2. Placebo	1. Inj semaglutide 0.5 mg 2. Inj semaglutide 1.0 mg 3. Placebo	1. Liraglutide 1.8 mg 2. Placebo	1. Empagliflozin 25 mg 2. Empagliflozin 10 mg 3. Placebo	1. Sitagliptin 100 mg* 2. Placebo
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, N: number of participants, T2DM: type 2 diabetes mellitus

*50 mg if eGFR ≥30 and <50

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.

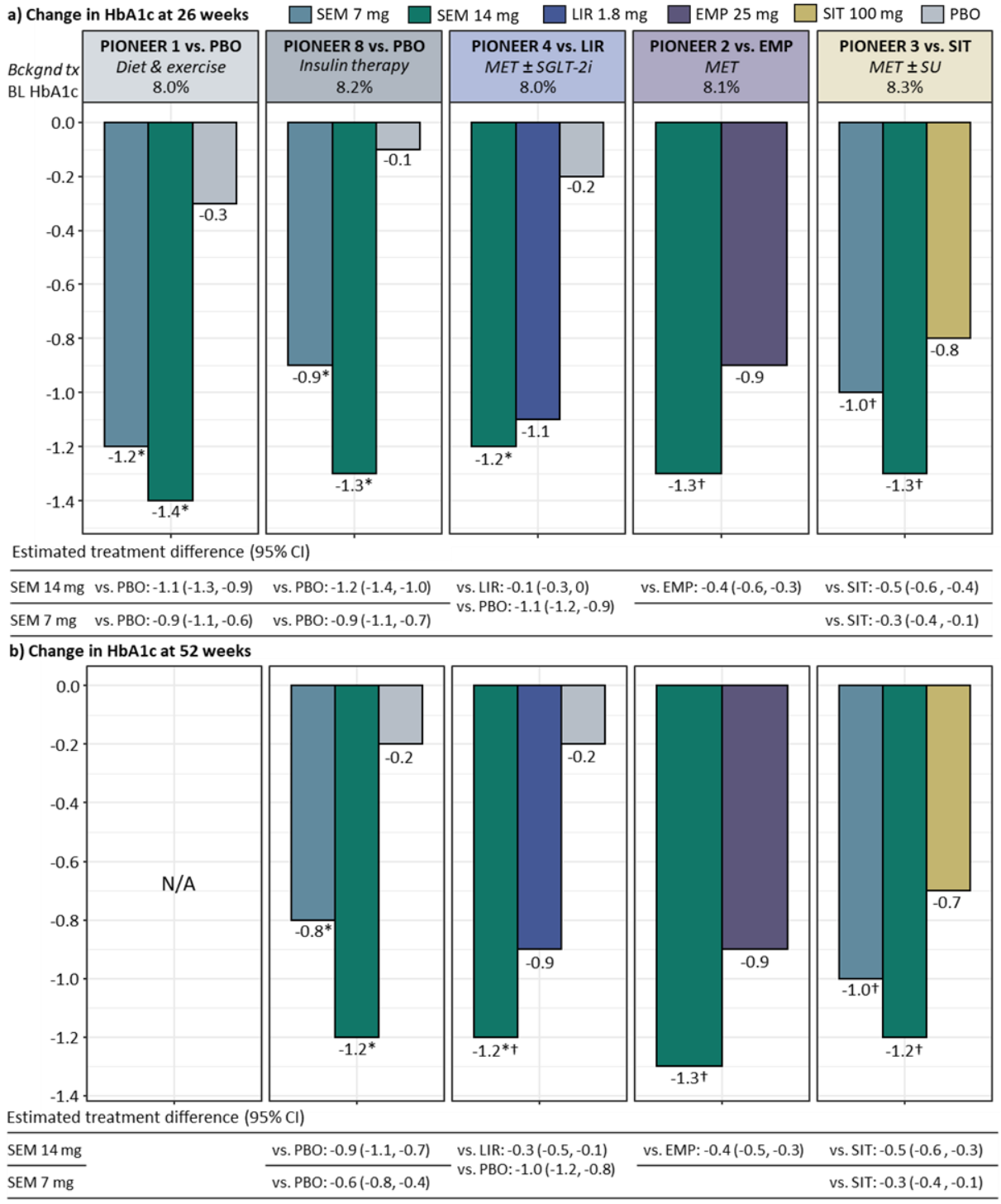
HbA1c

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 used as a monotherapy (PIONEER 1, -1.4% vs. -0.3%),[13] when added to insulin therapy (PIONEER 8, -1.3% vs. -0.1%),[15] and when added to metformin ± SGLT-2 inhibitor (PIONEER 4, -1.2% vs -0.2%)[12](Figure 3.1). Significant reductions with oral semaglutide 14 mg compared to placebo were also observed at 52 weeks in PIONEER 8 and PIONEER 4 (-1.2% vs -0.2% for both)(Figure 3.1). Oral semaglutide 3 mg and 7 mg also reduced HbA1c more than placebo at all timepoints in PIONEER 1 and PIONEER 8 (Figure 3.1 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%)[12] (Figure 3.1). 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%)[14] and sitagliptin 100 mg when added to metformin ± sulfonylurea (PIONEER 3, -1.3% vs. -0.8%)[8] (Figure 3.1). 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%)(Figure 3.1). 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 (Figure 3.1 and Appendix Table D5). In PIONEER 7, oral semaglutide flexible dose reduced HbA1c more than sitagliptin 100 mg when added to one to two oral antihyperglycemic agents at 52 weeks (-1.3% vs -0.8%);[11] results at 26 weeks were not reported (Appendix Table D5).

Figure 3.1. Change in HbA1c (Absolute Change in Percentage) at 26 and 52 Weeks



95% CI: 95% confidence interval, BL: baseline, bckgnd: background, EMP: empagliflozin; LIR: liraglutide, MET: metformin, N/A: not applicable, PBO: placebo SEM: semaglutide, SGLT-2i: SGLT-2 inhibitor, SIT: sitagliptin; SU: sulfonylurea, tx: treatment

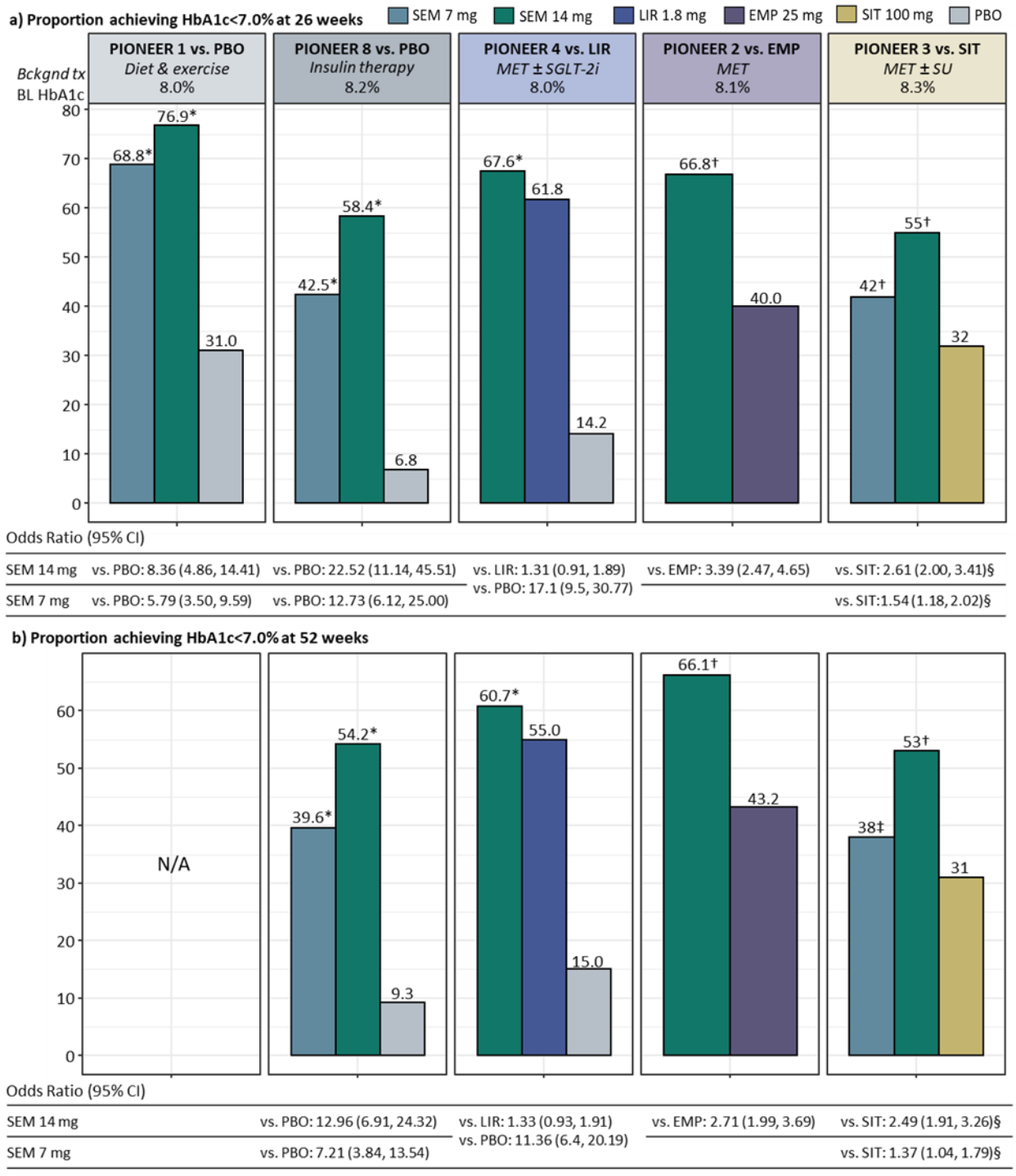
*p<0.001 vs placebo

†p<0.001 vs active comparator

More patients treated with oral semaglutide 14 mg achieved HbA1c<7.0% compared to placebo when used as a monotherapy at 26 weeks (PIONEER 1, 76.9% vs 31.0%),[13] when added to insulin therapy at 26 weeks (PIONEER 8, 58.4% vs. 6.8%) and 52 weeks (54.2% vs 9.3%),[15] and 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%)[12](Figure 3.2). 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 and PIONEER 8 (Figure 3.2 and Appendix Table D6).

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%)[12](Figure 3.2). 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%)[14] 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%)[8](Figure 3.2 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%);[11] results at 26 weeks were not reported (Appendix Table D5).

Figure 3.2. Proportion Achieving HbA1c<7.0% at 26 and 52 Weeks



95% CI: 95% confidence interval, BL: baseline, bckgnd: background, EMP: empagliflozin; LIR: liraglutide, MET: metformin, N/A: not applicable, PBO: placebo SEM: semaglutide, SGLT-2i: SGLT-2 inhibitor, SIT: sitagliptin; SU: sulfonylurea, tx: treatment

*p<0.001 vs. placebo

†p<0.001 vs. active comparator

‡p=0.04 vs. active comparator

§Odds ratios were calculated as the trial only reported estimated treatment differences

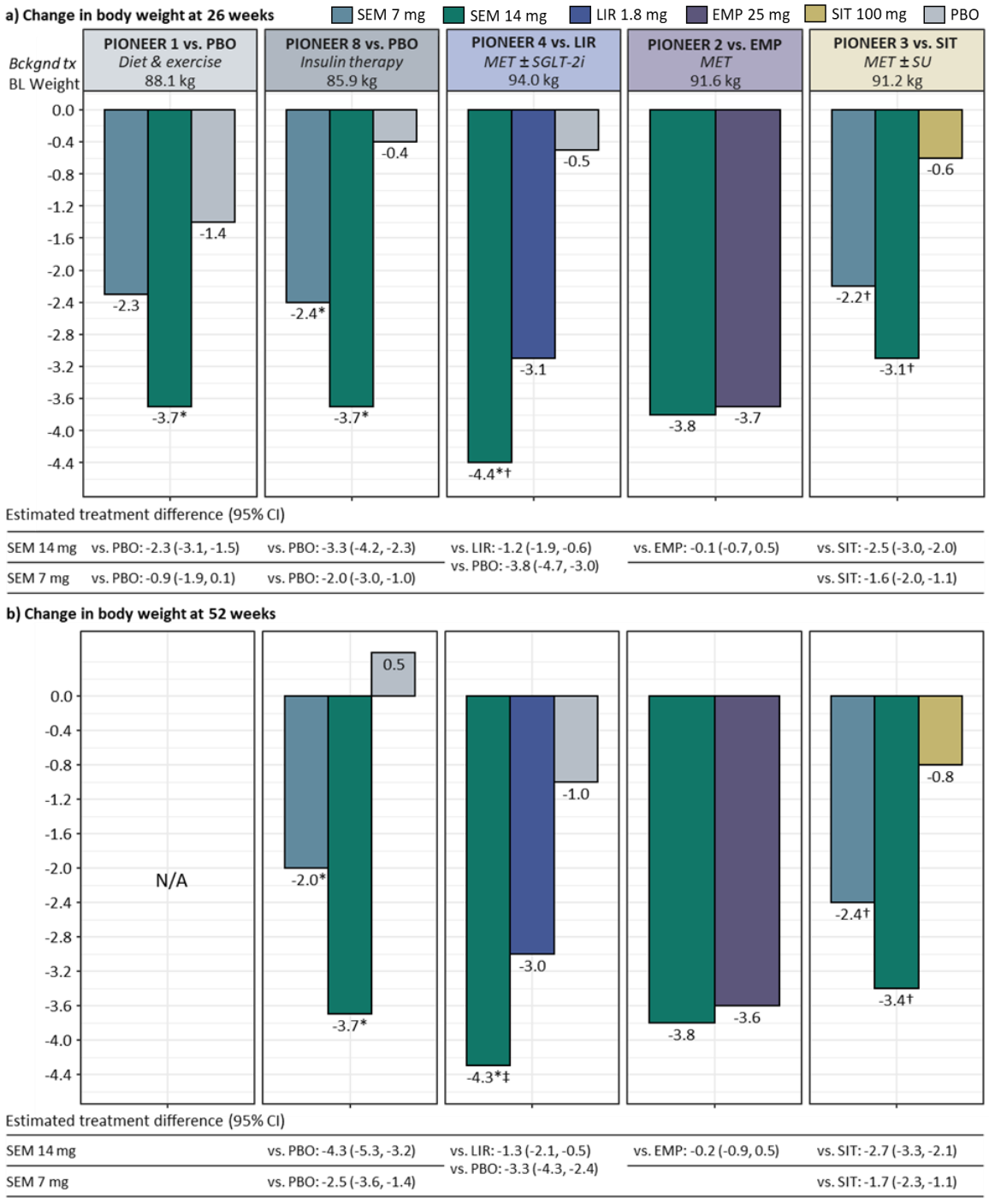
Changes in HbA1c were reported in PIONEER 6 as well as the other CVOTs included in this review. In PIONEER 6, HbA1c was decreased by -1.0% in the oral semaglutide 14 mg arm compared to -0.3% in the placebo arm at 1.3 years of follow-up.[9] In SUSTAIN 6, HbA1c was decreased by -1.1% and -1.4% in patients 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.[19] 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.[16] In TECOS, the mean difference in HbA1c reduction between sitagliptin 100 mg and placebo was -0.29% at three years.[17]

Body Weight

Oral semaglutide 14 mg reduced body weight more than placebo at 26 weeks when used as a monotherapy (PIONEER 1, -3.7 kg vs. -1.4 kg),[13] when added to insulin therapy (PIONEER 8, -3.7 kg vs. -0.4 kg),[15] and when added to metformin ± SGLT-2 inhibitor (PIONEER 4, -4.4 kg vs. -0.5 kg)[12](Figure 3.3). 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)(Figure 3.3). 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)(Figure 3.3 and 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)[12] and sitagliptin 100 mg when added to metformin ± sulfonylurea (PIONEER 3, -3.1 kg vs. -0.6 kg)[8](Figure 3.3). 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)[14](Figure 3.3). 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)(Figure 3.3). 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 (Figure 3.3 and Appendix Table D5). In PIONEER 7, oral semaglutide flexible dose reduced weight more than sitagliptin 100 mg when added to one to two oral antihyperglycemic agents at 52 weeks (-2.6 kg vs. –0.7 kg);[11] results at 26 weeks were not reported (Appendix Table D5).

Figure 3.3. Change from Baseline in Body Weight (kg) at 26 and 52 Weeks



95% CI: 95% confidence interval, BL: baseline, bckgnd: background, EMP: empagliflozin; LIR: liraglutide, MET: metformin, N/A: not applicable, PBO: placebo SEM: semaglutide, SGLT-2i: SGLT-2 inhibitor, SIT: sitagliptin; SU: sulfonylurea, tx: treatment

*p<0.001 vs. placebo

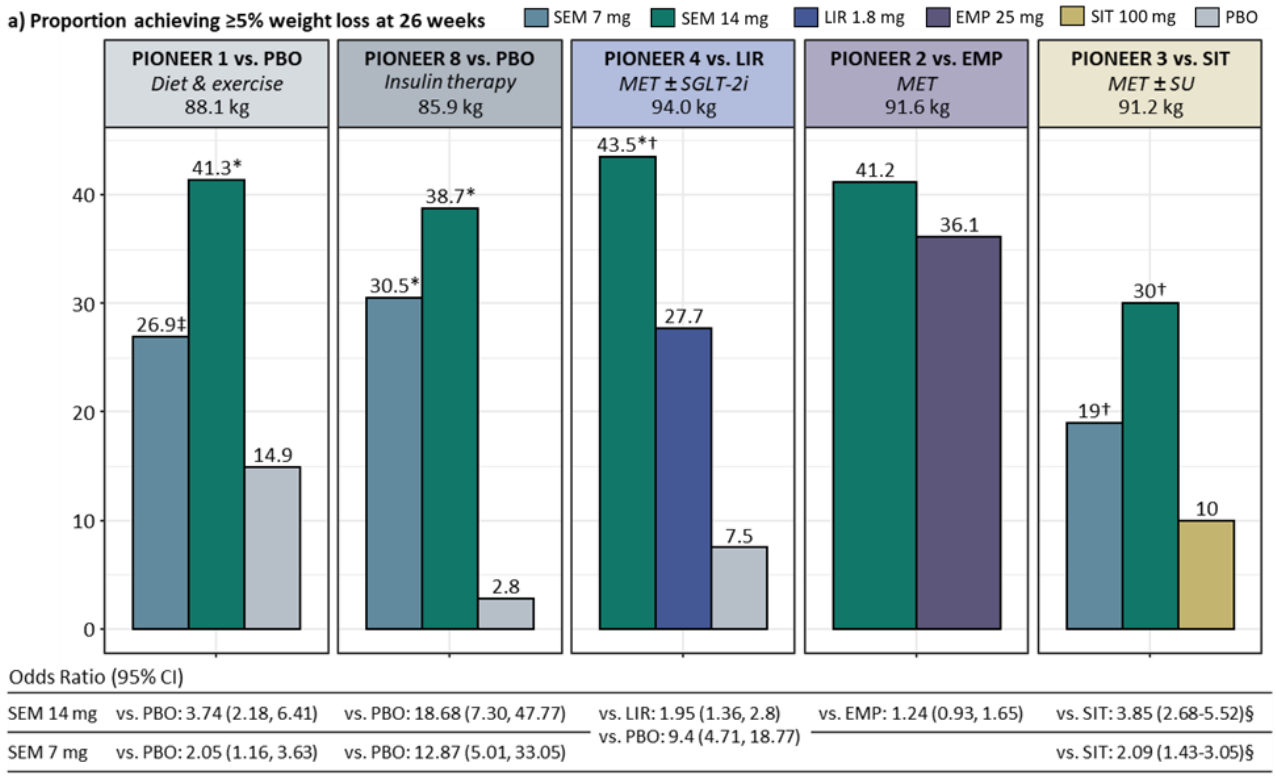
†p<0.001 vs. active comparator

‡p=0.0019 vs. active comparator

More patients achieved ≥5% weight loss with oral semaglutide 14 mg than placebo when used as a monotherapy at 26 weeks (PIONEER 1, 41.3% vs 14.9%),[13] when added to insulin therapy at 26 weeks (38.7% vs. 2.8%) and 52 weeks (39.4% vs. 5.2%),[15] and 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)[12](Figure 3.4). Oral semaglutide 3 mg and 7 mg had higher rates of achieving ≥5% weight loss compared to placebo when added to insulin therapy (PIONEER 8); oral semaglutide 7 mg but not 3 mg had significantly higher rates compared to placebo when used as a monotherapy (PIONEER 1)(Figure 3.4 and Appendix Table D6).

More patients achieved ≥5% weight loss with oral semaglutide 14 mg 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%)[12] and compared to sitagliptin 100 mg at 26 weeks (PIONEER 3, 30% vs. 10%), 52 weeks (34% vs 12%), and 78 weeks (33% vs 14%)[8](Figure 3.4). This was also seen with oral semaglutide flexible dose compared to sitagliptin 100 mg at 52 weeks (PIONEER 7, 27.0% vs 12.1%);[11] results at 26 weeks were not reported (Appendix Table D5). A similar proportion of patients treated with oral semaglutide 14 mg and empagliflozin 25 mg achieved ≥5% weight loss at 26 weeks (PIONEER 2, 41.2% vs 36.1%) and 52 weeks (40.4% vs. 39.2%)[14](Figure 3.4).

Figure 3.4. Proportion Achieving ≥5% Weight Loss at 26 and 52 Weeks



95% CI: 95% confidence interval, BL: baseline, bckgnd: background, EMP: empagliflozin; LIR: liraglutide, MET: metformin, N/A: not applicable, PBO: placebo SEM: semaglutide, SGLT-2i: SGLT-2 inhibitor, SIT: sitagliptin; SU: sulfonylurea, tx: treatment

*p<0.001 vs. placebo

†p<0.001 vs. active comparator

‡p=0.01 vs. placebo

§Odds ratios were calculated 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)[9] and with injectable semaglutide 0.5 mg and 1.0 mg compared to volume-matched placebo in SUSTAIN 6 at two years (-3.6 kg vs -0.7 kg and -4.9 vs -0.5 kg, respectively).[19] The mean difference in weight reduction between liraglutide 1.8 mg and placebo was -2.3 kg at three years in LEADER.[18] 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.[16] Changes in body weight were not reported in TECOS.[17]

Fasting Plasma Glucose

Oral semaglutide 14 mg reduced fasting plasma glucose (FPG) levels more than placebo when used as a monotherapy at 26 weeks (PIONEER 1),[13] when added to insulin therapy at 26 and 52 weeks (PIONEER 8),[15] and when added to metformin ± SGLT-2 inhibitor at 26 weeks and 52 weeks (PIONEER 4).[12] Oral semaglutide 3 mg and 7 mg also reduced FPG more than placebo in PIONEER 1; both oral semaglutide 3 mg and 7 mg reduced FPG more than placebo at 52 weeks in PIONEER 8, but only 7 mg reduced FPG more than placebo at 26 weeks (Appendix Table D6).

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 (PIONEER 4).[12] Oral semaglutide 14 mg did not reduce FPG more than empagliflozin 25 mg when added to metformin at any timepoint (PIONEER 2).[14] Oral semaglutide 14 mg reduced FPG more compared to sitagliptin 100 mg when added to metformin ± sulfonylurea at 26, 52, and 78 weeks.[8] Oral semaglutide flexible dose reduced FPG levels significantly more than sitagliptin 100 mg when added to one to two oral antihyperglycemic agents at 52 weeks;[11] results at 26 weeks were not reported (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)[12] and when added to insulin therapy at both 26 and 52 weeks (PIONEER 8).[15] No significant changes in systolic blood pressure were observed with oral semaglutide as a monotherapy compared to placebo at 26 weeks in PIONEER 1[13](Appendix Table D6).

There were no significant changes in systolic blood pressure with oral semaglutide 14 mg compared to liraglutide 1.8 mg when added to metformin ± SGLT-2 inhibitor (PIONEER 4)[12] or compared to empagliflozin 25 mg when added to metformin (PIONEER 2).[14] 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)[8] There were no significant changes in systolic blood pressure with oral semaglutide flexible dose compared to sitagliptin when added to one to two oral antihyperglycemic agents[11](Appendix Table D5).

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),[9] injectable semaglutide 1.0 mg at 104 weeks (SUSTAIN 6),[19] liraglutide 1.8 mg at three years (LEADER),[18] and empagliflozin 10 mg/25 mg at four years (EMPA-REG OUTCOME).[16] 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).[13] When added to insulin therapy, oral semaglutide 3 mg, 7 mg, and 14 mg reduced total cholesterol more than placebo at 26 and 52 weeks and reduced LDL-C more than placebo at 26 weeks but not at 52 weeks; in addition, oral semaglutide 14 mg reduced triglycerides more compared to placebo at 52 weeks but not 26 weeks (PIONEER 8).[15] Total cholesterol and triglycerides were reduced with oral semaglutide 14 mg compared to placebo when added to metformin ± SGLT-2 inhibitor at 26 and 52 weeks; additionally, oral semaglutide 14 mg reduced LDL-C more than placebo at 52 weeks but not at 26 weeks (PIONEER 4)[12](Appendix Table D6).

No significant changes in lipid levels with oral semaglutide 14 mg compared to liraglutide 1.8 mg when added to metformin ± SGLT-2 inhibitor were observed (PIONEER 4).[12] Oral semaglutide 14 mg reduced total cholesterol and LDL-C more than empagliflozin 25 mg when added to metformin at 26 and 52 weeks (PIONEER 2).[14] 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 (PIONEER 3).[8] 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)[11](Appendix Table D5).

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.[9] 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.[19] In EMPA-REG OUTCOME, examination of the curves of lipid levels suggest there were modest increases in HDL-C and in LDL-C with both placebo and empagliflozin; the effects on total cholesterol and triglycerides levels were not reported.[16] 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 1 (15.2% vs 1.1%),[13] PIONEER 8 (45.7% vs. 36.5%),[15] and PIONEER 4 (41.6% vs. 21.8%)[12](Table 3.3). There were also higher rates of rescue medication use with placebo compared to oral semaglutide 3 mg and 7 mg in PIONEER 1 and PIONEER 8 (Table 3.3).

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%[8,12,14] (Table 3.3). 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%)[12] and for empagliflozin 25 mg and oral semaglutide 14 mg (PIONEER 2, 21.5% vs 24.8%).[14] 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%).[8] In PIONEER 7, a similar proportion of patients treated with oral semaglutide flexible dose and sitagliptin 100 mg used rescue medication (19.8% vs. 24.3%).[11]

In all trials, the proportion of patients using rescue medication increased over the course of the trials (Table 3.3). In trials that evaluated multiple doses of oral semaglutide, there were generally 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%[8,12,14] (Table 3.3). 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 3.3. 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
Placebo-Controlled Trials						
PIONEER 1 26-Week RCT Diet & Exercise	Oral semaglutide 7 mg	NR	*N/A*	2.3	10.3	8.0
	Oral semaglutide 14 mg	NR	*N/A*	1.1	13.7	6.9
	Placebo	NR	*N/A*	15.2	10.7	4.5
PIONEER 8 52-Week RCT Insulin Therapy	Oral semaglutide 7 mg	1.1	18.1	36.8	18.7	4.9
	Oral semaglutide 14 mg	2.2	17.1	36.5	20.4	3.3
	Placebo	4.9	36.4	45.7	12.0	4.9
Head-to-Head Trials						
PIONEER 2 52-Week RCT MET	Oral semaglutide 14 mg	1.9	7.5	24.8	17.7	2.9
	Empagliflozin 25 mg	1.2	10.7	21.5	11.0	5.6
PIONEER 3 78-Week RCT MET ± SU	Oral semaglutide 7 mg	2.4	15.7	35.4	15.0	6.4
	Oral 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	Oral 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	Oral semaglutide flexible	NR	3.2	19.8	16.6	4.7
	Sitagliptin 100 mg	NR	15.9	24.3	9.2	2.8

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,[16-19] with the largest between-arm difference observed in SUSTAIN 6 (Table 3.4).[19] 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;[9] 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 3.4). 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 oral semaglutide 14 mg compared to placebo in PIONEER 6 while rates of all-cause discontinuation of the trial product were more similar between active agents and placebo in the other CVOTs (Table 3.4). The proportion of patients not completing the trial were generally similar between the placebo and active arms in all CVOTs (Table 3.4).

Table 3.4. 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	Inj 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	23.4	3.2
	Placebo	31.5	11.5	7.0	N/A	29.3	2.7
TECOS	Sitagliptin 100 mg	21.7	9.7	NR	NR	26.1	4.9
	Placebo	27.9	13.2	NR	NR	27.5	5.9

D/C: discontinuation, CVOTs: cardiovascular outcome trials, Inj: injectable, N/A: not applicable, NR: not reported, SGLT-2: sodium-glucose cotransporter 2, SU: sulfonylurea

*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. In the NMA, empagliflozin, but not semaglutide, reduced the risk of hospitalization for heart failure.

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)[9](Figure 3.5). 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)[19](Figure 3.5) 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 0.61), 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)[18] 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)[16](Figure 3.5). 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)[17](Figure 3.5).

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)[9,19](Figure 3.5). 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)[16], a nonsignificant risk reduction with liraglutide 1.8 mg compared to placebo (HR 0.87; 95%

CI: 0.73 to 1.05),[18] and no difference between sitagliptin 100 mg and placebo (HR 1.00; 95% CI: 0.83 to 1.20)[17](Figure 3.5).

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 mg/1.0 mg compared to placebo (HR 0.64; 95% CI: 0.46 to 0.88)[19](Figure 3.5). 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)[18,70](Figure 3.5). The incidence of nephropathy was not reported in TECOS.

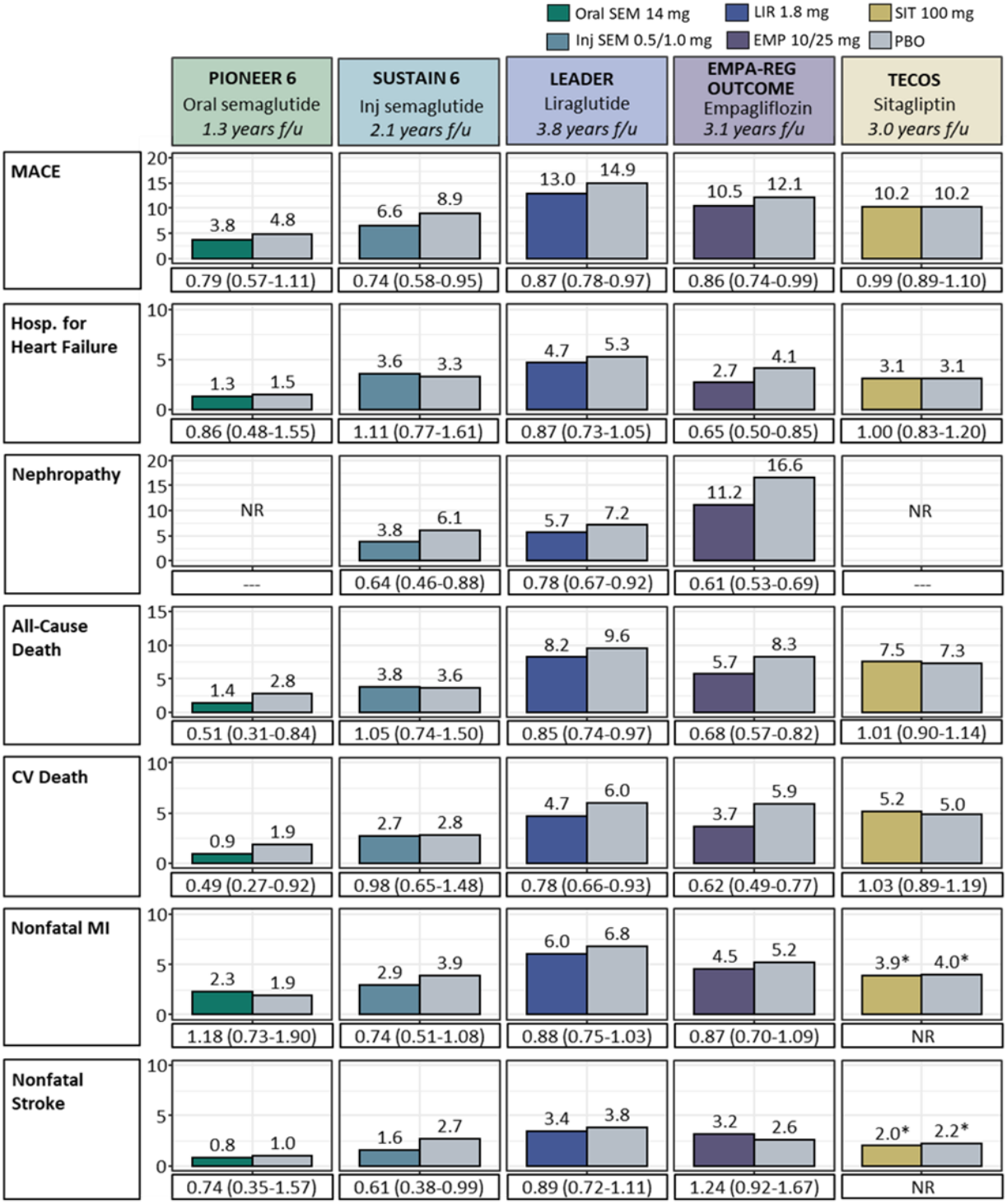
All-Cause Death

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),[9] liraglutide 1.8 mg (8.2% vs. 9.6%; HR 0.85; 95% CI: 0.74 to 0.97),[18] and empagliflozin 10 mg/25 mg (5.7% vs 8.3%; HR 0.68; 95% CI: 0.57 to 0.82)[16](Figure 3.5). 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 7.5% vs. 7.3%; HR 1.01; 95% CI: 0.90 to 1.14, respectively)[17,19](Figure 3.5).

Neuropathy

TECOS was the only CVOT that reported the incidence of neuropathy. The rate of neuropathy was 4.1% among patients treated with sitagliptin 100 mg and 3.8% among those treated with placebo.[17]

Figure 3.5. Rates and Hazard Ratios (95% CI) for Key Outcomes in Included CVOTs



95% CI: 95% confidence interval, CV: cardiovascular, CVOTs: cardiovascular outcomes trials, EMP: empagliflozin, Hosp.: hospitalization, HR: hazard ratio, LIR: liraglutide, MACE: major adverse cardiovascular event, MI: myocardial infarction, NR: not reported, PBO: placebo, SEM: semaglutide, SIT: sitagliptin

*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.[74] 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 D12.

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)(Table 3.5). Results also showed a nonsignificant risk reduction of semaglutide for MACE 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) (Table 3.5). Empagliflozin 10 mg/25 mg significantly reduced the risk for HHF compared to semaglutide (HR 0.63; 95% CI: 0.42 to 0.95) (Table 3.6). There were no significant differences with semaglutide and any of the active comparators of interest on nephropathy (Appendix Table D18).

Table 3.5. 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 3.6. 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.

Four of the head-to-head PIONEER trials measured changes from baseline in the Short Form-36 Version 2 (Acute Version) (PIONEER 2, 3, 7, and 8). In PIONEER 8, all doses of oral semaglutide (3, 7, 14 mg) improved the "general health" domain score more than placebo at 52 weeks but not 26 weeks; additionally, oral semaglutide 14 mg improved the "mental health" domain score more than placebo at 26 weeks but not 52 weeks.[15] In PIONEER 2, oral semaglutide 14 mg improved the "general health" domain score more than empagliflozin 25 mg at 26 weeks but not at 52 weeks, while empagliflozin 25 mg improved the "role physical" and "physical component summary" domain scores more at 52 weeks but not 26 weeks.[14] 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.[8] In PIONEER 7, oral semaglutide flexible dose did not result in any improvements compared to sitagliptin 100 mg.[11]

PIONEER 4, 7, and 8 measured changes in the Diabetes Treatment Satisfaction Questionnaire (DTSQ) scores. In PIONEER 8, oral semaglutide 7 mg and 14 mg improved the total DTSQ score more than placebo at both 26 and 52 weeks.[15] 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.[12] In PIONEER 7, there was no difference in the improvement in total score with oral semaglutide flexible dose compared to sitagliptin 100 mg.[11]

PIONEER 3 and 8 also measured changes in the Impact of Weight on Quality of Life (IWQOL-Lite) Questionnaire. In PIONEER 8, oral semaglutide 14 mg improved the total IWQOL-Lite score as well as the "psychosocial" domain score more than placebo at both 26 and 52 weeks.[15] In PIONEER 3, 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.[8]

PIONEER 2 and 3 also measured changes in the Control of Eating Questionnaire. In PIONEER 2, oral semaglutide 14 mg improved the "craving control" domain score more than empagliflozin 25 mg at

both 26 and 52 weeks and the "craving for savory" domain score more at 52 weeks but not 26 weeks.[14] In PIONEER 3, there were no significant changes with any dose of oral semaglutide compared to sitagliptin 100 mg on the Control of Eating Questionnaire domains.[8]

PIONEER 1 did not report any HRQoL outcomes or PROs.

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.

Across all PIONEER trials, most adverse events were mild-to-moderate in severity, and the most common adverse events were related to gastrointestinal effects (Table 3.7). 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 (Table 3.7).[8,12,14] 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 (PIONEER 2, 2.4% and PIONEER 3, 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 (Table 3.7).[11] 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)(Table 3.7).[13] 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).[15] 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. 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.[74]

Across the PIONEER trials, the rate of severe hypoglycemia was low (<2%). The rate of any hypoglycemia (i.e., blood-glucose confirmed symptomatic or severe) was highest in the trial in which patients were receiving background insulin therapy (PIONEER 8) followed by the trials in which around half of the patients were receiving background sulfonylurea therapy (PIONEER 3 and 7). In the other trials, the rate of hypoglycemia was generally low.

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 4.4% to 9% 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 head-to-head trials, the incidence of serious adverse events (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 8 (1.7% for oral semaglutide).

Table 3.7. 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	0	1.7	0
Severe AE	0.6	1.7	2.8	5.9	5.6	8.0	8.6	11.4	8	8	5	6	7	NR	NR	NR
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	6.6	10.5	0.5
Hypoglycemia*	1.1	0.6	0.6	1.7	2.0	5.2	7.7	8.4	1	2	2	5.5	5.6	26.0	26.5	29.3
Severe Hypoglycemia	0.6	0	0	0.2	0.2	0	0.2	0.9	0	0	0	0	0	0.6	1.1	0.5
Nausea	5.1	16	5.6	19.8	2.4	13.4	15.1	6.9	20	18	4	21	2	16.6	23.2	7.1
Diarrhea	5.1	5.1	2.2	9.3	3.2	11.4	12.3	7.9	15	11	8	9	3	12.2	14.9	6.0
Vomiting	4.6	6.9	2.2	7.3	1.7	6.0	9.0	4.1	9	5	2	6	1	7.7	9.9	3.8
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	—	—	9.9	12.7	1.1
Urinary Tract Infection	—	—	—	—	—	4.5	4.9	5.6	—	—	—	—	—	2.8	5.5	3.8
Diabetic Retinopathy	3.4	1.1	1.7	—	—	5.2	3.4	5.8	2.8	1.1	1.4	1.2	1.6	4.4	5.0	4.3

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

*Severe or blood-glucose confirmed symptomatic

Safety parameters were variably reported in the CVOTs (Table 3.8). Similar proportions of patients experienced any adverse event in the active and placebo arms in SUSTAIN 6 (injectable semaglutide),[19] LEADER (liraglutide),[18] and EMPA-REG OUTCOME (empagliflozin);[16] these rates were not reported in PIONEER 6 (oral semaglutide)[9] or TECOS (sitagliptin).[17] Compared to placebo, adverse events 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 adverse events 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.[9,16,18,19] The rate of SAEs was not reported in TECOS.[17] 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.[9] 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).[19] 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),[18] 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).[71] Numerically more patients treated with sitagliptin 100 mg experienced adverse events related to diabetic retinopathy compared to those receiving placebo (2.8% vs. 2.2%); no statistical test comparing these rates was reported.[17]

Table 3.8. 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, CVOTs: cardiovascular outcome trials, D/C: discontinuation, EMP: empagliflozin, GI: gastrointestinal, LIR: liraglutide, mg: milligram, NR: not reported, PBO: placebo, SAE: serious 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).[10] 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.[10] 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 74% of patients on oral semaglutide experienced an adverse event compared to 65% for placebo; there were similar rates of SAEs in both arms (10% 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,[20] it creates another level of indirectness in assessing the benefits and harms of oral semaglutide.

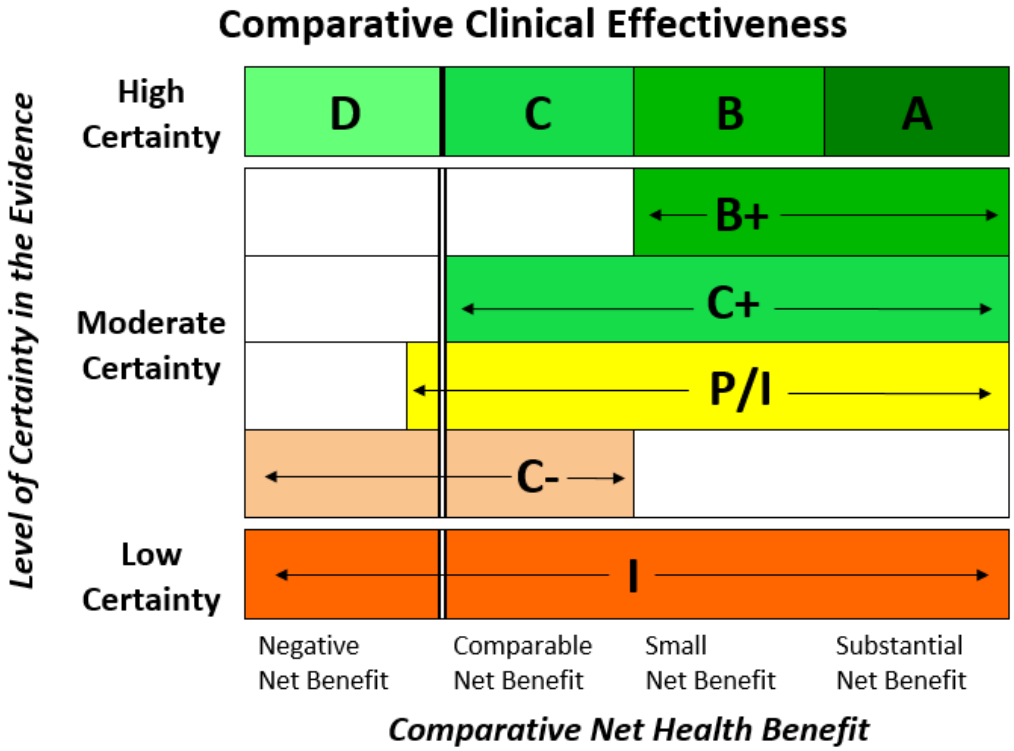
Adherence in the real world is important to the effectiveness of the therapies under review. The higher rates of gastrointestinal side effects with GLP-1 receptor agonists, including oral semaglutide, are likely to result in higher rates of discontinuation in real world use than in clinical trials. Thus, randomized trials may overstate the real-world comparative effectiveness of these therapies. Additionally, oral semaglutide is administered on an empty stomach and requires a period of dose adjustment/titration over 60 days, both of 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).[19] 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.[75] 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 FDA labels for both oral and injectable semaglutide state, "Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy."[21,22] 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 3.6. 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 3.9. Evidence Ratings

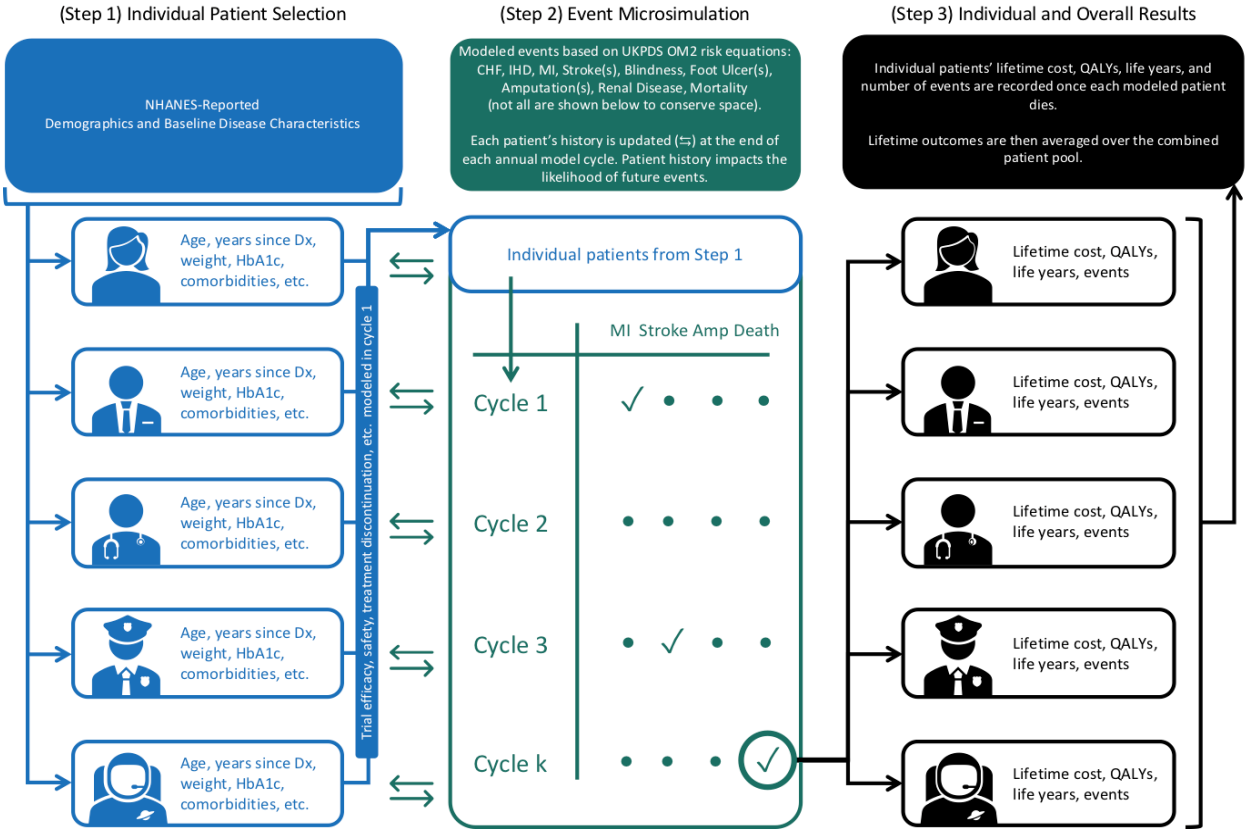
Comparison	ICER Evidence Rating
Oral Semaglutide vs. *Liraglutide*	Moderate certainty of a comparable, small, or substantial net health benefit, with a small likelihood of worse net health benefit ("P/I")
Oral Semaglutide vs. *Empagliflozin*	Low certainty in the net health benefit ("I")
Oral Semaglutide 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 added to ongoing antihyperglycemic treatment. The model estimates outcomes that include life years (LYs) in lieu of equal value life years gained (evLYGs), quality-adjusted life years (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, including a modified societal perspective. The analytic framework for this assessment is depicted in Figure 4.1 below.

Figure 4.1. Model Framework



Changes from Prior Version of the Report

We continued developing the model after the publication of the initial draft report and made a number of substantive changes. First, we updated the selection of NHANES patients that were included in the microsimulation, restricting the population to only those with a HbA1c ≥7 (the full T2DM NHANES population was retained as a scenario analysis).[23] Second, we corrected our implementation of the mortality risk equations to ensure they were applied in a mutually exclusive manner. Third, we updated the ESRD risk equation to better calibrate it to expected outcome rates. Fourth, we updated the price of oral semaglutide based on its now published wholesale acquisition cost (WAC). We also corrected the price of liraglutide to reflect the 1.8 mg daily dosage and updated the cost inputs for metformin and the sulfonylureas using average generic prices from RedBook,[34] replacing the prior estimates from the literature.

4.2 Methods

We developed an adaptation of a published microsimulation model[29] based on the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model 2 (OM2)[24] for this evaluation, informed by the PIONEER clinical trials,[8-15] relevant quality of life literature,[76,77] and other prior economic models.[78-82] 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.[23] In the first model cycle, we utilized the UKPDS OM2 risk equations[24] 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 head-to-head PIONEER trials for HbA1c change, weight change, hypoglycemia, and trial discontinuation due to AEs 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[24] 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, LYs, 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 (905,000 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). We utilized a representative population of patients from the US, drawing patient-level data from the NHANES program, which surveys approximately 5,000 people across the US each year in two-year survey populations.[23] The survey population consists of people from counties across the US. A cohort of US adults with self-reported diabetes and HbA1c ≥7 from NHANES 2013-14 and 2015-16 surveys (n=362) 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=362)[23]	Value
Age (years), mean (SD)	61.8 (12.6)
Female, %	45.3%
Black Race, %	45.0%
Current Smoker, %	34.5%
Duration of Diabetes (years), mean (SD)	13.1 (9.5)
Body Mass Index (kg/m^2), mean (SD)	34.4 (7.7)
Estimated Glomerular Filtration Rate (ml/min/m^2), mean (SD)	80.6 (31.4)
HbA1c (%), mean (SD)	8.7 (1.8)
Myocardial Infarction, %	11.6%
Stroke, %	8.0%
Heart Failure, %	10.5%
Ischemic Heart Disease, %	12.4%
Angina, %	5.8%
Renal Complications, %	22.7%

HbA1c: glycated hemoglobin, SD: standard deviation

Treatment Strategies

We compared the treatment of patients with oral semaglutide (14 mg) added to background treatment to each of the following treatments:

(1) Ongoing background antihyperglycemic treatment (e.g., metformin with or without sulfonylureas) alone
(2) Sitagliptin (Januvia®, Merck), a DPP-4 inhibitor, added to ongoing background treatment
(3) Empagliflozin (Jardiance®, Boehringer Ingelheim and Eli Lilly), a SGLT-2 inhibitor, added to ongoing background treatment
(4) 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	Rybelsus®	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 both renal failure and MACE beyond the health impacts 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. We modeled gradual declines in oral semaglutide efficacy for MACE and renal outcomes in scenario analyses.
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 are 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.

MACE: major adverse cardiovascular event, T2DM: type 2 diabetes mellitus

Model Inputs

Clinical Inputs

Clinical inputs regarding the efficacy of oral semaglutide compared to (1) ongoing background antihyperglycemic treatment, (2) sitagliptin, (3)empagliflozin, and (4) liraglutide on intermediate outcomes such as HbA1c and body weight were derived from the head-to-head PIONEER trials.[8,12,14] We also utilized the NMA of PIONEER 6, SUSTAIN 6, and the comparator CVOTs[9,16-18] 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 first applying the oral semaglutide versus placebo hazard ratios, then applying 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, NMA = network meta-analysis

*Background Tx = ongoing background antihyperglycemic treatment (corresponds to placebo arms in clinical studies)

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	-1.48	-0.99	PIONEER 2,3,4
Sitagliptin	-0.74	-0.88	-0.59	PIONEER 3
Empagliflozin	-0.84	-1.00	-0.67	PIONEER 2
Liraglutide	-0.94	-1.12	-0.75	PIONEER 4
Background Treatment	-0.24	-0.28	-0.19	PIONEER 4
Change in Weight (kg)				
Oral Semaglutide	-3.8	-4.5	-3.0	PIONEER 2,3,4
Sitagliptin	-1.1	-1.3	-0.9	PIONEER 3
Empagliflozin	-3.6	-4.3	-2.9	PIONEER 2
Liraglutide	-2.5	-3.0	-2.0	PIONEER 4
Background Treatment	-0.5	-0.6	-0.4	PIONEER 4
Severe Hypoglycemia (%)				
Oral Semaglutide	0.2	0.1	0.2	PIONEER 2,3,4
Sitagliptin	0.7	0.6	0.8	PIONEER 3
Empagliflozin	0.2	0.1	0.2	PIONEER 2
Liraglutide	0	0	0	PIONEER 4
Background Treatment	0	0	0	PIONEER 4
Discontinuation Due to Adverse Event (%)				
Oral Semaglutide	11.1	8.9	13.3	PIONEER 2,3,4
Sitagliptin	4.9	3.9	5.9	PIONEER 3
Empagliflozin	4.6	3.6	5.5	PIONEER 2
Liraglutide	9.4	7.5	11.2	PIONEER 4
Background Treatment	3.6	2.9	4.3	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.[24] 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.[24-27] The UKPDS OM2 complications (13 risk equations) include 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 ESRD.[24] 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 mutually exclusive mortality risk equations 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).[24]

Additional Modules

Treatment Discontinuation and Insulin Uptake. We applied pooled estimates of treatment discontinuation due to AEs 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 sitagliptin treatment and transition to insulin if their HbA1c reached 8.5 or above. Insulin treatment costs were based on a multivariate prediction model for estimating long-term HbA1c change, weight change, and hypoglycemic events associated with insulin rescue medication.[28] After cycle 1, clinical characteristics for patients pre- and post-insulin were modeled using the equations for HbA1c and weight change,[28] 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.[29] 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[30,31] and (for atrial fibrillation) relative risk estimates based on patients' HbA1c [32] to simulate these patient characteristics prior to each microsimulation. Peripheral vascular disease and atrial fibrillation prevalence were modeled independent of existing patient characteristics.

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.[76] We added missing regression coefficients for foot ulcer and amputation events by assuming values from a recent diabetes utility study by Sullivan and Ghushchyan that were applicable to the Shao et al. approach.[77] 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.[83] 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.[77] 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 (Table 4.6).[84]

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[76]	-0.089	0.022	-0.132	-0.047
Congestive Heart Failure History[76]	-0.041	0.010	-0.060	-0.022
Ischemic Heart Disease History*[76]	-0.016	0.005	-0.026	-0.006
Myocardial Infarction Event[76]	-0.042	0.016	-0.074	-0.010
Myocardial Infarction History[76]	-0.011	0.006	-0.022	0.001
Stroke Event[76]	-0.204	0.035	-0.272	-0.136
Stroke History[76]	-0.101	0.008	-0.117	-0.086
Microvascular Complication Coefficients				
Blindness History[76]	-0.057	0.009	-0.074	-0.040
Foot Ulcer Event[77]	-0.024	0.005	-0.033	-0.015
Amputation Event[77]	-0.051	0.029	-0.108	0.005
Renal Disease History[76]	-0.024	0.016	-0.056	0.008
Hypoglycemia Event[76]	-0.036	0.010	-0.056	-0.016
Hypoglycemia History[76]	-0.033	0.011	-0.054	-0.011
Demographic Characteristic Coefficients[76]†				
Annual Disutility of Daily Injection (liraglutide and insulin only)[84]	-0.054		-20%	+20%

SE: standard error

*Disutility for ischemic heart disease is based on "revascularization history" from Shao et al.[76]

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

Economic Inputs

Drug Acquisition Costs

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.[33] 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.[34] Finally, we applied this average discount to the most recent available WAC (accessed October 2019) to arrive at an estimated net price per unit (Table 4.7). For oral semaglutide, we applied the average discount from WAC for *injectable* semaglutide to arrive at an estimated net price.

The cost for background therapy was estimated from the average WAC prices for available metformin and sulfonylurea oral dosage forms, as a weighted average of patients receiving metformin monotherapy (57%), sulfonylurea monotherapy (26%), or combination metformin and sulfonylurea (17%).[34] These weights were calculated from the distribution of use of these medications in the NHANES patient population.[23]

Table 4.7. Drug Cost Inputs

Drug	WAC per Bottle/Pen[34]	Discount From WAC[33]	Net Price per Bottle/Pen/Insulin Unit	Net Price per Month	Net Price per Year‡
Oral Semaglutide (Rybelsus®), 30-Tablet Bottle*	$772.43	35.1%	$501.31	$508.62	$6,103.45
Sitagliptin (Januvia®), 30-Tablet Bottle	$451.20	72.6%	$123.62	$125.42	$1,505.07
Empagliflozin (Jardiance®), 30-Tablet Bottle	$492.85	65.2%	$171.51	$174.01	$2,088.13
Liraglutide (Victoza®), 18 mg/3mL Pen†	$307.26	28.6%	$219.38	$667.74	$8,012.85
Metformin					$194[23,34]
Sulfonylureas					$86[23,34]
Insulin					
Basal			$0.22[34]		Varies by patient weight
Bolus			$0.28[34]		
Premix			$0.14[34]		

WAC: wholesale acquisition cost

*WAC price published September 20, 2019; for net price, we assumed the same discount from WAC as that for injectable semaglutide.

†Prices for liraglutide are per 3 ml pen, and the annual price calculation assumes a 1.8 mg (0.3ml)/day dosage.

‡1 year = 365.25 days or 12 months or 52 weeks (note that rounding of the Net Price Per Month column results in slight discrepancies between the Per Month and Per Year columns).

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.[85] 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.[85] 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)[85,86]			
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)[85,86]			
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 [29]	$550	$440	$659
Outpatient visit: insulin[29]	$601	$481	$722

Model Analysis

The model estimated the average survival, quality-adjusted survival, drug cost, complication cost, and number of T2DM complications for 362 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 (905,000 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 LYs were discounted at 3% per year. We calculated the incremental results for each intervention versus background treatment alone as the incremental cost per LY and QALY, 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 a single UKPDS equation simulation for each of 362 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. Therefore, each low and high value represents the average impact over 362 individual patient simulations.

Probabilistic sensitivity analysis was performed in conjunction with the primary analysis by jointly varying all model parameters over 2,500 individual simulations for each individual patient, 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 performed the following scenario analyses by modifying the model's base-case assumptions. For each scenario, we performed 500 individual simulations per patient and calculated the 95% credible range estimates for each model outcome.

- *Modified societal perspective, adding productivity impact associated with T2DM*.
  We added age-specific annual estimates of indirect costs related to the burden of diabetes, accounting for patient age and work status, in the following categories: absenteeism, presenteeism, inability to work, and decreased productivity for those

not in the workforce. These four categories of indirect cost were abstracted from a previously published analysis that produced estimates from the National Health Interview Survey and applied as summary estimates separately for patients age 18-44 years ($5,580/year), age 45-64 years ($5,320/year), and 65 years of age and above ($1,480/year).[87]

- *5-year model time horizon*.

  We restricted the model's time horizon to a maximum of five years per patient simulation. Individual patients could still die before reaching the 5-year maximum horizon, but we did not calculate outcomes, including death, beyond five years.

- *Relative changes in the long-term duration of MACE and renal outcome effectiveness for oral semaglutide*.

  We adjusted the relative effect of oral semaglutide versus background treatment alone by annually increasing the MACE and nephropathy hazard ratios starting in year two of the model. We created scenarios specific to (1) MACE and (2) renal disease that applied a range of five to 10% relative adjustments in the incremental effectiveness per year until the hazard ratios reached 1.00 (no incremental effectiveness versus background treatment alone). We also created a scenario that applied the relative decrease in incremental effectiveness simultaneously to both MACE and renal outcomes using the same ranges.

- *Broad T2DM patient population, including T2DM patients regardless of their HbA1c level from NHANES*.

  We estimated the cost effectiveness of oral semaglutide using all available NHANES T2DM patients (n = 745), regardless of their HbA1c (range: 4.5 – 17.5) in order to estimate the potential comparative value in a broader T2DM population.

Model Validation

We used several approaches to validate the model. First, we shared preliminary methods to manufacturers, patient groups, and clinical experts. Second, we shared the model with the manufacturers for a review period of three weeks. Based on feedback from these different groups on our methodology and calculations, we refined our approach and data inputs used in the model, as relevant. Third, we varied model input parameters to evaluate face validity of changes in results. Fourth, 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. Additionally, all results are assuming the same net price discount from WAC for oral semaglutide as for injectable semaglutide. If the actual net price is different, these results would change.

The lifetime mean total cost for patients treated with oral semaglutide was $295,000 (Table 4.10) and costs for the other comparators ranged from $250,000 (background treatment alone) to $305,000 (liraglutide). Oral semaglutide resulted in the fewest MACE, including the fewest cardiovascular deaths. Among the five modeled treatment strategies, oral semaglutide had the highest LYs gained (8.18 vs. 7.55 [background treatment alone] and 8.07 [empagliflozin]) and the highest QALYs gained (4.03 vs. 3.63 [background treatment alone] and 3.97 [empagliflozin]).

Table 4.10. Results for the Base Case for Oral Semaglutide and Comparators

Treatment	Add-On Drug Cost	Complication Cost	Total Cost	MACE	CHF	ESRD	LYs	QALYs
Oral Semaglutide (Rybelsus®) + background treatment*	$46,000	$208,000	$295,000	59.9%	29.4%	13.0%	8.18	4.03
Sitagliptin (Januvia®) + background treatment	$5,000	$209,000	$254,000	65.8%	27.6%	14.8%	7.66	3.73
Empagliflozin (Jardiance®) + background treatment	$16,000	$204,000	$263,000	63.4%	22.8%	12.4%	8.07	3.97
Liraglutide (Victoza®) + background treatment	$60,000	$203,000	$305,000	62.2%	23.5%	12.4%	8.06	3.72
Background treatment alone	--	$208,000	$250,000	67.2%	27.7%	14.6%	7.55	3.63

MACE: major adverse cardiovascular event; ESRD: end stage renal disease; LYs: life years, QALY: quality-adjusted life year

*Results use an assumed annual net price of $6103 for oral semaglutide.

Oral semaglutide was cost-saving compared to liraglutide, and when compared with background treatment alone (incremental cost-effectiveness ratio = $110,000/QALY) and sitagliptin (incremental cost-effectiveness ratio = $140,000/QALY), was between $100,000 and

$150,000/QALY (Table 4.11). The incremental cost-effectiveness ratio for oral semaglutide compared with empagliflozin was approximately $480,000/QALY (Table 4.11).

Estimated costs per MACE avoided for oral semaglutide were $700,000 versus sitagliptin, $920,000 versus empagliflozin, and $630,000 versus background treatment alone; oral semaglutide was cost-saving versus liraglutide (Table 4.11). Of note, due to extreme average ratio outliers resulting from individual probabilistic simulations with high incremental cost and low incremental MACE, the cost per MACE avoided ratios were calculated using the average incremental cost divided by the average incremental MACE. Mean estimates of cost per MACE avoided from the probabilistic sensitivity analysis are available in Appendix Table E3.

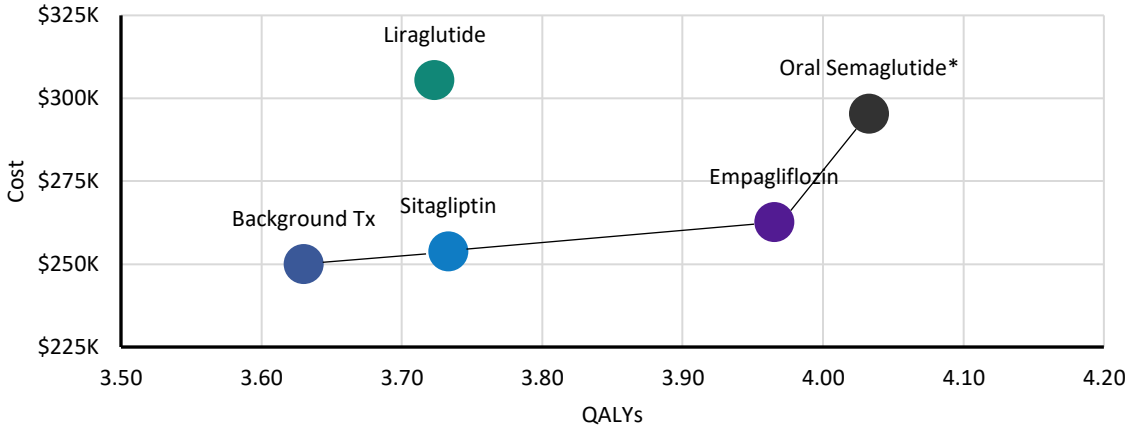
Table 4.11. Incremental Cost-Effectiveness Ratios: Oral Semaglutide versus Each Comparator

Comparator vs. Oral Semaglutide*	Cost per LY Gained	Cost per MACE Avoided	Cost per QALY Gained
Sitagliptin (Januvia®) + background treatment	$80,000	$700,000	$140,000
Empagliflozin (Jardiance®) + background treatment	$290,000	$920,000	$480,000
Liraglutide (Victoza®) + background treatment	Cost-Saving	Cost-Saving	Cost-Saving
Background treatment alone	$70,000	$630,000	$110,000

LY: life year; MACE: major adverse cardiovascular event; QALY: quality-adjusted life year
*Results use an assumed annual net price of $6103 for oral semaglutide.

Figure 4.2 displays the deterministic results of the simulations for each comparator, showing 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.

Figure 4.2. Cost-Effectiveness Frontier



Tx: treatment

*Results use an assumed annual net price of $6103 for oral semaglutide.

Sensitivity Analysis Results

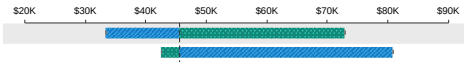
To demonstrate effects of individual parameter uncertainty on both costs and health outcomes, we varied each parameter using standard errors (if available) or by ±20% to evaluate changes in incremental cost, incremental QALYs, and the incremental cost-effectiveness ratio for the comparison of oral semaglutide versus background therapy alone. One-way sensitivity analysis results for oral semaglutide versus the other comparators are available in Appendix Figures E3-E5.

We performed a UKPDS equation simulation for each of the 362 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 362 individual patient simulations. 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-effectiveness ratios were the cost of CHF, the MACE hazard ratio for oral semaglutide versus background therapy alone, hypoglycemia-related parameters once patients transition to insulin therapy, the cost of IHD, and utility coefficients for IHD and patient demographics. 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 was more impactful in comparisons versus the other add-on therapies.

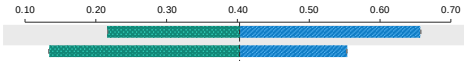
Figure 4.3. Tornado Diagrams for One-Way Sensitivity Analyses of Oral Semaglutide versus Background Therapy Alone

Incremental Cost



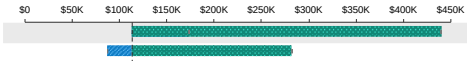
Parameter	Low Value	High Value	Low Result	High Result	Spread
Cost per Insulin Unit: Basal	$0.17	$0.26	$33,360	$72,907	$39,547
Severe Hypoglycemia (Cycles 2+): Insulin	0.168	0.252	$80,778	$42,539	$38,240
Cost (event history): Stroke	$14,663	$21,994	$56,811	$87,574	$30,763
Cost (year of event): Hypoglycemia Requiring Hospitaliz	$15,548	$23,322	$64,889	$34,933	$29,957
Starting insulin dose (IU/kg)	0.210	0.530	$64,127	$35,456	$28,671
HbA1c change: Oral Semaglutide	-1.482	-0.988	$42,399	$71,010	$28,611
Annual Cost: Metformin	$155	$233	$61,306	$33,957	$27,349
Cost (event history): Ischemic heart disease	$1,797	$2,695	$34,028	$60,723	$26,695
Ppn. Insulin Type: Basal	0.256	0.384	$54,066	$28,791	$25,274
Final insulin dose (IU/kg)	0.450	0.790	$72,166	$48,652	$23,514
Weight change: Oral Semaglutide	-4.5 kg	-3.0 kg	$37,406	$60,676	$23,269
Cost of Outpatient visit: noninsulin	$440	$659	$51,509	$73,673	$22,164
Discontinuation (Cycle 1): Oral Semaglutide	0.089	0.133	$37,067	$59,131	$22,065
Cost (event history): Myocardial infarction	$1,797	$2,695	$66,249	$46,281	$19,968
Cost (year of event): Ischemic heart disease	$20,198	$30,297	$36,305	$55,241	$18,937
CHF HR: Oral Semaglutide HR vs. Background Tx	0.76	1.40	$69,775	$50,882	$18,893
Mild/Moderate Hypoglycemia (Cycles 2+): Background T	0.264	0.396	$67,392	$48,976	$18,417
Cost per Insulin Unit: Premix	$0.11	$0.17	$63,443	$46,811	$16,632
Neph HR: Oral Semaglutide HR vs. Background Tx	0.46	0.89	$52,218	$66,441	$14,224
HbA1c change: Background Tx	-0.282	-0.188	$65,056	$51,062	$13,994

Incremental QALYs



Parameter	Low Value	High Value	Low Result	High Result	Spread
Change in insulin dose (IU/kg)	0.140	0.560	0.66	0.22	0.44
Utility coefficient: Hypoglycemia event	-0.056	-0.016	0.55	0.13	0.42
Mild/Moderate Hypoglycemia (Cycles 2+): Insulin	0.416	0.624	0.69	0.34	0.35
Final insulin dose (IU/kg)	0.450	0.790	0.58	0.25	0.34
CHF HR: Oral Semaglutide HR vs. Background Tx	0.76	1.40	0.54	0.25	0.29
Ppn. Insulin Type: Premix	0.496	0.744	0.59	0.31	0.28
MACE HR: Oral Semaglutide HR vs. Background Tx	0.63	0.93	0.51	0.23	0.28
Utility coefficient: Congestive heart failure history	-0.061	-0.021	0.29	0.55	0.26
Baseline T2DM Utility	0.755	0.845	0.32	0.57	0.25
HbA1c change: Background Tx	-0.282	-0.188	0.33	0.57	0.24
Weight change: Background Tx	-0.6 kg	-0.4 kg	0.56	0.33	0.24
Ppn. Insulin Type: Basal plus Bolus	0.024	0.036	0.27	0.50	0.23
Severe Hypoglycemia (Cycles 2+): Insulin	0.168	0.252	0.29	0.51	0.22
Utility coefficient: White	-0.029	-0.009	0.34	0.55	0.21
Mild/Moderate Hypoglycemia (Cycles 2+): Add-on Treati	0.264	0.396	0.39	0.58	0.18
Utility coefficient: Ischemic heart disease history *	-0.026	-0.006	0.42	0.24	0.18
Utility coefficient: Stroke history	-0.117	-0.085	0.40	0.58	0.18
Ppn. Insulin Type: Bolus	0.024	0.036	0.53	0.36	0.17
Ppn. Insulin Type: Basal	0.256	0.384	0.57	0.40	0.17
Weight change: Oral Semaglutide	-4.5 kg	-3.0 kg	0.54	0.37	0.16

Incremental Cost-Effectiveness Ratio



Parameter	Low Value	High Value	Low Result	High Result	Spread
Cost (event history): Congestive heart failure	$1,797	$2,695	$173,046	$440,300	$267,255
MACE HR: Oral Semaglutide HR vs. Background Tx	0.63	0.93	$86,902	$282,223	$195,321
Mild/Moderate Hypoglycemia (Cycles 2+): Add-on Treati	0.264	0.396	$199,678	$64,217	$135,460
Severe Hypoglycemia (Cycles 2+): Insulin	0.168	0.252	$123,794	$254,347	$130,553
Cost (event history): Ischemic heart disease	$1,797	$2,695	$98,343	$227,780	$129,437
Utility coefficient: Ischemic heart disease history *	-0.026	-0.006	$99,002	$216,581	$117,579
Utility coefficient: Hispanic	-0.061	-0.029	$79,359	$187,772	$108,413
Utility coefficient: White	-0.029	-0.009	$174,011	$65,861	$108,149
Cost per Insulin Unit: Bolus	$0.23	$0.34	$23,694	$128,740	$105,046
Cost per Insulin Unit: Basal	$0.17	$0.26	$143,100	$244,911	$101,811
Severe Hypoglycemia (Cycles 2+): Add-on Treatments	0.040	0.060	$33,723	$118,636	$84,913
Cost (year of event): Hypoglycemia Requiring ED visit	$1,237	$1,856	$149,144	$67,798	$81,346
HbA1c change: Oral Semaglutide	-1.482	-0.988	$41,269	$109,142	$67,873
Utility coefficient: Age at diagnosis (per year ≥52)	-0.003	-0.002	$97,580	$164,090	$66,510
Utility coefficient: Renal disease history	-0.055	0.007	$168,310	$103,207	$65,103
Cost (year of event): Amputation	$8,531	$12,796	$55,960	$120,124	$64,165
Cost per Insulin Unit: Premix	$0.11	$0.17	$79,566	$143,366	$63,800
Utility coefficient: Female	-0.051	-0.035	$196,193	$138,974	$57,219
Cost (year of event): Congestive heart failure	$22,417	$33,626	$182,570	$129,228	$53,342
Cost (year of event): Ischemic heart disease	$20,198	$30,297	$126,127	$75,760	$50,368

Results use an assumed annual net price of $6103 for oral semaglutide.

We also produced estimates of the probability of cost-effectiveness at a range of willingness to pay thresholds between $50,000 per QALY and $250,000 per QALY based on the 2500 individual simulations per patient used to calculate the base-case result. Table 4.12 reports the percentage out of the 2500 simulations that indicated that oral semaglutide was predicted to be cost-effective at each of the threshold values against each comparator. Appendix Figure E2 displays the continuous output of the probabilistic sensitivity analysis, with the probability of cost-effectiveness

plotted against the willingness to pay threshold from $0 to $300,000 per QALY. Oral semaglutide was predicted to be cost-effective compared to liraglutide across the range of thresholds, and to have a more than 50% chance of being cost-effective against sitagliptin or background treatment alone at a threshold of $150,000 per QALY or higher. However, even at a threshold of $250,000 per QALY, oral semaglutide had only a 27% chance of being cost-effective compared to empagliflozin.

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	2%	19%	59%	82%	91%
Empagliflozin	2%	3%	8%	18%	27%
Liraglutide	96%	100%	100%	100%	100%
Background Treatment Alone	3%	34%	83%	96%	99%

QALY: quality-adjusted life year

Results use an assumed annual net price of $6103 for oral semaglutide.

Scenario Analyses Results

Modified Societal Perspective

Adding productivity costs to the model resulted in similar incremental cost-effectiveness ratios for oral semaglutide compared to each of the comparators (Table 4.13) compared to the base case without these societal costs. Small differences in incremental cost-effectiveness ratios compared to the base case were due to incremental societal costs which largely canceled out between comparators except for differences driven by incremental survival; i.e., patients in treatment regimens with longer survival, such as with oral semaglutide, tended to accrue more indirect costs related to the burden of diabetes than those in regimens with shorter survival, such as background treatment alone.

Table 4.13. Modified Societal Perspective Results: Oral Semaglutide versus Each Comparator

Comparator	Cost per LY Gained*	Cost per MACE Avoided*	Cost per QALY Gained*
Sitagliptin (Januvia®) + background treatment	$80,000	$740,000	$150,000
Empagliflozin (Jardiance®) + background treatment	$280,000	$870,000	$470,000
Liraglutide (Victoza®) + background treatment	Cost-saving	Cost-saving	Cost-saving
Background treatment alone	$70,000	$660,000	$120,000

LY: life year; MACE: major adverse cardiovascular event; QALY: quality-adjusted life year
*Results use an assumed annual net price of $6103 for oral semaglutide.

Long-Term Duration of Incremental Outcomes

When we gradually reduced the efficacy of oral semaglutide for both MACE and renal outcomes by 5% and 10% per year, this increased the lifetime incidence of MACE and renal outcomes, which led to increased cost and decreased LY and QALYs for oral semaglutide. This also impacted the other add-on agents because MACE and renal outcomes for sitagliptin, empagliflozin, and liraglutide were calculated relative to oral semaglutide (i.e., [baseline UKPDS equation]*[oral semaglutide HR vs. placebo]*[comparator HR vs. oral semaglutide]). In general, incremental cost-effectiveness ratios tended to increase for oral semaglutide versus each comparator, with a greater increase seen in the 10% annual efficacy reduction scenario compared to the 5% annual efficacy reduction scenario. Scenarios in which MACE and renal efficacy were independently modeled are presented in Appendix Tables E5-E8.

Table 4.14. Annual 5% Efficacy Decline (MACE and Renal Outcomes) for Oral Semaglutide

Comparator	Cost per LY Gained*	Cost per MACE Avoided*	Cost per QALY Gained*
Sitagliptin (Januvia®) + background treatment	$100,000	$1,290,000	$160,000
Empagliflozin (Jardiance®) + background treatment	$460,000	$4,310,000	$680,000
Liraglutide (Victoza®) + background treatment	Cost-saving	$1,550,000 (lower cost, lower effectiveness)	Cost-saving
Background treatment alone	$80,000	$1,090,000	$130,000

LY: life year; QALY: quality-adjusted life year; MACE: major adverse cardiovascular event; CHF: congestive heart failure; ESRD: end stage renal disease
*Results use an assumed annual net price of $6103 for oral semaglutide.

Table 4.15. Annual 10% Efficacy Decline (MACE and Renal Outcomes) for Oral Semaglutide

Comparator	Cost per LY Gained*	Cost per MACE Avoided*	Cost per QALY Gained*
Sitagliptin (Januvia®) + background treatment	$110,000	$2,030,000	$180,000
Empagliflozin (Jardiance®) + background treatment	Dominated	Dominated	$5,480,000
Liraglutide (Victoza®) + background treatment	$340,000 (lower cost, lower effectiveness)	$600,000 (lower cost, lower effectiveness)	Cost-saving
Background treatment alone	$90,000	$1,430,000	$130,000

LY: life year; QALY: quality-adjusted life year; MACE: major adverse cardiovascular event; CHF: congestive heart failure; ESRD: end stage renal disease

*Results use an assumed annual net price of $6103 for oral semaglutide.

Other Scenario Analyses

Scenario analysis results for the five-year time horizon, independently declining MACE and renal outcome efficacy, and broad T2DM patient population from NHANES (n=745) are located in Appendix Tables E4-E9.

Threshold Analyses Results

The annual drug costs at which oral semaglutide would reach cost-effectiveness thresholds ranging from $50,000 to $150,000 per LY gained as well as per QALY gained are presented below.

Table 4.16. Threshold Analysis Results: Oral Semaglutide (14 mg) versus Background Treatment Alone

Outcome	Annual Price to Achieve $50,000 Threshold	Annual Price to Achieve $100,000 Threshold	Annual Price to Achieve $150,000 Threshold
Cost Per QALY Gained	$5,569	$5,983	$6,396
Cost Per LY Gained	$5,807	$6,428	$7,110

LY: life year; QALY: quality-adjusted life year

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 also shared the model with each of the manufacturers involved in this review.

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.[26,79-82,88-93] 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[24], a model predicting health outcomes in T2DM, and a microsimulation cost utility model by Laiteerapong et al.[29]

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. 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, we limited patients to only receive insulin after discontinuation or HbA1c increase, 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 the equations were not developed based on 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 this assumption. We tested this assumption in a scenario analysis and showed that a gradual decrease in long-term efficacy led to increased cost and decreased LYs and QALYs for oral semaglutide, and incremental cost-effectiveness ratios tended to increase versus each comparator.

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.

All incremental value estimates were coupled with high levels of uncertainty. This uncertainty is a combination of 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 definite conclusions for results comparing oral semaglutide and the other add-on treatments.

At an estimated net price of $6,103 per year, oral semaglutide was estimated to be dominant compared with liraglutide (more QALYs at a lower cost) and to have incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY versus sitagliptin and background therapy alone.

Results versus an SGLT-2 inhibitor may be most clinically relevant (oral treatments for T2DM that can be added on to background therapy and which improve CV outcomes), however in the absence of head-to-head trials there are particular uncertainties comparing oral semaglutide with empagliflozin since clinical outcomes were relatively similar. However, unless the net price of oral semaglutide is substantially lower than the net price of injectable semaglutide, oral semaglutide is unlikely to meet usual cost-effectiveness thresholds versus empagliflozin.

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 comorbidities, 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 at lower cost for some patients. Based on the current clinical evidence, with limited follow-up, it is difficult to draw conclusions on its cost effectiveness with a high level of certainty and the ultimate value of oral semaglutide will be determined by its long-term effectiveness and its actual net price.

At its estimated net price, oral semaglutide is likely to meet usual cost-effectiveness thresholds compared with background therapy but is unlikely to meet these thresholds compared with empagliflozin.

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, socioeconomic, 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. Additionally, oral semaglutide, unlike many injectable treatments for diabetes including injectable semaglutide and dulaglutide, does not require refrigeration. However, the dose titration of oral semaglutide and requirements for administration on an empty stomach are more burdensome than requirements for the comparator oral treatments assessed in this report.

5.2 Contextual Considerations

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

6. Value-Based Price Benchmarks

Annual value-based price benchmarks (VBPBs) of oral semaglutide are presented in Table 6.1. The value-based benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. For oral semaglutide, price discounts of approximately 32% to 36% from the list price (WAC) would be required to reach the $100,000 to $150,000 per QALY threshold prices, respectively (Table 6.1).

Table 6.1. Value-Based Price Benchmarks for Oral Semaglutide

	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Change from WAC to Reach Threshold Prices
Per QALY Gained	$9,404	$5,983	$6,396	-32% to -36%
Per LY Gained	$9,404	$6,428	$7,110	-24% to -32%

LY: life year, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

We are including results for price per LY gained to ensure that policymakers are aware of the complementary information these results can provide to the cost per QALY findings. The annual price at which oral semaglutide meets the $100,000 to $150,000 per LY range for use in these patients is $6,428 to $7,110. The cost per LY price range is somewhat higher than the cost per QALY range because incremental LY's gained are estimated to be higher than the incremental QALYs gained in this case.

7. Potential Budget Impact

7.1 Overview

We used the cost-effectiveness model to estimate the total potential budgetary impact of oral semaglutide in adults in the US with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s). We used oral semaglutide's list price (WAC), assumed net price, and the three threshold prices in our estimates of potential 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 oral semaglutide can be a potential replacement for 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-1 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%.[35] 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.[94] The estimate of 48% of 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 average 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 displace 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%[36], and then applied the above 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[95] 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 switch in therapy from DPP-4, GLP-1 and SGLT-2. These results are based on its WAC ($9,404 per year), assumed net price ($6,103 per year), and annual prices to reach cost-effectiveness thresholds of $150,000, $100,000, and $50,000 per QALY versus background antihyperglycemics ($6,396, $5,983, and $5,569, respectively).

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

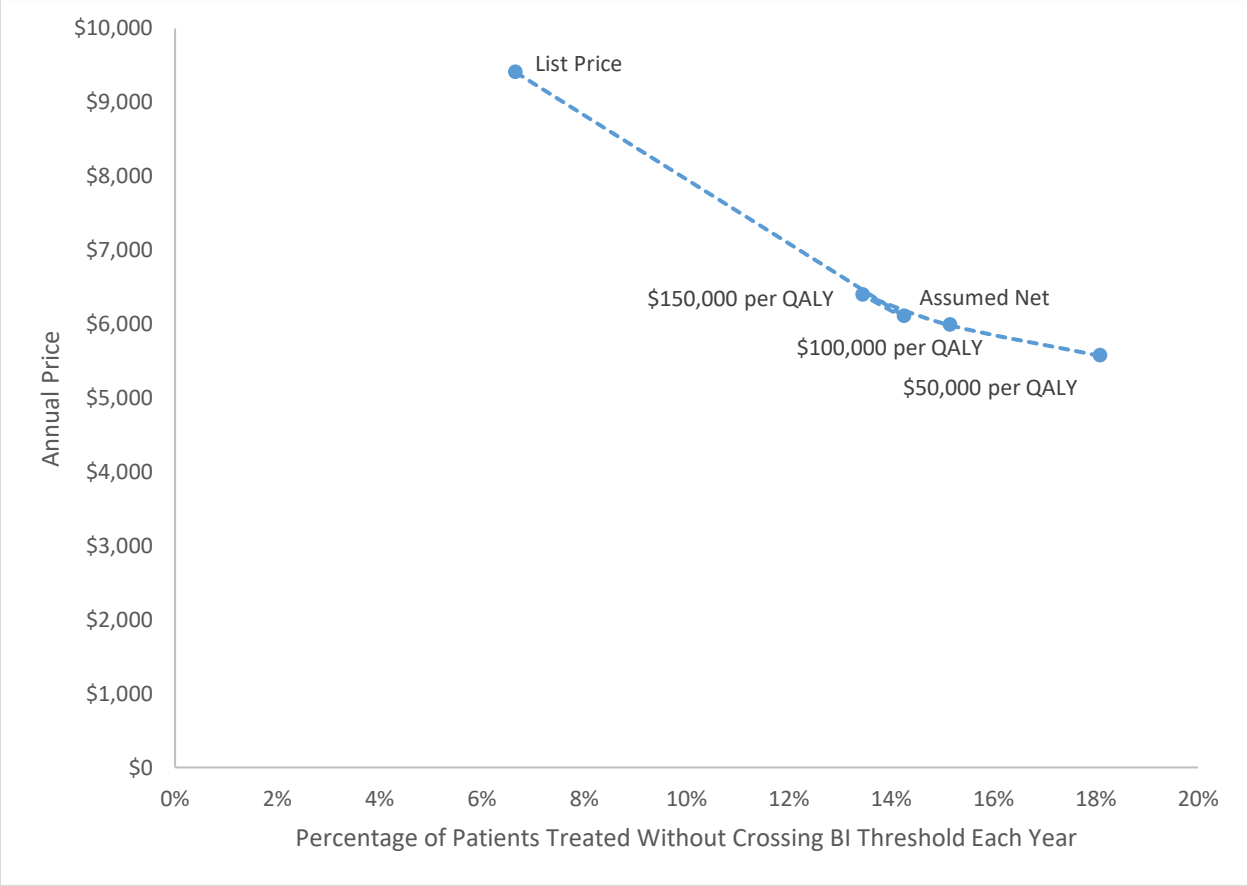
	Average Annual Per Patient Budget Impact				
	WAC List Price	Assumed Net Price	At Price to Reach $150,000/QALY	At Price to Reach $100,000/QALY	At Price to Reach $50,000/QALY
Oral Semaglutide	$33,700	$30,600	$30,800	$30,500	$30,100
DPP-4 + GLP-1 + SGLT-2	$28,000				
Oral Semaglutide Budget Impact	$5,700	$2,600	$2,800	$2,500	$2,100

All annualized costs include drug and non-drug health care costs.
DPP-4: dipeptidyl peptidase-4 inhibitor, GLP-1: glucagon-like peptide-1, QALY: quality-adjusted life year, SGLT-2: sodium-glucose cotransporter-2, WAC: wholesale acquisition cost

In a prevalent population where patients are switched from a DPP-4, GLP-1 or SGLT-2 to oral semaglutide, the average annualized potential budgetary impact when using its list price and assumed net price was an additional per-patient cost of approximately $5,700 and $2,600, respectively, versus a market share weighted mix of DPP-4 inhibitors, GLP-1 receptor agonists, or SGLT-2 inhibitors. Its average annualized 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 $2,100 per patient to approximately $2,800 per patient.

In this population, as shown in Figure 7.1, approximately 7% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at oral semaglutide's list price (WAC) and approximately 14% of patients at its assumed net price. Between 13% and 18% 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 list price ($9,404 per year), assumed net price ($6,103 per year) and annual prices to reach cost-effectiveness thresholds of $150,000, $100,000, and $50,000 per QALY ($6,396, $5,983 and $5,569, respectively) for oral semaglutide.

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

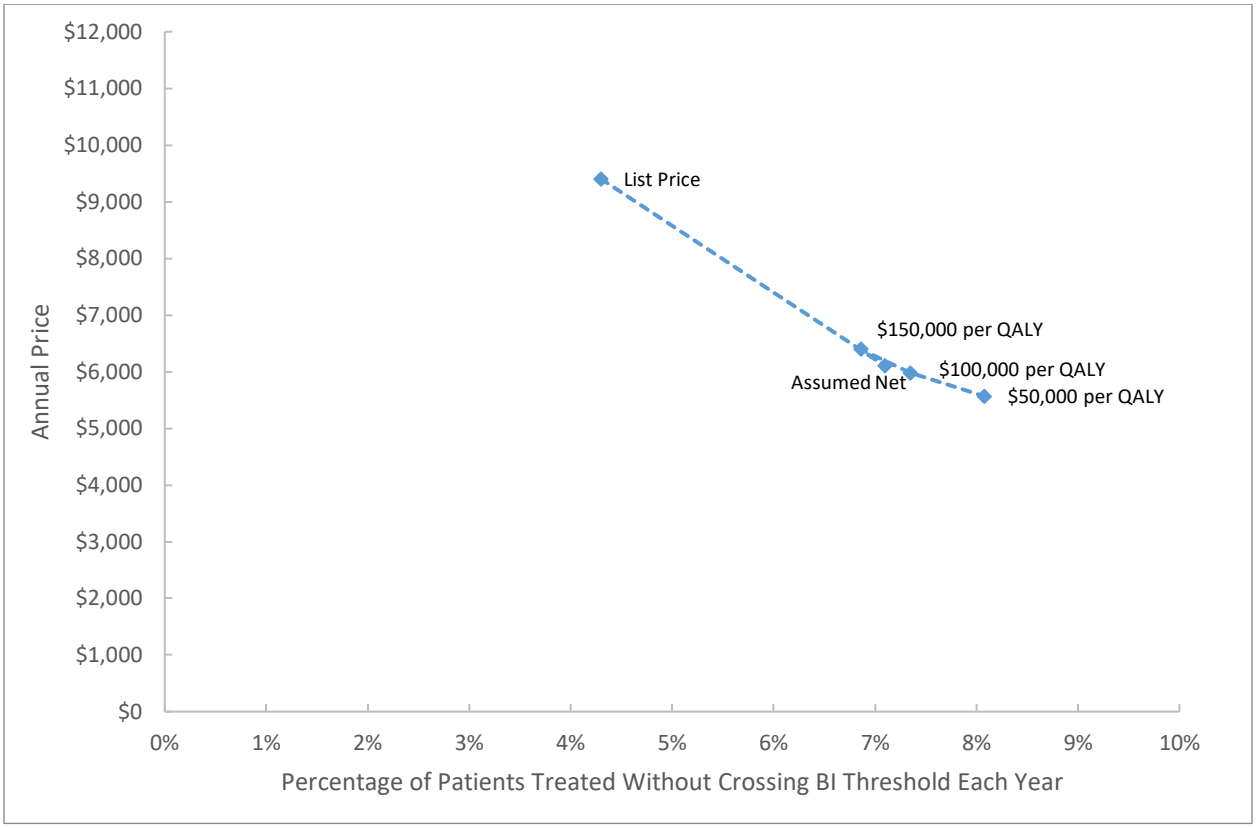
	Average Annual Per Patient Budget Impact				
	List Price	Assumed Net Price	At Price to Reach $150,000/QALY	At Price to Reach $100,000/QALY	At Price to Reach $50,000/QALY
Oral Semaglutide	$33,700	$30,600	$30,800	$30,500	$30,100
Background Antihyperglycemics	$25,900				
Oral Semaglutide Budget Impact	$7,800	$4,700	$4,900	$4,600	$4,200

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 list price and assumed net price was an additional per-patient cost of approximately $7,800 and $4,700, 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 $4,200 per patient to approximately $4,900 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 list price and approximately 7.1% could be treated at its assumed net price before the budget exceeded this threshold. Between 6.9% and 8.1% 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

7.4 Access and Affordability Alert

As discussed above, at oral semaglutide's estimated net price, despite meeting common lifetime cost-effectiveness thresholds versus background therapy alone, only approximately 7% to 14% of eligible US patients could be treated in a given year before exceeding ICER's potential budget impact threshold of $819 million. At the public meeting, clinical experts stated their belief that, because primary care providers are often uncomfortable prescribing injectable GLP-1 receptor agonists, oral semaglutide would be an attractive alternative for up to 50% of the eligible patient population. Given that the clinical goal for uptake would exceed the potential budget impact threshold at the national level, ICER is issuing an access and affordability alert. Currently, this alert is based on the assumed net price, and it should be noted that the findings are subject to change if and when the actual net price becomes available. The purpose of an ICER affordability and access alert is to signal stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health care system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs that threaten sustainable access to high-value care for all patients.

8. Summary of the Votes and Considerations for Policy

8.1 About the New England CEPAC Process

During New England CEPAC public meetings, the New England CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to New England CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the New England CEPAC Panel during their deliberation and help to shape recommendations on ways the evidence can apply to policy and practice.

After the New England CEPAC Panel votes, a policy roundtable discussion is held with the New England CEPAC Panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the November 14, 2019 meeting, the New England CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of oral semaglutide for type 2 diabetes. Following the evidence presentation and public comments (public comments from the meeting can be accessed here [starting at minute 1:24:00]), the New England CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and potential other benefits and contextual considerations related to the use of oral semaglutide for type 2 diabetes. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by New England CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the New England CEPAC Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 8.1 below):

1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The New England CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

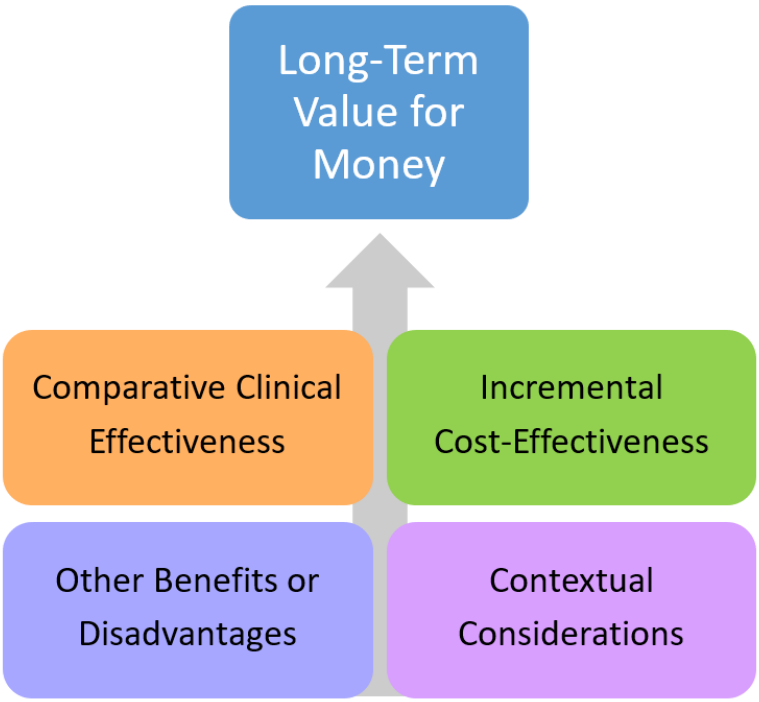
2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the New England CEPAC voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

3. Potential other benefits refer to any significant benefits or disadvantages 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. Examples of potential other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether potential other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for potential other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the

condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 8.1. Conceptual Structure of Long-term Value for Money



8.2 Voting Results

Clinical Evidence

1. Is the evidence adequate to demonstrate that adding **oral semaglutide** (Rybelsus®) to ongoing background therapy provides a positive net health benefit?

Yes: 12 votes	No: 0 votes

The Council unanimously judged that the evidence was adequate to demonstrate that adding oral semaglutide (Rybelsus®) to ongoing background therapy provides a positive net health benefit in patients with type 2 diabetes**.**

2. Is the evidence adequate to demonstrate that the net health benefit of adding **oral semaglutide** is superior to that provided by adding **sitagliptin** (Januvia®)?

Yes: 12 votes	No: 0 votes

The Council unanimously judged that the evidence was adequate to demonstrate that the net health benefit of adding oral semaglutide is superior to that provided by adding sitagliptin (Januvia®). This vote reflects a judgement on the specific treatments in question rather than the classes to which these drugs belong.

3. Is the evidence adequate to demonstrate that the net health benefit of adding **oral semaglutide** is superior to that provided by adding **liraglutide** (Victoza®)?

Yes: 1 vote	No: 11 votes

A majority of the Council determined that the evidence was inadequate to demonstrate that the net health benefit of adding oral semaglutide is superior to that provided by adding liraglutide (Victoza®).

4. Is the evidence adequate to distinguish the net health benefit of adding **oral semaglutide** from that provided by adding **empagliflozin** (Jardiance®)?

Yes: 1 vote	No: 11 votes

A majority of the Council determined that the evidence was inadequate to distinguish the net health benefit of adding oral semaglutide from that provided by adding empagliflozin (Jardiance®).

If yes:

4a. Which treatment provides greater net health benefit?

c. Oral semaglutide
d. Empagliflozin

No vote taken

Because a majority of the council voted no on question 4, we did not take a vote on question 4a.

Potential Other Benefits and Disadvantages

5. For patients currently receiving ongoing background therapy, does adding treatment with **oral semaglutide** offer one or more of the following potential "other benefits or disadvantages." (select all that apply)

This intervention offers reduced complexity compared to liraglutide that will significantly improve patient outcomes.	***9/12***
There are other important benefits or disadvantages that should have an important role in judgements of the value of this intervention.	6/12

A majority of the council judged that oral semaglutide offers reduced complexity compared to liraglutide that will significantly improve patient outcomes. The Council made a note that this intervention's oral administration will reduce the burden for primary care doctors, who may be more comfortable prescribing oral semaglutide than instructing patients to use the injectable form. It also provides a new option for patients who prefer to avoid using needles.

Half of the Council judged there are other important benefits or disadvantages that should have an important role in judgements of the value of oral semaglutide. They expressed that treating patients with oral semaglutide will significantly reduce caregiver or broader family burden, as caregivers responsible for administering treatment may not feel comfortable administering the injectable form of the drug. The Council also noted that oral semaglutide may present certain disadvantages compared to other oral interventions for type 2 diabetes, such as empagliflozin. Disadvantages include the pill's comparatively large size, the initial requirements for dose titration, the need for dosing on an empty stomach, and the adverse gastrointestinal side effects.

Contextual Considerations

6. Are any of the following contextual considerations important in assessing the long-term value for money of **oral semaglutide**? (select all that apply)

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.	5/12
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	***7/12***
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	5/12
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	5/12
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	0/12

Almost half of all Councilmembers judged that oral semaglutide 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, that there is significant uncertainty about the long-term risk of serious side effects of oral semaglutide, and that there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention. Slightly more than half of all Councilmembers judged that oral semaglutide is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.

The Council discussed many common outcomes included in type 2 diabetes' lifetime burden of illness, including blindness, amputations, renal disease, sexual dysfunction, and psychological burden.

Long-Term Value for Money

7. Given the available evidence on comparative effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **oral semaglutide** versus **ongoing background therapy alone** at current pricing?

Low: 4 votes	***Intermediate: 6 votes***	High: 2 votes

At current estimated net price of oral semaglutide, half of the Council voted that there is intermediate long-term value for money of treatment with oral semaglutide versus ongoing

background therapy alone. Two Council members voted that long-term value for money of treatment is high, one of whom reasoned that this judgment of value was higher due to important contextual considerations related to how our modern socioeconomic infrastructure has likely led to the widespread development of type 2 diabetes.

Four members of the Council voted that the long-term value for money of oral semaglutide is low. These Council members noted that real-world use of type 2 diabetes treatments rarely mirrors the carefully scheduled administration of drugs within regulatory phase studies. A large proportion of type 2 diabetes patients habitually ration insulin because they cannot afford the appropriate dose. Therefore, due to questions of patient access, it was difficult to forecast how the results from the PIONEER studies will be translated into real-world use.

8.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the New England CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on the use of oral semaglutide for T2DM to policy and practice. The policy roundtable members included one patient advocate, two clinical experts, two payers, and three representatives from pharmaceutical manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix G.

Table 8.1 Policy Roundtable Members

Name	Title and Affiliation
Jeff Casberg, MS, RPh	Director of Clinical Pharmacy, IPD Analytics
Bonnie Donato, MA, PhD	Executive Director of Primary Care, Health Economics, and Outcomes Research, Boehringer Ingelheim
Todd Hobbs, MD	Vice President, Chief Medical Officer of North America, Novo Nordisk
Bill McQuade, DSc, MPH	Senior Health Policy Analyst, Rhode Island Executive Office of Health and Human Services, Office of Medicaid
Joanna Mitri, MD, MS	Staff Endocrinologist, Joslin Diabetes Center
Lisa Murphy, MD, DPhil	Chief, Division of Endocrinology and Metabolism, San Francisco General Hospital, University of California, San Francisco
David Strutton, PhD	Vice President, Global Pharmaceuticals & Policy Research, Center for Observational and Real-World Evidence, Merck
Susan Weiner, MS, RDN, CDE, FAADE	Scientific Council Member, Beyond Type 2

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Manufacturers

Manufacturers with new agents for diabetes mellitus should seize the opportunity to come to market with a lower list price to benefit patients.

We heard about how financial toxicity has led to poor patient outcomes as patients underdose certain therapies to reduce costs. Manufacturers can reduce financial toxicity for many uninsured patients with lower list prices, and employers and PBMs can benefit patients by passing along net price savings to patients.

To provide high quality head-to-head evidence on the comparative effectiveness of emerging treatment options for patients with diabetes, manufacturers should look to the example set by the PIONEER trials of oral semaglutide.

The PIONEER trials provide extensive information on the comparative effectiveness of oral semaglutide versus other relevant treatments across an appropriate spectrum of background populations and therapies. Novo Nordisk should be commended for their support of these trials.

Payers

Prior authorization criteria for antihyperglycemic products should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for submitting prior authorization material should be clear and efficient for providers. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.

Patient Eligibility Criteria

a. **Diagnosis**: Inadequate control of T2DM will vary by patient age and some payers may consider looking at specific A1c criteria for control in the 2019 ADA Guidelines. This is not intended to account for any possible future indications for CV risk reduction in patients with T2DM with controlled A1c.
b. **Clinical criteria:** Given that nearly all the evidence on the effectiveness of semaglutide has come from studies of patients who have had inadequate control on metformin, payers may consider requiring attestation from clinicians that patients have had an adequate trial of metformin with A1c levels remaining above clinical targets. However, we heard from clinical experts that metformin is used nearly universally as first-line therapy and that adding a prior authorization requirement would add administrative overhead without additional benefit.
c. **Step Therapy:** We heard from payer representatives that there is very little insurer management of treatment for T2DM, but that patient resistance to injectable treatments

limited the early-line use of GLP-1 therapies. This resistance will be removed with an oral GLP-1 therapy and, as a result, some payers may consider instituting step therapy. However, we heard from clinical experts that some drug classes are preferable for specific patients based on a number of interacting clinical criteria, and that a routine step through SGLT-2s or DPP-4s would be viewed as lacking clinical nuance. We heard from payer analysts that some payers have instituted a step therapy requirement for an injectable GLP-1 RA prior to receiving coverage for oral semaglutide. Clinical experts felt this was not clinically sensible. More broadly, clinical experts acknowledged that they will have some patients whom they believe would do equally well with an SGLT-2i or a GLP-1 RA, and in those cases it would be appropriate for clinicians to pick the substantially cheaper agent (currently an SGLT-2i) given the lack of evidence demonstrating clear superiority of one therapy over the other for many patients. Payers considering step therapy with other oral agents prior to access to coverage for oral semaglutide should consult with patients and clinical experts to determine whether step therapy can be targeted to appropriate patients without undue administrative burden.

d. **Other Clinical Criteria:** We heard from clinical experts that concurrent therapy with an SGLT-2i and a GLP-1 RA is common. Some payers may wish to consider limiting an initial trial or oral therapy to one agent after metformin, but there may be considerable resistance from clinicians and patients given the lack of prior experience with active management in this disease space.
e. **Renewal Criteria:** A1c criterion for renewal would not be appropriate given benefits of oral semaglutide beyond A1c control.
f. **Prescriber Criteria**: Given the prevalence of T2DM and the safety profile for oral semaglutide, there appear to be no evidence-based reasons to consider restricting providers to specialists.

Clinicians

As the treatment options for T2DM continue to evolve, primary care providers should make themselves aware of the 2019 ADA Guidelines on treatment of T2DM to ensure that all treating clinicians know how to identify the varying risks and benefits of different agents for particular subpopulations.

Appropriate management of T2DM is changing as new medications and new evidence become available. The 2019 ADA Guidelines incorporate best evidence and provide figures that allow quick decision making when starting or adding medication therapy. It is imperative that primary care providers familiarize themselves with these guidelines. As part of this, providers should note that therapies have different benefits and harms and it is important to engage in shared decision making with patients in choosing therapies. Additionally, clinicians should remember that drug therapy is only a portion of the necessary care and education of people with diabetes.

Clinicians should not "threaten" patients with treatment with insulin if they "fail" other therapies.

Many patients with T2DM will eventually need to be treated with an insulin preparation. Many patients will have been told that if they are unable to reduce their glucose levels with lifestyle changes and oral medications, that they will be prescribed insulin, and clinicians will use the possibility of needing insulin as a motivating factor for lifestyle changes and medication adherence. This creates a fear among patients far out of proportion to the actual difficulty of insulin therapy for T2DM and causes many patients who would benefit from insulin therapy to postpone or refuse the treatment.

Researchers

Given the high rate of gastrointestinal side effects with oral semaglutide, real world evidence on adherence should be studied and reported.

An important uncertainty around oral semaglutide is whether its effectiveness in the real world will match its efficacy seen in randomized trials. Real world evidence is needed to address this issue.

It will be important to understand the relative benefits of GLP-1 RAs and SGLT-2i's on patient important outcomes such as cardiovascular events; these can likely best be assessed in head-to-head pragmatic clinical trials.

Because of the concerns around adherence, and the importance of knowing whether the "next" therapy for a patient with T2DM should be a GLP-1 RA or an SGLT-2i, head-to-head trials using pragmatic designs that can better assess effectiveness should be performed.

Trials of combination therapies, particularly of GLP-1 RAs and SGLT-2i's, should be performed.

It is currently uncertain whether combining GLP-1 RAs and SGLT-2i's achieves patient-important benefits that are additive or whether the benefits are smaller or larger than would be expected when considering these classes individually. These agents are already being used in combination, and clinical research is needed to guide appropriate practice and patient counseling.

****

This is the second ICER review of T2DM.

References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report. 2017; https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf.
2. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2018;41(12):2669-2701.
3. McCulloch DK. Glycemic control and vascular complications in type 2 diabetes mellitus. In: Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc.
4. Cohen RA, Cha AE. Strategies Used by Adults With Diagnosed Diabetes to Reduce Their Prescription Drug Costs, 2017-2018. *NCHS data brief.* 2019(349):1-8.
5. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019. *Diabetes Care.* 2019;42(Suppl 1):S90-S102.
6. Novo Nordisk. ADA investor and analyst event. Orlando, FL. 24 June. 2018; https://www.novonordisk.com/content/dam/Denmark/HQ/investors/irmaterial/investor_presentations/2018/20180625_ADA_2018_investor_presentation.pdf.
7. Novo Nordisk. Press Release: Novo Nordisk files for US FDA approval of oral semaglutide for blood sugar control and cardiovascular risk reduction in adults with type 2 diabetes. 2019; https://www.novonordisk-us.com/media/news-releases.html?122958.
8. Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. *Jama.* 2019;321(15):1466-1480.
9. Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine.* 2019;381:841-851.
10. Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. *Lancet Diabetes Endocrinol.* 2019;7(7):515-527.
11. Pieber TR, Bode B, Mertens A, et al. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial. *Lancet Diabetes Endocrinol.* 2019;7(7):528-539.
12. Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. *Lancet.* 2019;394(10192):39-50.
13. Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: Randomized Clinical Trial Comparing the Efficacy and Safety of Oral Semaglutide Monotherapy with Placebo in Patients with Type 2 Diabetes. *Diabetes Care.* 2019.
14. Rodbard HW, Rosenstock J, Canani LH, et al. Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. *Diabetes Care.* 2019:dc190883.
15. Zinman B, Aroda VR, Buse JB, et al. Efficacy, Safety, and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients With Type 2 Diabetes: The PIONEER 8 Trial. *Diabetes Care.* 2019:dc190898.
16. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New England Journal of Medicine.* 2015;373(22):2117-2128.
17. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine.* 2015;373(3):232-242.

18. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine.* 2016;375(4):311-322.
19. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine.* 2016;375(19):1834-1844.
20. 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.
21. Food Drug Administration. Rybelsus® Prescribing Information. 2019.
22. Food Drug Administration. Ozempic® Prescribing Information. 2019.
23. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Survey Years: 2013-14, 2015-16; https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes/Default.aspx?BeginYear=2015. Accessed August 20, 2019.
24. Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. *Diabetologia.* 2013;56(9):1925-1933.
25. Lundqvist A, Steen Carlsson K, Johansen P, Andersson E, Willis M. Validation of the IHE Cohort Model of Type 2 Diabetes and the impact of choice of macrovascular risk equations. *PLoS One.* 2014;9(10):e110235.
26. McEwan P, Foos V, Palmer JL, Lamotte M, Lloyd A, Grant D. Validation of the IMS CORE Diabetes Model. *Value Health.* 2014;17(6):714-724.
27. Palmer AJ, Clarke P, Gray A, et al. Computer modeling of diabetes and its complications: a report on the Fifth Mount Hood challenge meeting. *Value Health.* 2013;16(4):670-685.
28. Willis M, Asseburg C, Nilsson A, Johnsson K, Kartman B. Multivariate Prediction Equations for HbA1c Lowering, Weight Change, and Hypoglycemic Events Associated with Insulin Rescue Medication in Type 2 Diabetes Mellitus: Informing Economic Modeling. *Value Health.* 2017;20(3):357-371.
29. Laiteerapong N, Cooper JM, Skandari MR, et al. Individualized Glycemic Control for U.S. Adults With Type 2 Diabetes: A Cost-Effectiveness Analysis. *Ann Intern Med.* 2018;168(3):170-178.
30. Weng LC, Preis SR, Hulme OL, et al. Genetic Predisposition, Clinical Risk Factor Burden, and Lifetime Risk of Atrial Fibrillation. *Circulation.* 2018;137(10):1027-1038.
31. Allison MA, Ho E, Denenberg JO, et al. Ethnic-specific prevalence of peripheral arterial disease in the United States. *Am J Prev Med.* 2007;32(4):328-333.
32. Aune D, Feng T, Schlesinger S, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose and the risk of atrial fibrillation: A systematic review and meta-analysis of cohort studies. *J Diabetes Complications.* 2018;32(5):501-511.
33. SSR Health L. 2018; https://www.ssrhealth.com/.
34. Truven Health Analytics. Red Book Online Search. http://www.micromedexsolutions.com. Accessed October 1, 2019.
35. Bullard KM, Cowie CC, Lessem SE, et al. Prevalence of Diagnosed Diabetes in Adults by Diabetes Type — United States, 2016. *MMWR Morb Mortal Wkl Rep.* 2016;2018(67):359-361.
36. Centers for Disease Control and Prevention. *National Diabetes Statistics Report, 2017: Estimates of Diabetes and Its Burden in the United States.* 2017.
37. American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2019. *Diabetes Care.* 2019;42(Suppl 1):S61-S70.
38. Regier EE, Venkat MV, Close KL. More Than 7 Years of Hindsight: Revisiting the FDA's 2008 Guidance on Cardiovascular Outcomes Trials for Type 2 Diabetes Medications. *Clinical diabetes : a publication of the American Diabetes Association.* 2016;34(4):173-180.

39. Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a Diabetes Care Editors' Expert Forum. *Diabetes Care.* 2018;41(1):14-31.
40. Endocrinologic and Metabolic Drugs Advisory Committee Meeting. FDA Background Document: October 24-25. 2018; https://www.fda.gov/media/121272/download. Accessed 4/30/2019.
41. Thornberry NA, Gallwitz B. Mechanism of action of inhibitors of dipeptidyl-peptidase-4 (DPP-4). *Best practice & research Clinical endocrinology & metabolism.* 2009;23(4):479-486.
42. Scirica BM, Braunwald E, Raz I, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation.* 2014;130(18):1579-1588.
43. Clar C, Gill JA, Court R, Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. *BMJ open.* 2012;2(5).
44. Lee YS, Jun HS. Anti-diabetic actions of glucagon-like peptide-1 on pancreatic beta-cells. *Metabolism: clinical and experimental.* 2014;63(1):9-19.
45. Nauck MA, Friedrich N. Do GLP-1-based therapies increase cancer risk? *Diabetes Care.* 2013;36 Suppl 2:S245-252.
46. Woolf S. An organized analytic framework for practice guideline development: using the analytic logic as a guide for reviewing evidence, developing recommendations, and explaining the rationale. *Clinical Practice Guideline Development: Methodology Perspectives AHCPR Pub.* 1994(95-0009):105-113.
47. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2019. *Diabetes Care.* 2019;42(Supplement 1):S13-S28.
48. Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. *Biomarker insights.* 2016;11:BMI. S38440.
49. Scheen AJ. Cardiovascular effects of new oral glucose-lowering agents: DPP-4 and SGLT-2 inhibitors. *Circulation research.* 2018;122(10):1439-1459.
50. Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Medical care.* 1992:473-483.
51. Saisho Y. Use of Diabetes Treatment Satisfaction Questionnaire in diabetes care: importance of patient-reported outcomes. *International journal of environmental research and public health.* 2018;15(5):947.
52. Kolotkin RL, Head S, Brookhart A. Construct validity of the Impact of Weight on Quality of Life Questionnaire. *Obesity Research.* 1997;5(5):434-441.
53. Dalton M, Finlayson G, Hill A, Blundell J. Preliminary validation and principal components analysis of the Control of Eating Questionnaire (CoEQ) for the experience of food craving. *European journal of clinical nutrition.* 2015;69(12):1313.
54. ABIM Foundation. Choosing Wisely. https://www.choosingwisely.org/. Accessed August 16, 2019.
55. Centers for Medicare and Medicaid Services. Medicare Coverage Database. 2019; https://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. Accessed August 15, 2019.
56. Neighborhood Health Plan of Rhode Island. 2019 Pharmacy Resources. 2019; https://www.nhpri.org/providers/provider-resources/pharmacy/. Accessed August 15, 2019.
57. MassHealth. MassHealth Drug List A - Z. 2019; https://masshealthdruglist.ehs.state.ma.us/MHDL/pubdruglist.do. Accessed August 15, 2019.
58. CVS Caremark. CVS Caremark Value Formulary. 2019; https://www.caremark.com/portal/asset/Value_Formulary.pdf. Accessed August 15, 2019.

59. Express Scripts. 2019 Express Scripts National Preferred Formulary. 2019; http://www.mympcbenefits.com/Documents/MPC-2019-Express-Scripts-Preferred-Brand-Drugs-List.pdf. Accessed August 15, 2019.
60. Humana. 2019 Rx4 Drug List. 2019; https://apps.humana.com/marketing/documents.asp?file=3312816. Accessed August 15, 2019.
61. Blue Cross Blue Shield of Massachusetts. Medication Lookup. 2019; https://home.bluecrossma.com/medication/?cid=pri646. Accessed August 15, 2019.
62. American Diabetes Association. 5. Lifestyle management: standards of medical care in diabetes—2019. *Diabetes care.* 2019;42(Supplement 1):S46-S60.
63. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *European Heart Journal.* 2019.
64. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
65. Higgins JP. Cochrane Collaboration Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. 2008.
66. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* 2010;8(5):336-341.
67. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Med Care.* 2010;48(6 Suppl):S145-152.
68. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software.* 2010;36(3):1--48.
69. van Valkenhoef G, Kuiper J. gemtc: Network Meta-Analysis Using Bayesian Methods. R package version 0.8-2. 2016.
70. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *New England Journal of Medicine.* 2016;375(4):323-334.
71. Inzucchi SE, Wanner C, Hehnke U, et al. Retinopathy Outcomes With Empagliflozin Versus Placebo in the EMPA-REG OUTCOME Trial. *Diabetes Care.* 2019;42(4):e53-e55.
72. Yamada Y, Katagiri H, Hamamoto Y, et al. Efficacy and safety of oral semaglutide monotherapy vs placebo or liraglutide in Japanese T2D patients: PIONEER 9 trial. *The 11th Scientific Meeting of the Asian Association for the Study of Diabetes (AASD).* 2019;J Diabetes Investig 10(S1):30.
73. Yabe D, Nakamura J, Kaneto H, et al. Safety and efficacy of oral semaglutide vs dulaglutide in Japanese T2D patients: The PIONEER 10 trial. *The 11th Scientific Meeting of the Asian Association for the Study of Diabetes (AASD).* 2019;J Diabetes Investig 10(S1):30.
74. Davies M, Pieber TR, Hartoft-Nielsen ML, Hansen OKH, Jabbour S, Rosenstock J. Effect of Oral Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial. *Jama.* 2017;318(15):1460-1470.
75. Vilsboll T, Bain SC, Leiter LA, et al. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. *Diabetes, obesity & metabolism.* 2018;20(4):889-897.
76. Shao H, Yang S, Fonseca V, Stoecker C, Shi L. Estimating Quality of Life Decrements Due to Diabetes Complications in the United States: The Health Utility Index (HUI) Diabetes Complication Equation. *Pharmacoeconomics.* 2019;37(7):921-929.
77. Sullivan PW, Ghushchyan VH. EQ-5D Scores for Diabetes-Related Comorbidities. *Value Health.* 2016;19(8):1002-1008.
78. Abramson A, Halperin F, Kim J, Traverso G. Quantifying the Value of Orally Delivered Biologic Therapies: A Cost-Effectiveness Analysis of Oral Semaglutide. *J Pharm Sci.* 2019.

79. Hunt B, McConnachie CC, Gamble C, Dang-Tan T. Evaluating the short-term cost-effectiveness of liraglutide versus lixisenatide in patients with type 2 diabetes in the United States. *J Med Econ.* 2017;20(11):1117-1120.
80. Li Q, Ganguly R, Ganz ML, Gamble C, Dang-Tan T. Real-World Clinical Effectiveness and Cost Savings of Liraglutide Versus Sitagliptin in Treating Type 2 Diabetes for 1 and 2 Years. *Diabetes Ther.* 2018;9(3):1279-1293.
81. Nguyen E, Coleman CI, Nair S, Weeda ER. Cost-utility of empagliflozin in patients with type 2 diabetes at high cardiovascular risk. *J Diabetes Complications.* 2018;32(2):210-215.
82. Shah D, Risebrough NA, Perdrizet J, Iyer NN, Gamble C, Dang-Tan T. Cost-effectiveness and budget impact of liraglutide in type 2 diabetes patients with elevated cardiovascular risk: a US-managed care perspective. *Clinicoecon Outcomes Res.* 2018;10:791-803.
83. Gerstein HC, Miller ME, Genuth S, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med.* 2011;364(9):818-828.
84. Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. *Eur J Health Econ.* 2011;12(3):219-230.
85. Ward A, Alvarez P, Vo L, Martin S. Direct medical costs of complications of diabetes in the United States: estimates for event-year and annual state costs (USD 2012). *J Med Econ.* 2014;17(3):176-183.
86. Bureau of Labor Statistics. Medical care in U.S. city average, all urban consumers, not seasonally adjusted. 2019; https://data.bls.gov/timeseries/CUUR0000SAM. Accessed 7/15/2019, 2019.
87. Dall TM, Yang W, Gillespie K, et al. The Economic Burden of Elevated Blood Glucose Levels in 2017: Diagnosed and Undiagnosed Diabetes, Gestational Diabetes Mellitus, and Prediabetes. *Diabetes Care.* 2019;42(9):1661-1668.
88. Shao H, Fonseca V, Stoecker C, Liu S, Shi L. Novel Risk Engine for Diabetes Progression and Mortality in USA: Building, Relating, Assessing, and Validating Outcomes (BRAVO). *Pharmacoeconomics.* 2018;36(9):1125-1134.
89. McEwan P, Ward T, Bennett H, Bergenheim K. Validation of the UKPDS 82 risk equations within the Cardiff Diabetes Model. *Cost Effectiveness and Resource Allocation.* 2015;13(1):12.
90. Herman WH, Hoerger TJ, Brandle M, et al. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med.* 2005;142(5):323-332.
91. Neslusan C, Teschemaker A, Willis M, Johansen P, Vo L. Cost-Effectiveness Analysis of Canagliflozin 300 mg Versus Dapagliflozin 10 mg Added to Metformin in Patients with Type 2 Diabetes in the United States. *Diabetes Ther.* 2018;9(2):565-581.
92. Kuo S, Ye W, Duong J, Herman WH. Are the favorable cardiovascular outcomes of empagliflozin treatment explained by its effects on multiple cardiometabolic risk factors? A simulation of the results of the EMPA-REG OUTCOME trial. *Diabetes research and clinical practice.* 2018;141:181-189.
93. Curtis BH, Curtis S, Murphy DR, et al. Evaluation of a patient self-directed mealtime insulin titration algorithm: a US payer perspective. *J Med Econ.* 2016;19(6):549-556.
94. Montvida O, Shaw J, Atherton JJ, Stringer F, Paul SK. Long-term Trends in Antidiabetes Drug Usage in the U.S.: Real-world Evidence in Patients Newly Diagnosed With Type 2 Diabetes. *Diabetes Care.* 2018;41(1):69-78.
95. Pearson SD. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value Health.* 2018;21(3):258-265.
96. Agency for Healthcare Research and Quality. U.S. Preventive Services Task Force Procedure Manual. 2008.

97. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama.* 2016;316(10):1093-1103.

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

Originally ran search on June 11, 2019; updated search on October 4, 2019.

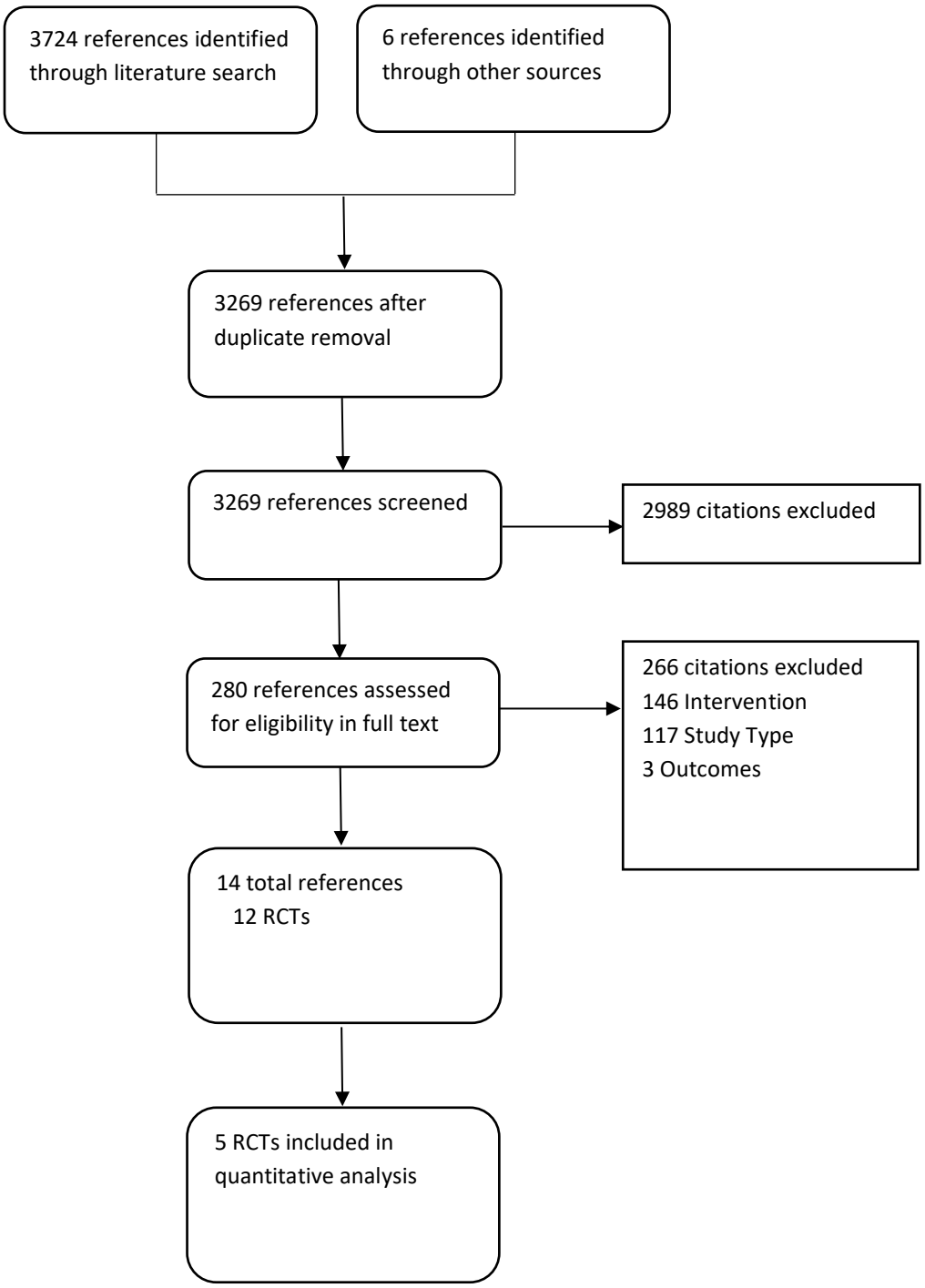
*Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials

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

Originally ran search on June 11, 2019; updated search on October 4, 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 identified two prior systematic reviews of oral semaglutide which are summarized below. We did not identify any completed or ongoing health technology assessments of oral semaglutide.

Avgerinos I, Michailidis T, Liakos A, et al. Oral Semaglutide for type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes, Obesity and Metabolism. 2019.
We identified a systematic review and network meta-analysis assessing the GLP-1 receptor agonist oral semaglutide compared to placebo or other antidiabetic agents for patients with T2DM. Outcomes included change from baseline in HbA1c, weight, blood pressure, cardiovascular endpoints, severe hypoglycemia, gastrointestinal adverse events and diabetic retinopathy. This review included 11 RCTs with 9890 patients. The active comparators included liraglutide, empagliflozin, and sitagliptin. Compared with placebo, oral semaglutide reduced HbA1c by 0.89% (95% CI: -1.07 to -0.71). Oral semaglutide reduced HbA1c by 0.35% (95% CI: -0.43 to -0.26) compared to the active comparators. Oral semaglutide reduced body weight by 2.99 kg (95% CI: -3.69 to -2.30) compared with placebo. Compared to placebo, reduction of systolic blood pressure was 3.16 mmHg (95% CI: -4.56 to -1.77) and 1.46 mmHg (95% CI: -2.53 to – 0.40) compared with the antidiabetic agents. Compared to placebo, oral semaglutide reduced both cardiovascular mortality (OR 0.55, 95% CI 0.31-0.98) and all-cause mortality (OR 0.58, 95% CI 0.37-0.92). With regards to myocardial infarction, stroke, severe hypoglycemia and diabetic retinopathy, oral semaglutide had a neutral effect compared to placebo and other active comparators.

Nuhoho S, Gupta J, Hansen BB, Fletcher-Louis M, Dang-Tan T, Paine A. Orally Administered Semaglutide Versus GLP-1 RAs in Patients with Type 2 Diabetes Previously Receiving 1-2 Oral Antidiabetics: Systematic Review and Network Meta-Analysis. Diabetes Ther. 2019.
We identified a systematic review and network meta-analysis of GLP-1 receptor agonists assessing changes from baseline for HbA1c and weight, as well as percent of patient reaching target HbA1c levels less than 7.0% and less than or equal to 6.5% for patients with T2DM who previously received one to two oral antidiabetic agents. This review consisted of six agents (dulaglutide, exenatide, liraglutide, lixisenatide, injectable semaglutide, and oral semaglutide). For reduction in HbA1c from baseline, oral semaglutide had a significant reduction compared all the GLP-1 receptor agonists except for both doses of injectable semaglutide, liraglutide 1.8 mg once daily, and dulaglutide 1.5 mg once weekly which had no significant results. For the odds of reaching a target HbA1c level of less than 7.0%, oral semaglutide only had a significant improvement compared to exenatide 5µg twice daily, exenatide 5µg twice daily, and all strengths of lixisenatide, while the remaining medications and strengths had no significant differences. For the odds of reaching a target HbA1c level of less than 6.5%, oral semaglutide had a significant improvement compared to all medications except for dulaglutide 1.5mg once weekly, exenatide 2mg once weekly, liraglutide 1.8mg once daily, and both strengths of injectable semaglutide which all had no significant differences. For the reduction of weight from baseline, oral semaglutide had a significant reduction compared to all agents except for both strengths of injectable semaglutide which had no significant difference.

In addition, 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					
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 Placebo in People With Type 2 Diabetes (PIONEER 11) **Novo Nordisk A/S** **NCT04109547**	Phase III, randomized, blinded, parallel assignment Enrollment: 664	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: Placebo once daily Treatment Duration: 26 weeks	Inclusion: • Age ≥ 18 • Diagnosed with T2DM • HbA1c between 7.0-10.0% (53-86 mmol/mol) (both inclusive) 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) above 2.5 x upper limit of the normal (ULN) • Presence or history of malignant neoplasms within the past 5 years prior to the day of screening	Primary: Change in HbA1c Secondary (selected): Change in body weight, fasting plasma glucose, lipid levels and Short-Form-36 version 2	September 1, 2021

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

Title/ Trial Sponsor	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
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)[96] 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.*

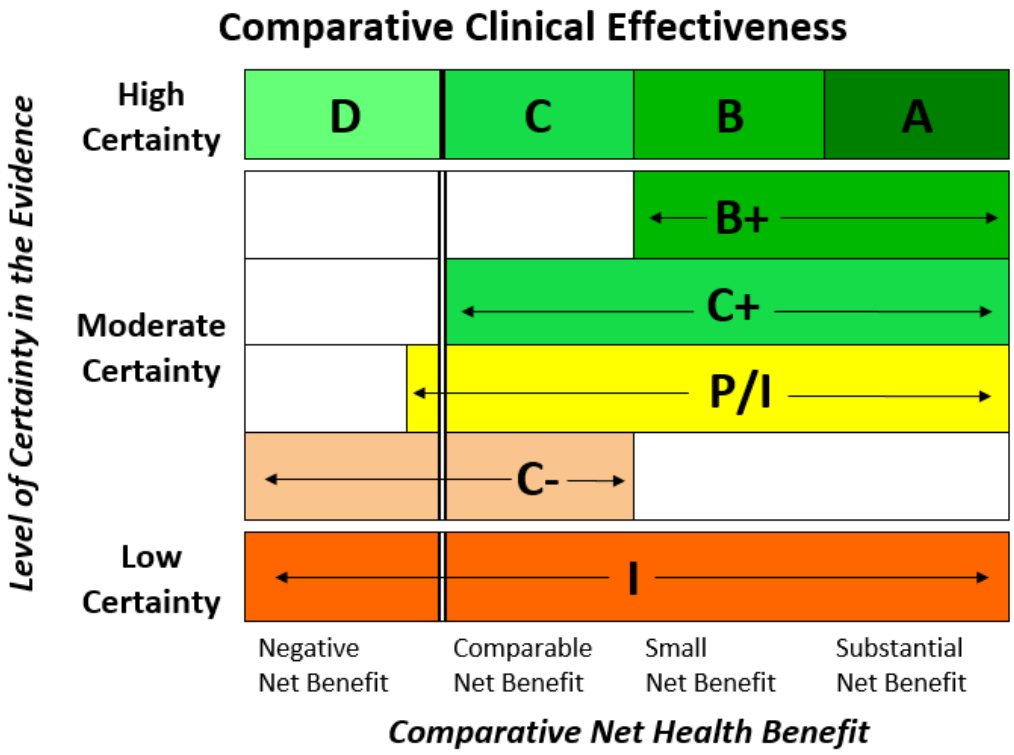
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

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.[67]

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	Yes	Yes	Yes	Yes	Yes	Yes	Good
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	Yes	Yes	Yes	Yes	Yes	Yes	Good
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

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=822	1. Oral semaglutide 14 mg (n=412) 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)	FPG >260 mg/dL from week 8 to 13, >240 mg/dL from week 14 to 25, or >200 mg/dL or HbA1c >8.5% from week 26+
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 7.5%-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)	Two measures of FPG >200 mg/dL from week 16 +, or HbA1c >8.5% from week 26+
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 from 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

*Exclusion criteria for PIONEER 1 through PIONEER 8 consisted of: MI, stroke, or hospitalization for unstable angina or TIA within 180 days; stage IV heart failure; planned revascularization; renal impairment defined as eGFR <60 mL/min/1.73 m2; history of pancreatitis (acute or chronic); history of major surgical procedures involving the stomach potentially affecting absorption of trial product; treatment with any other medication for diabetes or obesity within past 90 days (exception: short-term insulin treatment for acute illness for a total of ≤14 days); proliferative retinopathy or maculopathy requiring acute treatment; history or presence of malignant neoplasms within the last 5 years; family or personal history of MEN2 or MTC; alanine aminotransferase >2.5x upper normal limit; and/or history of diabetic ketoacidosis. PIONEER 5 and PIONEER 6 did not have the above listed renal impairment exclusion. PIONEER 6 also did not have the exclusion criteria listed above of recent MI, stroke, or hospitalization for unstable angina or TIA. PIONEER 5 had additional exclusion criteria that consisted of: rapidly progressing renal disease or known nephrotic albuminuria; and use of systemic immunosuppressive treatment <90 days prior to screening. PIONEER 6 had additional exclusion criteria that consisted of: chronic or intermittent hemodialysis or peritoneal dialysis or severe renal impairment (eGFR <30); MI, stroke, or hospitalization for unstable angina or TIA within 60 days; and/or current or previous (within 90 days prior to screening) treatment with any GLP-1RA, DPP-4 inhibitor, or pramlintide.

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	355 (86.4%)	353 (86.1%)	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	26 (6.3%)	33 (8.0%)	38 (8.2%)	38 (8.2%)	45 (9.7%)	39 (8.4%)	12 (4%)	9 (3%)	8 (6%)	22 (9%)	25 (10%)
Asian	28 (6.8%)	21 (5.1%)	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	91 (22.1%)	108 (26.3%)	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/m^2	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	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 m^2	96 (15)	95 (15)	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 either mean (SD) or n (%).

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

*Data are reported in mmol/L

†Data are reported in mg/dL

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 (47.0%)	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%)	89 (48.4%)	95 (52.2%)	94 (51.9%)	98 (53.3%)
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%)	15 (8.2%)	10 (5.5%)	11 (6.1%)	13 (7.1%)
Asian	31 (17.7%)	30 (17.1%)	29 (16.6%)	31 (17.4%)	1 (1%)	0.0	324 (20.4%)	306 (19.2%)	66 (35.9%)	66 (36.3%)	66 (36.5%)	65 (35.3%)
Hispanic or Latino	52 (29.7%)	31 (17.7%)	46 (26.3%)	51 (28.7%)	7 (4%)	14 (9%)	NR	NR	18 (9.8%)	24 (13.2%)	30 (16.6%)	25 (13.6%)
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)	15.1 (7.9)	16.2 (8.6)	14.1 (8.0)	14.8 (7.9)
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)	31.0 (6.8)	31.1 (7.0)	30.8 (6.3)	31.0 (6.5)
Fasting Plasma Glucose	158 (42)†	162 (42)†	158 (39)†	160 (39)†	9.1 (2.7)*	9.1 (2.8) *	155.0 (58.1)†	157.3 (60.8)†	8.8 (3.2)*	8.5 (2.7)*	8.3 (2.6)*	8.3 (2.6)*
eGFR, mL/min per 1.73 m²	99 (14)	95 (16)	97 (16)	100 (15)	47 (10)	48 (10)	74 (21)	74 (21)	92 (16)	92 (16)	91 (14)	91 (15)
Metformin	*N/A*				132 (81.0%)	110 (68.3%)	1221 (76.7%)	1242 (78.0%)	NR‡	NR‡	NR‡	NR‡
Sulfonylurea					65 (39.9%)	66 (41.0%)	517 (32.5%)	510 (32.0%)	*N/A*			
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 either mean (SD) or n (%).

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

*Data are reported in mmol/L

†Data are reported in mg/dL

‡Of all patients enrolled, 67.2% were on metformin; arm-level data is NR

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											
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)	*NR*	
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											
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											
Mean change	*N/A*		-0.6	-0.8	-1.1	-0.7	*N/A*			*N/A*	
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											
%	66.8	40	27	42	55	32	67.6	61.8	14.2	*NR*	
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											

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
%	66.1	43.2	27	38	53	31	60.7	55	15	58	25
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/A*		27	37	44	29	*N/A*			*N/A*	
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											
%	186 (47.4)	68 (17.2)	13	26	36	14	48	43	5	*NR*	
OR (95% CI); p-value	4.62 (3.28, 6.52); p<0.001	reference	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											
%	182 (47.4)	83 (21.7)	14	22	32	14	43	33	4	33.0	12.2
OR (95% CI); p-value	3.36 (2.43, 4.66); p<0.001	reference	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/A*		13	23	29	14	*N/A*			*N/A*	
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											

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
Week 26											
%	237 (60.5)	141 (35.7)	20	34	46	20	60.8	53.5	11.2	*NR*	
OR (95% CI); p-value	2.88 (2.12, 3.91); p<0.001	reference	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											
%	214 (55.7)	149 (39.0)	20	30	43	20	56.4	48.3	11.3	45.2	14.7
OR (95% CI); p-value	2.03 (1.50, 2.74); p<0.001	reference	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/A*		20	31	34	19	*N/A*			*N/A*	
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											
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)	*NR*	
ETD (95% CI), p-value	-0.1 (-0.7, 0.5); p=0.759	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											
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)

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
ETD (95% CI), p-value	-0.2 (-0.9, 0.5); p=0.623	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											
Mean change	*N/A*		-1.9	-2.7	-3.2	-1	*N/A*			*N/A*	
ETD (95% CI), p-value			-0.8 (-1.5, -0.1) p=0.02	-1.7 (-2.3, -1.0) p<0.001	-2.1 (-2.8, -1.5) p<0.001	reference					
Proportion with Weight Loss≥5.0%											
Week 26											
%	41.2	36.1	13	19	30	10	43.5	27.7	7.5	*NR*	
OR (95% CI); p-value	1.24 (0.93, 1.65); p=0.150	reference	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											
%	40.4	39.2	17	27	34	12	44.7	24.5	12	27.0	12.1
OR (95% CI); p-value	1.04 (0.78, 1.39); p=0.780	reference	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/A*		21	27	33	14	*N/A*			*N/A*	
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%											

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
Week 26											
%	49 (12.5)	27 (6.8)	1	5	7	2	14	6	0	*NR*	
OR (95% CI); p-value	1.98 (1.21, 3.25); p=0.007	reference	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											
%	58 (15.0)	30 (7.8)	4	7	11	3	16	7	3	6.4	2.1
OR (95% CI); p-value	2.05 (1.28, 3.28); p=0.003	reference	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/A*		4	10	11	4	*N/A*			*N/A*	
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											
%	177 (45.2)	111 (28.1)	13	26	37	9	130 (46.8)	93 (34.3)	5 (3.7)	*NR*	
OR (95% CI); p-value	2.10 (1.55, 2.85); p<0.001	reference	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											
%	164 (42.7)	101 (26.4)	17	24	36	12	43.6	28.6	6.8	34.8	10.5

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**
OR (95% CI); p-value	2.10 (1.54, 2.87); p<0.001	reference	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/A		18	26	34	14	*N/A*			*N/A*	
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/m²											
Week 26											
Mean change	-1.4	-1.4	-0.4	-0.8	-1.1	-0.2	-1.6 (0.1)	-1.1 (0.1)	-0.2 (0.1)	*NR*	
ETD (95% CI), p-value	-0.0 (-0.2, 0.2); p=0.697	reference	-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											
Mean change	-1.4	-1.3	-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	-0.1 (-0.3, 0.2); p=0.489	reference	-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											
Mean change	*N/A*		-0.7	-1	-1.1	-0.4	*N/A*			*N/A*	
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					

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 Fasting Plasma Glucose, mg/dL or mmol/L (noted)											
Week 26											
Mean change	-1.99, mmol/L	-2.01	-13.6 mg/dL	-21.3	-30.5	-15.4	-2 (0.1) mmol/L	-1.87 (0.1)	-0.36 (0.2)	*NR*	
ETD (95% CI), p-value	0.02 (-0.24, 0.28); p=0.881	reference	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											
Mean change	-2.01, mmol/L	-2.09	-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	0.08 (-0.20, 0.36); p=0.576	reference	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											
Mean change (SE)	*N/A*		-17.1	-18.1	-30.8	-15	*N/A*			*N/A*	
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											
Mean change	-2.2, mmol/L	-1.9	-20 mg/dL	-26.8	-29.3	-21.2	-2.2 (0.1) mmol/L	-1.9 (0.1)	-0.8 (0.1)	*NR*	

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
ETD (95% CI), p-value	-0.3 (-0.5, -0.0); p=0.027	reference	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											
Mean change	-2.3, mmol/L	-2.0	-21.7	-26.9	-33.1	-24.7	-2.1 (0.1)	-1.6 (0.1)	-1.0 (0.1)	*NR*	
ETD (95% CI), p-value	-0.3 (-0.5, -0.0); p=0.033	reference	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											
Mean change	*N/A*		-22.6	-25.3	-30.4	-22.7	*N/A*			*N/A*	
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											
Mean change	-5	-5	-1	-3	-3	-2	-4	-3	-2	*NR*	
ETD (95% CI), p-value	0 (-1, 2); p=0.745	reference	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		
Week 52											
Mean change	-4	-4	-2	-5	-3	-1	-3	-2	0	-4	-2
ETD (95% CI), p-value	0 (-2, 2); p=0.937	reference	-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											
Mean change (SE)	*N/A*		-1	-3	-3	0	*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
N at baseline	411	410	466	465	465	467	285	284	142	253	251
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											
Mean change	-2	-3	-1	-1	-1	0	-1	-1	0	*NR*	
ETD (95% CI), p-value	1 (0,2); p=0.047	reference	-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											
Mean change	-2	-2	-2	-1	-2	-1	-1	-1	1	-1	-1
ETD (95% CI), p-value	0 (-1, 2); p=0.655	reference	-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											
Mean change	*N/A*		-1	-1	-1	-1	*N/A*			*N/A*	
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											
Ratio to baseline	0.95	1.02	1	0.98	0.97	1	0.96	0.97	1	*NR*	
ETR (95% CI), p-value	0.93 (0.91, 0.95); p<0.001	reference	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											
Ratio to baseline	0.97	1.02	1	1	0.99	1.01	0.98	0.98	1.02	0.96	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
N at baseline	411	410	466	465	465	467	285	284	142	253	251
ETR (95% CI), p-value	0.95 (0.93, 0.97); p<0.001	reference	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											
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											
Ratio to baseline	0.96	1.04	1.02	0.99	0.98	1.02	0.96	0.97	0.99	*NR*	
ETR (95% CI), p-value	0.92 (0.89, 0.96); p<0.001	reference	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											
Ratio to baseline	0.96	1.03	1.01	1	1	1.03	0.99	1	1.06	0.97	1.03
ETR (95% CI), p-value	0.94 (0.90, 0.98); p=0.002	reference	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											
Ratio to baseline	*N/A*		1.02	1	1	1.03	*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
N at baseline	411	410	466	465	465	467	285	284	142	253	251
ETR (95% CI), p-value			1.00 (0.96, 1.04) p=0.99	0.98 (0.94, 1.02) p=0.23	0.98 (0.94, 1.02) p=0.31	reference					
HDL-C—Ratio to Baseline											
Week 26											
Ratio to baseline	1.01	1.07	0.97	0.99	0.98	0.99	1.02	1.02	1.03	*NR*	
ETR (95% CI), p-value	0.94 (0.92, 0.96); p<0.001	reference	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											
Ratio to baseline	1.01	1.06	0.99	1.01	1.01	1	1.02	1	1.01	1	1.01
ETR (95% CI), p-value	0.95 (0.93, 0.97); p<0.001	reference	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											
Ratio to baseline	*N/A*		0.97	0.99	1	0.99	*N/A*			*N/A*	
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											

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
Ratio to baseline	0.88	0.90	0.99	0.96	0.92	0.97	0.89	0.91	0.99	*NR*	
ETR (95% CI), p-value	0.97 (0.92, 1.02); p=0.187	reference	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											
Ratio to baseline	0.89	0.90	1	0.98	0.93	0.99	0.87	0.9	0.96	0.89	0.91
ETR (95% CI), p-value	0.98 (0.93, 1.04); p=0.538	reference	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											
Ratio to baseline	*N/A*		0.96	0.95	0.92	0.94	*N/A*			*N/A*	
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											
Geometric mean (CV)	*NR*		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)	*NR*	
Week 52											
Geometric mean (CV)	*NR*		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)	*NR*	
Week 78											

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
Geometric mean (CV)	*N/A*		0.99 (14.6)	0.98 (10.7)	0.98 (12.7)	0.98 (10.8)	*N/A*	*N/A*		*N/A*	
Proportion on Rescue Medication											
Week 26											
%	1.9	1.2	5.4	2.4	1.1	2.8	3.5	3.2	7.7	*NR*	
Week 52											
%	7.5	10.7	26.0	15.7	6.7	20.1	7.0	6.3	30.3	3.2	15.9
Week 78											
%	*N/A*		34.3	22.2	10.1	27.6	*N/A*			*N/A*	
Overall											
%	24.8	21.5	47.9	35.4	28	39.4	21.8	18.7	41.6	19.8	24.3
Proportion on Additional Glucose-Lowering Medication											
Week 26											
%	4.1	3.2	7.1	4.3	3.2	4.3	7.0	5.6	8.5	*NR*	
Week 52											
%	12.7	13.7	29.4	18.5	11.0	23.8	13.7	10.2	32.4	8.7	18.7
Week 78											
%	*N/A*		38.4	25.6	16.1	31.7	*N/A*			*N/A*	
All-Cause Discontinuation of Trial Product											
End of trial											
%	17.7	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											
%	2.9	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										
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										
Mean change (SE)	*N/A*				*N/A*		-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										
%	55.1	68.8	76.9	31	57.8	22.6	50 (28.4)	74 (42.5)	101 (58.4)	12 (6.8)
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		5.61 (2.77, 11.37); p<0.001	12.73 (6.12, 25.00); p<0.001	22.52 (11.14, 45.51); p<0.001	reference
Week 52										
%	*N/A*				*N/A*		50 (28.9)	67 (39.6)	91 (54.2)	16 (9.3)
OR (95% CI); p-value							4.02 (2.13, 7.58); p<0.001	7.21 (3.84, 13.54); p<0.001	12.96 (6.91, 24.32); p<0.001	reference
Proportion Achieving HbA1c≤6.5%										
Week 26										
%	35.9	47.5	63.8	17.9	39	7.7	24 (13.6)	45 (25.9)	74 (42.8)	6 (3.4)

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	4.55 (1.75, 11.84); p=0.002	12.05 (4.77, 30.45); p<0.001	25.92 (10.34, 64.95); p<0.001	reference
Week 52										
%	*N/A*				*N/A*		20 (11.6)	33 (19.5)	65 (38.7)	4 (2.3)
OR (95% CI); p-value							5.07 (1.68, 15.26); p=0.004	10.34 (3.53, 30.30); p<0.001	28.27 (9.82, 81.36); p<0.001	reference
Proportion with HbA1c<7.0% without Hypoglycemia or Weight Gain										
Week 26										
%	37.1	56.9	68.8	23.2	51	17	18.2	27.0	43.9	2.3
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	9.41 (3.20, 27.68); p<0.001	17.54 (6.04, 50.95); p<0.001	37.73 (13.10, 108.70); p<0.001	reference
Week 52										
%	*N/A*				*N/A*		15.6	25.4	36.3	4.7
OR (95% CI); p-value							3.82 (1.66, 8.82); p=0.002	7.49 (3.34, 16.82); p<0.001	13.50 (6.08, 30.00); p<0.001	reference
Change in Body Weight, kg										
Week 26										
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										
Mean change	*N/A*				*N/A*		-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										
%	19.6	26.9	41.3	14.9	35.7	9.7	13.0	30.5	38.7	2.8
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	4.23 (1.57, 11.35); p=0.004	12.87 (5.01, 33.05); p<0.001	18.68 (7.30, 47.77); p<0.001	reference
Week 52										
%	*N/A*				*N/A*		17.2	28.1	39.4	5.2
OR (95% CI); p-value							3.63 (1.66, 7.93); p=0.0012	7.12 (3.35, 15.12); p<0.0001	11.96 (5.69, 25.14); p<0.0001	reference
Proportion with Weight Loss≥10.0%										
Week 26										
%	2.4	8.1	14.4	1.2	8.4	0	2 (1.1)	12 (6.9)	19 (11.0)	1 (0.6)
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	1.41 (0.20, 9.88); p=0.730	8.68 (1.70, 44.35); p=0.009	12.92 (2.59, 64.39); p=0.002	reference
Week 52										
%	*N/A*				*N/A*		4 (2.3)	17 (9.9)	21 (12.4)	1 (0.6)
OR (95% CI); p-value							2.85 (0.48, 17.04); p=0.2514	13.48 (2.67, 68.08); p=0.0016	17.71 (3.55, 88.25); p=0.0005	reference
Proportion with HbA1c reduction ≥1.0% and Weight Loss≥3.0%										
Week 26										
%	18	36.9	50.6	10.7	39	7.7	28 (15.9)	51 (29.3)	76 (43.9)	7 (4.0)
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	4.57 (1.93, 10.81); p<0.001	9.90 (4.33, 22.64); p<0.001	18.56 (8.19, 42.03); p<0.001	reference
Week 52										
%	*N/A*				*N/A*		20 (11.6)	37 (21.9)	64 (38.1)	5 (2.9)

OR (95% CI); p-value							4.23 (1.54, 11.58); p=0.005	9.11 (3.47, 23.90); p<0.001	20.10 (7.80, 51.81); p<0.001	reference
Change in Body Mass Index, kg/m²										
Week 26										
Mean change	-0.5	-0.8	-1.4	-0.5	-1.2	-0.3	-0.5	-0.9	-1.4	-0.1
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	-0.4 (-0.7, -0.0); p=0.024	-0.8 (-1.1, -0.4); p<0.001	-1.2 (-1.5, -0.9); p<0.001	reference
Week 52										
Mean change	*N/A*				*N/A*		-0.3	-0.7	-1.4	0.2
ETD (95% CI), p-value							-0.5 (-0.9, -0.1); p=0.006	-1.0 (-1.3, -0.6); p<0.001	-1.6 (-2.0, -1.3); p<0.001	reference
Change in Fasting Plasma Glucose, mg/dL or mmol/L (noted)										
Week 26										
Mean change	-16.2 mg/dL	-27.9	-32.9	-3.2	-1.5 mmol/L	-0.4	-0.22, mmol/L	-1.08	-1.33	0.29
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	-0.52 (-1.08, 0.04); p=0.070	-1.38 (-1.93, -0.83); p<0.001	-1.62 (-2.17, -1.07); p<0.001	reference
Week 52										
Mean change	*N/A*				*N/A*		-0.66	-1.03	-1.58	-0.13
ETD (95% CI), p-value							-0.53 (-1.05, -0.01); p=0.045	-0.90 (-1.42, -0.39); p<0.001	-1.45 (-1.96, -0.94); p<0.001	reference
Change in Seven-point Self-Measured Whole-Blood Glucose, mg/dL or mmol/L (noted)										
Week 26										
Mean change	-30.1 mg/dL	-35.5	-40.1	-7.5	*NR*		-1.1, mmol/L	-1.7	-1.9	-0.3

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			-0.8 (-1.3, -0.3); p=0.006	-1.4 (-1.8, -0.9); p<0.001	-1.7 (-2.1, -1.2); p<0.001	reference
Week 52										
Mean change	*N/A*				*N/A*		-1.5	-1.6	-2.0	-0.8
ETD (95% CI), p-value							-0.6 (-1.2, -0.1); p=0.016	-0.8 (-1.3, -0.3); p=0.004	-1.1 (-1.7, -0.6); p<0.001	reference
Change in Systolic Blood Pressure (mmHg)										
Week 26										
Mean change	-3	-3	-5	-3	-7	0	-1	-3	-3	1
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	-3 (-6, 0); p=0.070	-4 (-7, -1); p=0.006	-4 (-7, -1); p=0.005	reference
Week 52										
Mean change	*N/A*				*N/A*		-1	-2	-4	-0
ETD (95% CI), p-value							-0 (-3, 2); p=0.841	-2 (-4, 1); p=0.207	-4 (-7, -1); p=0.004	reference
Change in Diastolic Blood Pressure (mmHg)										
Week 26										
Mean change (SE)	-1	-1	-1	-1	-2	1	0	-1	-1	0
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	-0 (-2, 1); p=0.805	-1 (-3, 0); p=0.149	-2 (-3, 0); p=0.068	reference
Week 52										
Mean change (SE)	*N/A*				*N/A*		-1	-2	-2	-1
ETD (95% CI), p-value							-1 (-2, 1); p=0.4954	-1 (-3, 1); p=0.3230	-1 (-3, 0); p=0.0799	reference
Total Cholesterol—Ratio to Baseline										
Week 26										
Ratio to baseline	0.98	0.99	0.95	1	0.96	1	0.99	0.95	0.95	1.03

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	0.96 (0.92, 0.99); p=0.014	0.92 (0.89, 0.95); p<0.001	0.92 (0.89, 0.96); p<0.001	reference
Week 52										
Ratio to baseline	*N/A*				*N/A*		0.97	0.97	0.95	1.01
ETR (95% CI), p-value							0.96 (0.93, 1.00); p=0.046	0.96 (0.93, 1.00); p=0.048	0.95 (0.91, 0.98); p=0.003	reference
LDL-C—Ratio to Baseline										
Week 26										
Ratio to baseline	0.95	0.98	0.93	0.99	0.97	0.99	0.97	0.94	0.94	1.04
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	0.94 (0.88, 0.99); p=0.023	0.91 (0.85, 0.96); p<0.001	0.90 (0.85, 0.96); p<0.001	reference
Week 52										
Ratio to baseline	*N/A*				*N/A*		0.96	0.97	0.96	1.00
ETR (95% CI), p-value							0.95 (0.90, 1.01); p=0.102	0.97 (0.91, 1.03); p=0.331	0.96 (0.90, 1.01); p=0.140	reference
HDL-C—Ratio to Baseline										
Week 26										
Ratio to baseline	1.03	1.05	1.02	1.03	1.02	1.02	1.00	0.98	0.98	1.02
ETR (95% CI), p-value	1.00 (0.97 , 1.03) p=0.83	1.03 (0.99, 1.06) p=0.10	1.00 (0.97 , 1.03) p=0.88	reference	1.01 (0.97, 1.04) p= 0.7391	reference	0.98 (0.95, 1.01); p=0.228	0.96 (0.94, 0.99); p=0.015	0.97 (0.94, 1.00); p=0.037	reference
Week 52										
Ratio to baseline	*N/A*				*N/A*		1.01	0.98	1.01	1.00
ETR (95% CI), p-value							1.01 (0.98, 1.04); p=0.588	0.97 (0.94, 1.01); p=0.121	1.00 (0.97, 1.04); p=0.809	reference
Triglycerides—Ratio to Baseline										
Week 26										

Ratio to baseline	1.01	0.92	0.9	0.99	0.86	0.96	0.98	0.91	0.92	0.98
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	1.00 (0.92, 1.08); p=0.918	0.93 (0.86, 1.01); p=0.083	0.93 (0.86, 1.01); p=0.101	reference
Week 52										
Ratio to baseline	*N/A*				*N/A*		0.93	0.93	0.86	0.97
ETR (95% CI), p-value							0.96 (0.88, 1.04); p=0.299	0.96 (0.88, 1.04); p=0.333	0.89 (0.82, 0.97); p=0.006	reference
eGFR—Ratio to Baseline										
Week 26										
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)	0.99 (11.0)	0.99 (8.6)	0.99 (10.0)	1.01 (10.1)
Week 52										
Geometric mean (CV)	*N/A*				*N/A*		1.00 (10.7)	1.00 (10.4)	0.98 (9.1)	0.99 (11.9)
Proportion on Rescue Medication										
Week 26										
%	*NR*				*NR*	*NR*	5 (2.7)	2 (1.1)	4 (2.2)	9 (4.9)
Week 52										
%	*N/A*				*N/A*		54 (29.3)	33 (18.1)	31 (17.1)	67 (36.4)
Overall										
%	13 (7.4)	4 (2.3)	2 (1.1)	27 (15.2)	7 (4.3)	16 (9.9)	74 (40.2)	67 (36.8)	66 (36.5)	84 (45.7)
Proportion on Additional Glucose-Lowering Medication										
Week 26										
%	16 (9.1)	8 (4.6)	7 (4.0)	35 (19.7)	12 (7.4)	21 (13.0)	9 (4.9)	8 (4.4)	8 (4.4)	11 (6.0)
Week 52										
%	*N/A*				*N/A*		61 (33.2)	45 (24.7)	44 (24.3)	75 (40.8)
All-Cause Discontinuation of Trial Product										
End of trial										
%	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										
%	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 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	410		409		466		464		465		466		285		284		142		253		250	
Week	52		52		78		78		78		78		52		52		52		52		52	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any AE	289	70.5	283	69.2	370	79.4	363	78.2	370	76.9	388	83.3	229	80	211	74	95	67	197	78	172	69
SAE	27	6.6	37	9.0	64	13.7	47	10.1	44	9.5	58	12.4	31	11	22	8	15	11	24	9	24	10
Death	0	0	1	0.2	5	1.1	3	0.6	1	0.2	3	0.6	3	1.1	4	1.4	1	0.7	0	0	1	0.4
Mild AE	242	59.0	240	58.7	232	69.3	318	68.5	321	69	340	73	192	67	180	63	87	61	167	66	144	58
Moderate AE	140	34.1	118	28.9	186	39.9	171	36.9	199	42.8	197	42.3	120	42	102	36	32	23	104	41	75	30
Severe AE	24	5.9	23	5.6	47	10.1	37	8	40	8.6	53	11.4	23	8	22	8	7	5	16	6	18	7
AE leading to d/c	44	10.7	18	4.4	26	5.6	27	5.8	54	11.6	24	5.2	31	11	26	9	5	4	22	9	8	3
GI AE leading to d/c	33	8.0	3	0.7	11	2.4	16	3.4	32	6.9	12	2.6	22	8	17	6	3	2	14	6	2	1
Hypoglycemia	7	1.7	8	2.0	2.3	4.9	24	5.2	36	7.7	39	8.4	2	1	7	2	3	2	14	5.5	14	5.6
Severe hypoglycemia	1	0.2	1	0.2	0	0	0	0	1	0.2	4	0.9	0	0	0	0	0	0	0	0	0	0
Nausea	81	19.8	10	2.4	34	7.3	62	13.4	70	15.1	62	6.9	56	20	51	18	5	4	53	21	6	2
Diarrhea	38	9.3	13	3.2	45	9.7	53	11.4	57	12.3	37	7.9	43	15	31	11	11	8	22	9	8	3
Nasopharyn-gitis	—	—	—	—	53	11.4	49	10.6	47	10.1	47	10.1	41	14	37	13	15	11	26	10	13	5
Vomiting	30	7.3	7	1.7	13	2.8	28	6	42	9	19	4.1	25	9	13	5	3	2	14	6	2	1
Headache	—	—	—	—	29	6.2	30	6.5	37	8	36	7.7	27	9	17	6	9	6	25	10	15	6
Decreased appetite	21	5.1	2	0.5	8	1.7	14	3	32	6.9	14	3	16	6	20	7	0	0	—	—	—	—
Upper respiratory tract infection	—	—	—	—	36	7.7	35	7.5	26	5.6	32	6.9	—	—	—	—	—	—	9	4	15	6
Hypertension	—	—	—	—	30	6.4	24	5.2	26	5.6	29	6.2	—	—	—	—	—	—	—	—	—	—
Back pain	—	—	—	—	24	5.2	25	5.4	25	5.4	29	6.2	11	4	18	6	5	4	—	—	—	—

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	
Urinary tract infection	—	—	—	—	30	6.4	21	4.5	23	4.9	26	5.6	—	—	—	—	—	—	—	—	—	—
Arthralgia	—	—	—	—	22	4.7	14	3	21	4.5	30	6.4	—	—	—	—	—	—	—	—	—	—
Influenza	8	2.0	21	5.1	30	6.4	25	5.4	18	3.9	30	6.4	—	—	—	—	—	—	—	—	—	—
Diabetic retinopathy	13	3.2	4	1.0	27	5.8	24	5.2	16	3.4	27	5.8	8	2.8	3	1.1	2	1.4	3	1.2	4	1.6

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. Key Safety Parameters 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		Placebo		SEM 3mg		SEM 7mg		SEM 14mg		PBO	
N	175		175		175		175		163		161		184		181		181		184	
Week	26		26		26		26		26		26		52		52		52		52	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any AE	101	57.7	93	53.1	99	56.6	99	55.6	120	74	105	65	137	74.5	142	78.5	151	83.4	139	75.5
SAE	5	2.9	3	1.7	2	1.1	8	4.5	17	10	17	11	25	13.6	19	10.5	12	6.6	17	9.2
Death	0	0	0	0	0	0	0	0	1	1	2	1	0	0	0	0	3	1.7	0	0
Mild AE	89	50.9	84	48	81	46.3	81	45.5	106	65	89	55	NR	NR	NR	NR	NR	NR	NR	NR
Moderate AE	40	22.9	29	16.6	34	19.4	47	26.4	61	37	42	26	NR	NR	NR	NR	NR	NR	NR	NR
Severe AE	8	4.6	1	0.6	3	1.7	5	2.8	10	6	15	9	NR	NR	NR	NR	NR	NR	NR	NR
AE leading to d/c	4	2.3	7	4	13	7.4	4	2.2	24	15	8	5	13	7.1	16	8.8	24	13.3	5	2.7
GI AE leading to d/c	3	1.7	4	2.3	9	5.1	1	0.6	19	12	3	2	9	4.9	12	6.6	19	10.5	1	0.5
Hypoglycemia	5	2.9	2	1.1	1	0.6	1	0.6	9	6	3	2	52	28.3	47	26.0	48	26.5	54	29.3
Severe hypoglycemia	0	0	1	0.6	0	0	0	0	0	0	0	0	5	2.7	1	0.6	2	1.1	1	0.5
Nausea	14	8	9	5.1	28	16	10	5.6	31	19	12	7	21	11.4	30	16.6	42	23.2	13	7.1
Diarrhea	15	8.6	9	5.1	9	5.1	4	2.2	17	10	6	4	16	8.7	22	12.2	27	14.9	11	6.0
Nasopharyn-gitis	10	5.7	11	6.3	3	1.7	6	3.4	—	—	—	—	27	14.7	21	11.6	18	9.9	27	14.7
Vomiting	5	2.9	8	4.6	12	6.9	4	2.2	19	12	2	1	11	6.0	14	7.7	18	9.9	7	3.8
Headache	6	3.4	10	5.7	9	5.1	9	5.1	10	6	8	5	—	—	—	—	—	—	—	—
Decreased appetite	2	1.1	3	1.7	9	5.1	1	0.6	11	7	0	0	8	4.3	18	9.9	23	12.7	2	1.1
Upper respiratory tract infection	—	—	—	—	—	—	—	—	—	—	—	—	8	4.3	6	3.3	13	7.2	13	7.1
Hypertension	—	—	—	—	—	—	—	—	—	—	—	—	3	1.6	4	2.2	1	0.6	11	6.0
Back pain	—	—	—	—	—	—	—	—	1	1	9	6	—	—	—	—	—	—	—	—

Trial	PIONEER 1								PIONEER 5				PIONEER 8							
Arm	SEM 3 mg		SEM 7 mg		SEM 14 mg		PBO		SEM 14 mg		Placebo		SEM 3mg		SEM 7mg		SEM 14mg		PBO	
Urinary tract infection	—	—	—	—	—	—	—	—	—	—	—	—	6	3.3	5	2.8	10	5.5	7	3.8
Constipation	—	—	—	—	—	—	—	—	19	12	6	4	8	4.3	15	8.3	12	6.6	5	2.7
Dyspepsia	—	—	—	—	—	—	—	—	16	10	2	1	—	—	—	—	—	—	—	—
Influenza	9	5.1	5	2.9	4	2.3	2	1.1	—	—	—	—	—	—	—	—	—	—	—	—
Diabetic retinopathy	1	0.6	6	3.4	2	1.1	3	1.7	2	1.2	2	1.2	7	3.8	8	4.4	9	5.0	8	4.3

*PIONEER 6 results are presented alongside other included CVOTs.

AE: adverse event, d/c: discontinuation, GI: gastrointestinal, mg: milligram, PBO: placebo, SAE: serious adverse event, SEM: semaglutide

Table D9. 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	None	≥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 90 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
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

	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
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%	17.0%	18.7%	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%	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					
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)

	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 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 D10. Key Safety Parameters in Cardiovascular Outcomes Trials

	PIONEER 6		SUSTAIN 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
Hypoglycemia	NR	NR	22.4	21.2	43.7	45.6	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	0.1	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

Table D11. 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 D12. 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 D13. 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 D14. 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 D15. 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 D16. 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 D17. 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 D18. 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

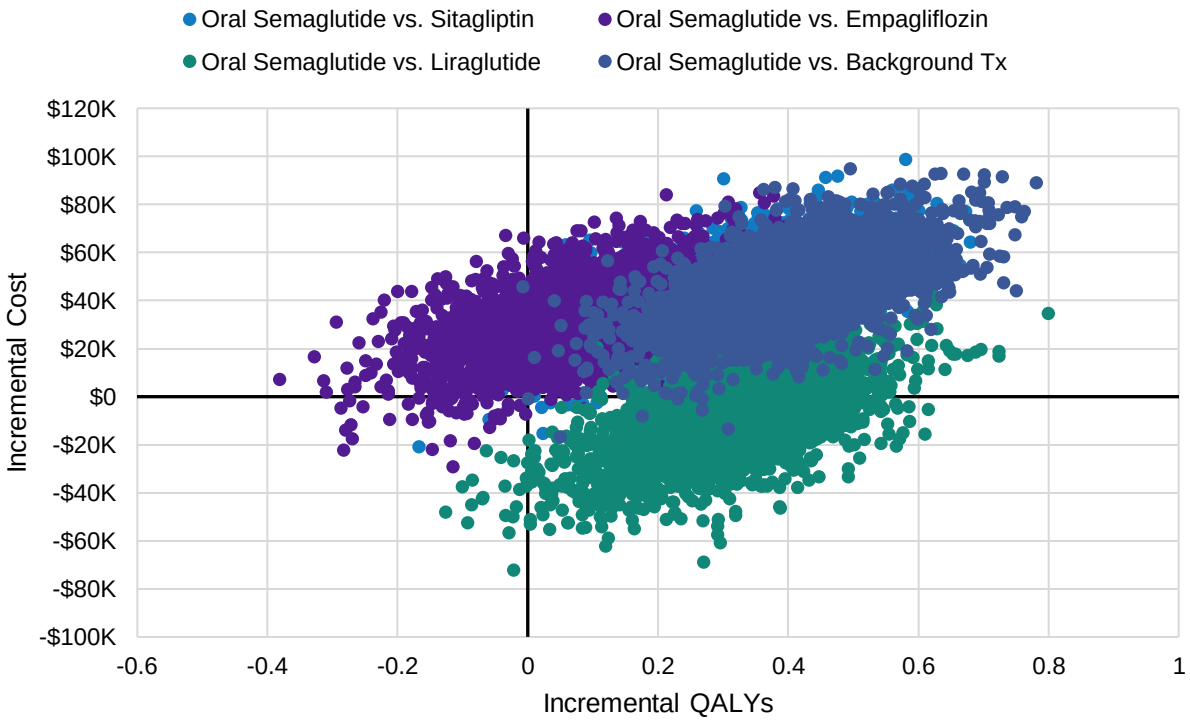
Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health outcomes	Longevity effects	X	X	
	Health-related quality of 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	X	☐	
	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.[97]

Additional Sensitivity Analysis Results

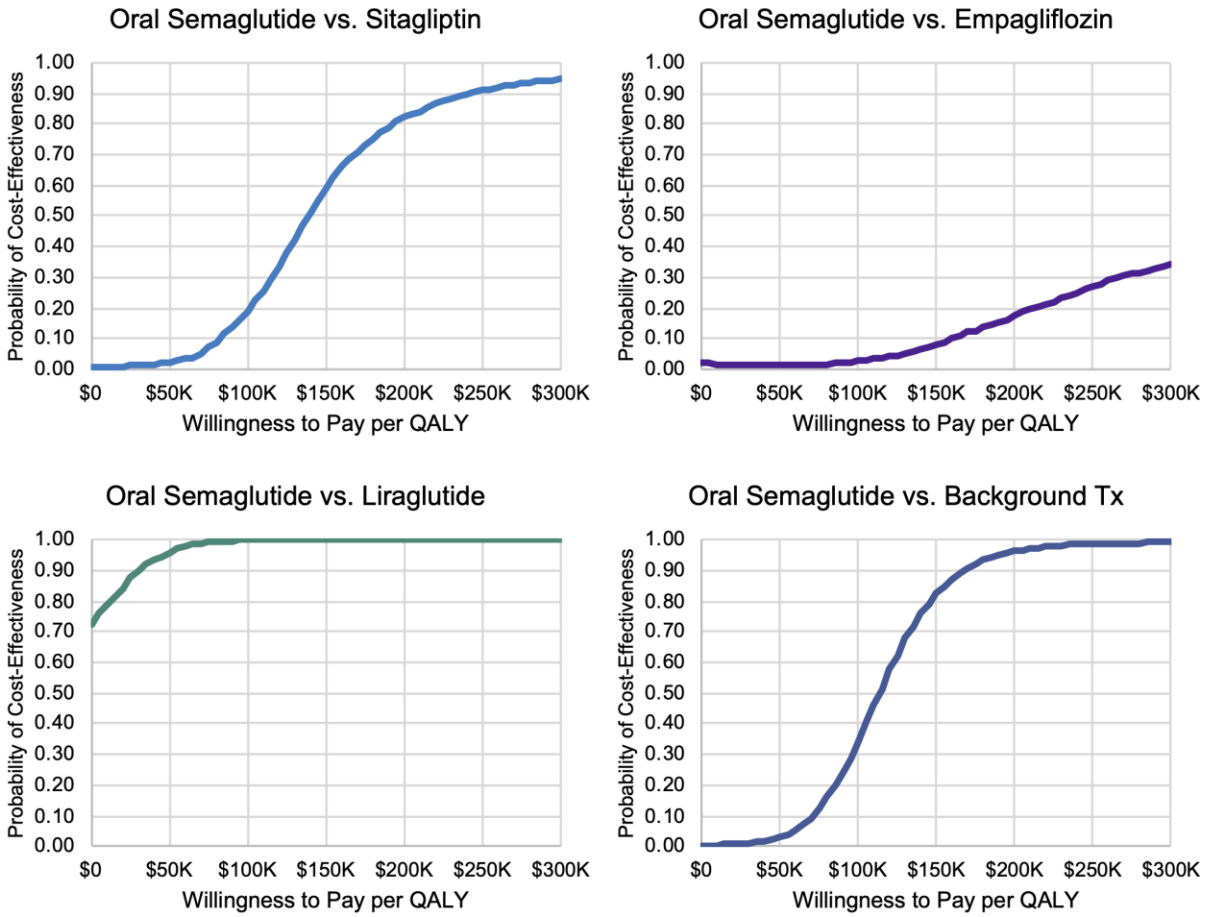
Figure E1. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds



QALY: quality-adjusted life year

Results use an assumed annual net price of $6103 for oral semaglutide.

Figure E2. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Acceptability Curves for Oral Semaglutide versus Each Comparator



QALY: quality-adjusted life year, Tx: treatment
Results use an assumed annual net price of $6103 for oral semaglutide.

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	$295,360	($272,020 - $320,750)	$253,805	($231,403 - $277,454)	$262,538	($239,787 - $287,162)	$305,457	($280,957 - $331,287)	$249,839	($227,367 - $273,127)
Add-on Agent	$45,859	($43,003 - $48,801)	$4,836	($4,504 - $5,181)	$16,284	($15,407 - $17,225)	$60,155	($56,589 - $63,957)	$0	($ - $)
Background Tx	$1,477	($1,400 - $1,554)	$1,383	($1,309 - $1,456)	$1,457	($1,384 - $1,533)	$1,456	($1,383 - $1,532)	$1,362	($1,290 - $1,434)
Insulin	$10,253	($9,398 - $11,135)	$10,198	($9,346 - $11,085)	$10,459	($9,617 - $11,407)	$10,590	($9,716 - $11,495)	$11,115	($10,226 - $11,979)
Healthcare	$4,734	($4,481 - $4,978)	$4,441	($4,201 - $4,682)	$4,676	($4,438 - $4,933)	$4,675	($4,434 - $4,928)	$4,397	($4,166 - $4,634)
CHF	$9,867	($8,437 - $11,287)	$9,268	($7,911 - $10,622)	$7,729	($6,471 - $9,035)	$7,911	($6,615 - $9,135)	$9,270	($7,874 - $10,638)
IHD	$4,676	($3,740 - $5,595)	$4,283	($3,387 - $5,203)	$4,494	($3,606 - $5,425)	$4,135	($3,338 - $4,943)	$4,212	($3,388 - $5,163)
MI	$16,505	($13,869 - $19,291)	$18,251	($15,597 - $20,973)	$17,250	($14,628 - $19,948)	$16,914	($14,369 - $19,649)	$18,628	($15,869 - $21,383)
Stroke	$27,310	($22,295 - $32,404)	$28,195	($23,306 - $33,400)	$28,403	($23,472 - $33,964)	$28,066	($22,956 - $33,470)	$28,643	($23,734 - $33,817)
Blindness	$963	($541 - $1,480)	$904	($502 - $1,398)	$981	($553 - $1,467)	$934	($508 - $1,453)	$955	($535 - $1,430)
Foot Ulcer	$295	($184 - $426)	$297	($189 - $433)	$309	($195 - $457)	$308	($190 - $448)	$320	($200 - $460)
Amputation	$2,439	($1,830 - $3,120)	$2,343	($1,769 - $3,002)	$2,555	($1,954 - $3,243)	$2,487	($1,886 - $3,157)	$2,505	($1,890 - $3,196)
Renal Disease	$145,603	($126,073 - $166,212)	$145,045	($124,334 - $165,644)	$142,452	($122,874 - $163,687)	$142,301	($122,801 - $163,310)	$143,095	($123,150 - $164,041)
Hypoglycemia	$25,379	($22,950 - $27,938)	$24,359	($21,997 - $26,872)	$25,488	($23,060 - $28,067)	$25,526	($23,120 - $28,045)	$25,338	($22,897 - $27,844)
Survival										
QALYs	4.03	(3.84 - 4.22)	3.73	(3.55 - 3.91)	3.97	(3.79 - 4.15)	3.72	(3.55 - 3.90)	3.63	(3.46 - 3.80)
Life Years	8.18	(7.75 - 8.59)	7.66	(7.27 - 8.06)	8.07	(7.68 - 8.49)	8.06	(7.67 - 8.47)	7.55	(7.16 - 7.94)
Complications										
CHF	29.4%	(25.1% - 34.0%)	27.6%	(23.3% - 32.0%)	22.8%	(18.5% - 27.1%)	23.5%	(19.3% - 27.3%)	27.7%	(23.5% - 32.0%)
IHD	12.7%	(9.4% - 16.0%)	11.6%	(8.6% - 14.9%)	12.0%	(8.8% - 15.5%)	13.3%	(9.7% - 17.1%)	11.4%	(8.3% - 14.6%)

1st MI	22.8%	(18.8% - 26.5%)	25.3%	(21.4% - 29.3%)	23.8%	(19.9% - 27.6%)	23.2%	(19.3% - 27.1%)	25.8%	(21.8% - 29.8%)
Subs. MI	4.1%	(2.2% - 6.4%)	4.7%	(2.8% - 6.9%)	4.4%	(2.5% - 6.6%)	4.3%	(2.5% - 6.6%)	4.8%	(2.8% - 6.9%)
1st Stroke	23.3%	(19.3% - 27.6%)	25.7%	(21.5% - 30.1%)	25.2%	(21.0% - 29.6%)	24.8%	(20.7% - 29.3%)	26.4%	(22.4% - 30.7%)
Subs. Stroke	9.7%	(5.2% - 16.0%)	10.1%	(5.8% - 15.7%)	10.0%	(5.5% - 16.3%)	9.9%	(5.5% - 15.5%)	10.1%	(5.8% - 15.7%)
Blindness	8.3%	(5.5% - 11.3%)	8.1%	(5.2% - 10.9%)	8.4%	(5.8% - 11.3%)	8.0%	(5.5% - 11.0%)	8.5%	(5.7% - 11.3%)
Foot Ulcer	17.2%	(10.5% - 25.7%)	16.8%	(10.5% - 25.4%)	17.9%	(11.0% - 27.1%)	17.8%	(10.8% - 26.2%)	17.9%	(11.0% - 26.5%)
1st Amp, No Ulc	17.0%	(13.3% - 20.7%)	16.3%	(12.7% - 19.9%)	17.7%	(13.9% - 21.8%)	17.4%	(13.7% - 21.3%)	17.1%	(13.5% - 21.0%)
1st Amp, Ulcer	3.7%	(1.9% - 5.8%)	3.5%	(1.9% - 5.5%)	3.7%	(1.9% - 5.8%)	3.7%	(1.9% - 5.8%)	3.6%	(1.9% - 5.8%)
Subs. Amp	14.6%	(7.5% - 24.0%)	13.0%	(6.9% - 21.5%)	15.2%	(8.3% - 24.3%)	14.3%	(7.7% - 22.7%)	14.0%	(7.5% - 22.5%)
Renal Disease	13.0%	(9.9% - 16.3%)	14.8%	(11.6% - 18.2%)	12.4%	(9.4% - 15.5%)	12.4%	(9.4% - 15.5%)	14.6%	(11.3% - 18.0%)
CV Death	7.3%	(4.7% - 9.9%	9.4%	(6.6% - 12.2%)	9.0%	(6.4% - 11.6%)	9.4%	(6.6% - 12.2%)	9.6%	(6.9% - 12.4%)

Results use an assumed annual net price of $6103 for oral semaglutide.

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)	$138,658	($44,186 - $398,415)	$484,635	(-$2,445,316 - $3,161,171)	-$32,613	(-$421,236 - $61,772)	$112,988	($45,325 - $215,823)
ICER (Life Years)	$79,637	(-$48,328 - $293,091)	$288,542	(-$1,311,199 - $1,639,191)	-$85,513	(-$823,128 - $911,828)	$71,505	($24,655 - $214,067)
Total Cost	$41,555	($10,163 - $72,729)	$32,822	($2,055 - $64,067)	-$10,098	(-$43,198 - $22,960)	$45,520	($14,387 - $77,615)
Add-on Agent	$41,022	($38,163 - $43,891)	$29,574	($26,693 - $32,541)	-$14,296	(-$19,143 - - $9,973)	$45,859	($43,003 - $48,801)
Background Tx	$94	(-$7 - $195)	$21	(-$79 - $115)	$21	(-$83 - $116)	$115	($14 - $213)
Insulin	$56	(-$1,086 - $1,186)	-$206	(-$1,340 - $861)	-$337	(-$1,460 - $822)	-$862	(-$2,021 - $271)
Healthcare	$294	(-$34 - $623)	$58	(-$264 - $364)	$60	(-$276 - $379)	$337	($9 - $659)
CHF	$599	(-$1,170 - $2,323)	$2,137	($444 - $3,801)	$1,956	($297 - $3,607)	$597	(-$1,137 - $2,338)
IHD	$393	(-$859 - $1,652)	$182	(-$1,064 - $1,456)	$541	(-$657 - $1,677)	$464	(-$845 - $1,664)
MI	-$1,746	(-$5,053 - $1,537)	-$745	(-$4,155 - $2,724)	-$409	(-$3,701 - $2,921)	-$2,123	(-$5,503 - $1,323)
Stroke	-$885	(-$7,527 - $5,344)	-$1,093	(-$8,156 - $5,468)	-$756	(-$7,694 - $6,091)	-$1,333	(-$8,174 - $5,283)
Blindness	$59	(-$591 - $710)	-$18	(-$662 - $618)	$29	(-$602 - $671)	$8	(-$597 - $656)
Foot Ulcer	-$2	(-$142 - $136)	-$14	(-$151 - $123)	-$13	(-$150 - $119)	-$25	(-$164 - $110)
Amputation	$96	(-$662 - $886)	-$116	(-$896 - $676)	-$48	(-$783 - $723)	-$66	(-$839 - $703)
Renal Disease	$557	(-$24,555 - $26,032)	$3,151	(-$22,535 - $28,881)	$3,302	(-$23,231 - $29,567)	$2,508	(-$22,700 - $27,884)
Hypoglycemia	$1,020	(-$2,265 - $4,338)	-$109	(-$3,484 - $3,133)	-$147	(-$3,494 - $3,150)	$41	(-$3,330 - $3,394)
Survival								

QALYs	0.30	(0.06 - 0.54)	0.07	(-0.17 - 0.30)	0.31	(0.06 - 0.54)	0.40	(0.16 - 0.64)
Life Years	0.52	(-0.05 - 1.07)	0.11	(-0.43 - 0.63)	0.12	(-0.45 - 0.65)	0.64	(0.08 - 1.18)
Complications								
CHF	1.8%	(-3.9% - 7.2%)	6.6%	(1.1% - 12.0%)	6.0%	(0.8% - 11.3%)	1.8%	(-3.6% - 7.2%)
IHD	1.1%	(-3.6% - 5.5%)	0.7%	(-3.9% - 5.0%)	-0.7%	(-5.5% - 4.0%)	1.3%	(-3.3% - 5.5%)
1st MI	-2.5%	(-7.5% - 2.5%)	-1.1%	(-5.8% - 3.9%)	-0.4%	(-5.2% - 4.4%)	-3.1%	(-8.0% - 1.9%)
Subs. MI	-0.6%	(-3.6% - 2.2%)	-0.3%	(-3.0% - 2.5%)	-0.2%	(-3.0% - 2.8%)	-0.7%	(-3.6% - 2.2%)
1st Stroke	-2.4%	(-8.0% - 3.0%)	-1.9%	(-7.2% - 3.9%)	-1.5%	(-6.9% - 3.9%)	-3.1%	(-8.6% - 2.4%)
Subs. Stroke	-0.4%	(-6.9% - 5.8%)	-0.4%	(-6.6% - 6.1%)	-0.2%	(-6.6% - 6.1%)	-0.4%	(-6.6% - 6.1%)
Blindness	0.3%	(-3.3% - 4.1%)	-0.1%	(-3.6% - 3.6%)	0.3%	(-3.3% - 4.1%)	-0.2%	(-3.9% - 3.6%)
Foot Ulcer	0.3%	(-8.3% - 8.8%)	-0.7%	(-9.7% - 8.3%)	-0.6%	(-9.1% - 8.0%)	-0.8%	(-9.4% - 8.0%)
1st Amp, No Ulc	0.7%	(-3.9% - 5.2%)	-0.7%	(-5.5% - 3.9%)	-0.4%	(-5.0% - 3.9%)	-0.1%	(-5.0% - 4.4%)
1st Amp, Ulcer	0.1%	(-2.2% - 2.5%)	-0.1%	(-2.5% - 2.2%)	-0.1%	(-2.5% - 2.4%)	0.0%	(-2.5% - 2.5%)
Subs. Amp	1.6%	(-8.3% - 11.3%)	-0.6%	(-10.8% - 9.9%)	0.3%	(-9.4% - 10.5%)	0.6%	(-9.4% - 11.0%)
Renal Disease	-1.7%	(-5.2% - 1.7%)	0.7%	(-2.8% - 3.9%)	0.7%	(-2.8% - 4.1%)	-1.6%	(-5.0% - 1.7%)
CV Death	-2.0%	(-5.8% - 1.7%)	-1.6%	(-5.2% - 1.9%)	-2.0%	(-5.8% - 1.7%)	-2.2%	(-6.1% - 1.7%)
Cost per Event Avoided								
MACE*	6.04E+18	(-$6,202,705 - $8,851,858)	3.30E+18	(-$6,000,128 - $7,145,096)	1.08E+18	(-$3,421,402 - $4,226,370)	-1.16E+18	(-$4,881,103 - $6,220,739)
Renal Disease	$1,668,767	(-$12,728,749 - $15,286,917)	-$699,754	(-$12,928,132 - $13,541,312)	$128,236	(-$6,769,931 - $7,335,986)	$1,804,627	(-$13,865,856 - $17,034,905)
Cong. Heart Failure	-$862,499	(-$11,614,018 - $11,516,453)	-$595,450	(-$1,991,496 - $871)	$268,598	(-$478,190 - $1,867,722)	-$949,126	(-$13,102,298 - $10,890,371)
Threshold Price/QALY								
$50,000/QALY	$5,545	($4,316 - $6,798)	$5,486	($4,293 - $6,716)	$6,622	($5,210 - $8,115)	$5,569	($4,377 - $6,808)
$100,000/QALY	$5,852	($4,550 - $7,155)	$5,553	($4,337 - $6,809)	$6,940	($5,428 - $8,496)	$5,983	($4,684 - $7,300)

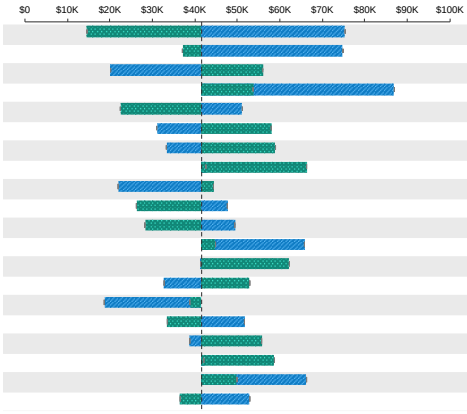
$150,000/QALY	$6,158	($4,799 - $7,531)	$5,621	($4,372 - $6,953)	$7,257	($5,657 - $8,889)	$6,396	($5,002 - $7,861)
Threshold Price/Life Year								
$50,000/LY	$5,775	($4,523 - $7,092)	$5,549	($4,350 - $6,854)	$6,424	($5,058 - $7,883)	$5,807	($4,585 - $7,138)
$100,000/LY	$6,303	($4,834 - $7,976)	$5,674	($4,335 - $7,225)	$6,538	($5,021 - $8,191)	$6,458	($5,023 - $8,047)
$150,000/LY	$6,831	($5,041 - $8,941)	$5,800	($4,121 - $7,715)	$6,653	($4,803 - $8,618)	$7,110	($5,275 - $9,186)

Results use an assumed annual net price of $6103 for oral semaglutide.

*Due to extreme average ratio outliers resulting from individual probabilistic simulations with high incremental cost and low incremental MACE, the cost per MACE avoided ratios presented in the main text of the report were calculated using the average incremental cost divided by the average incremental MACE. The values presented in the above table represent the mean ratios calculated within the probabilistic sensitivity analysis.

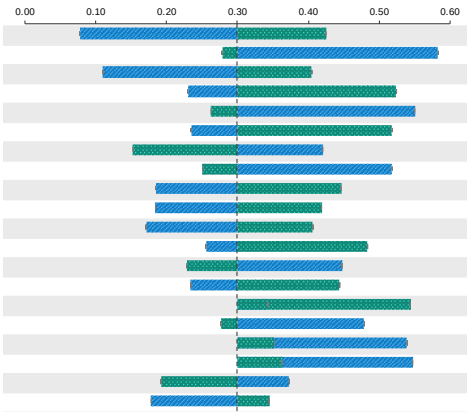
Figure E3. Tornado Diagrams for One-Way Sensitivity Analyses of Oral Semaglutide vs. Sitagliptin

Incremental Cost



Parameter	Low Value	High Value	Low Result	High Result	Spread
Cost (year of event): Foot ulcer	$2,026	$3,039	$75,264	$14,565	$60,700
Cost (event history): Renal Disease	$67,666	$101,499	$74,719	$37,172	$37,548
Cost of Outpatient visit: noninsulin	$440	$659	$20,087	$55,958	$35,871
HbA1c change: Oral Semaglutide	-1.482	-0.988	$86,889	$53,769	$33,120
Mild/Moderate Hypoglycemia (Cycles 2+): Add-on Treati	0.264	0.396	$51,113	$22,526	$28,587
Cost (year of event): Hypoglycemia Requiring ED visit	$1,237	$1,856	$31,033	$58,048	$27,015
Change in insulin dose (IU/kg)	0.140	0.560	$33,341	$58,888	$25,547
Annual Cost: Oral Semaglutide	$4,883	$7,324	$42,667	$66,311	$23,643
MACE HR: Oral Semaglutide HR vs. Background Tx	0.63	0.93	$21,968	$44,477	$22,509
Severe Hypoglycemia (Cycles 2+): Background Treatm	0.040	0.060	$47,673	$26,256	$21,417
Cost (event history): Stroke	$14,663	$21,994	$49,458	$28,281	$21,178
Severe Hypoglycemia (Cycles 2+): Add-on Treatments	0.040	0.060	$65,796	$44,782	$21,014
MACE HR: Sitagliptin HR vs.Oral Semaglutide	1.04	1.63	$41,325	$62,137	$20,812
Annual Cost: Metformin	$155	$233	$32,757	$52,898	$20,141
Cost (year of event): Hypoglycemia Requiring Glucagon	$166	$249	$18,791	$38,896	$20,104
Sev. Hypoglycemia: Oral Semaglutide	0.001	0.002	$51,780	$33,484	$18,296
Annual Cost: Sulfonyuria	$69	$103	$38,810	$55,756	$16,946
Starting insulin dose (IU/kg)	0.210	0.530	$42,137	$58,701	$16,563
Cost (year of event): Congestive heart failure	$22,417	$33,626	$66,251	$49,797	$16,453
Discontinuation (Cycle 1): Sitagliptin	0.039	0.059	$52,902	$36,544	$16,358

Incremental QALYs

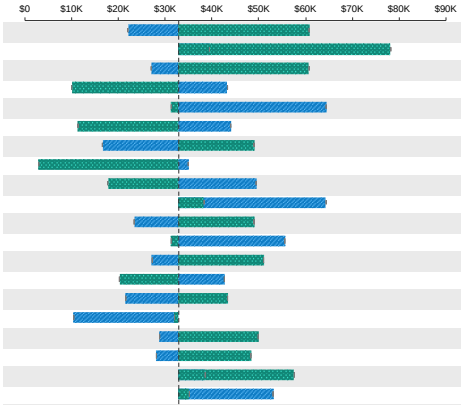


Parameter	Low Value	High Value	Low Result	High Result	Spread
Discontinuation (Cycle 1): Sitagliptin	0.039	0.059	0.08	0.43	0.35
Utility coefficient: Female	-0.051	-0.035	0.58	0.28	0.31
Utility coefficient: Stroke event	-0.273	-0.135	0.11	0.41	0.29
Utility coefficient: Ischemic heart disease history *	-0.026	-0.006	0.23	0.52	0.29
Severe Hypoglycemia (Cycles 2+): Insulin	0.168	0.252	0.55	0.26	0.29
Utility coefficient: Foot ulcer event	-0.034	-0.014	0.23	0.52	0.28
Utility coefficient: Others	-0.024	0.004	0.42	0.15	0.27
Utility coefficient: Myocardial infarction event	-0.073	-0.011	0.52	0.25	0.27
Final insulin dose (IU/kg)	0.450	0.790	0.18	0.45	0.26
Mild/Moderate Hypoglycemia (Cycles 2+): Add-on Treati	0.264	0.396	0.18	0.42	0.24
Utility coefficient: Age at diagnosis (per year ≥52)	-0.003	-0.002	0.17	0.41	0.23
CHF HR: Sitagliptin HR vs.Oral Semaglutide	0.68	1.40	0.26	0.48	0.23
Utility coefficient: Renal disease history	-0.055	0.007	0.45	0.23	0.22
Utility coefficient: Stroke history	-0.117	-0.085	0.23	0.44	0.21
Utility coefficient: BMI (per unit ≥32)	-0.008	-0.007	0.34	0.55	0.20
Severe Hypoglycemia (Cycles 2+): Add-on Treatments	0.040	0.060	0.48	0.28	0.20
Ppn. Insulin Type: Premix	0.496	0.744	0.54	0.35	0.19
HbA1c change: Background Tx	-0.282	-0.188	0.55	0.36	0.18
Severe Hypoglycemia (Cycles 2+): Background Treatm	0.040	0.060	0.37	0.19	0.18
Neph HR: Sitagliptin (no data; =Background Tx)	0.80	1.20	0.18	0.35	0.17

Results use an assumed annual net price of $6103 for oral semaglutide.

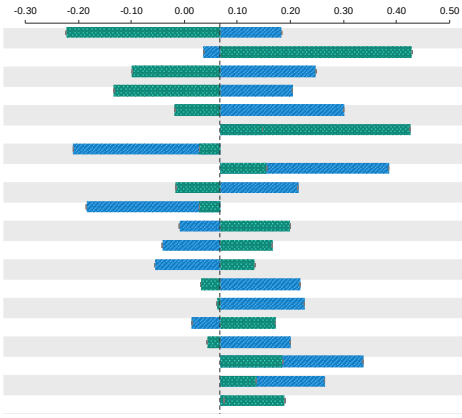
Figure E4. Tornado Diagrams for One-Way Sensitivity Analyses of Oral Semaglutide vs. Empagliflozin

Incremental Cost



Parameter	Low Value	High Value	Low Result	High Result	Spread
Cost (year of event): Hypoglycemia Requiring Glucagon	$166	$249	$22,058	$60,868	$38,809
Weight change: Oral Semaglutide	-4.5 kg	-3.0 kg	$39,481	$78,211	$38,730
Cost (year of event): Stroke	$39,742	$59,612	$27,060	$60,780	$33,720
Cost (event history): Congestive heart failure	$1,797	$2,695	$43,305	$10,064	$33,241
Cost of Outpatient visit: noninsulin	$440	$659	$64,472	$31,304	$33,168
HbA1c change: Background Tx	-0.282	-0.188	$44,119	$11,321	$32,798
Discontinuation (Cycle 1): Oral Semaglutide	0.089	0.133	$16,671	$49,014	$32,343
CHF HR: Empagliflozin HR vs.Oral Semaglutide	0.42	0.95	$35,008	$2,964	$32,044
Change in insulin dose (IU/kg)	0.140	0.560	$49,550	$17,718	$31,832
Annual Cost: Metformin	$155	$233	$64,330	$38,280	$26,050
MACE HR: Empagliflozin HR vs.Oral Semaglutide	0.89	1.44	$23,423	$49,001	$25,579
Annual Cost: Empagliflozin (Jardiance®)	$1,671	$2,506	$55,635	$31,295	$24,340
HbA1c change: Empagliflozin	-1.002	-0.668	$27,161	$51,049	$23,888
Annual Cost: Sulfonyuria	$69	$103	$42,738	$20,283	$22,455
Cost per Insulin Unit: Bolus	$0.23	$0.34	$21,514	$43,328	$21,814
Severe Hypoglycemia (Cycles 2+): Insulin	0.168	0.252	$10,354	$31,891	$21,537
Cost (event history): Myocardial infarction	$1,797	$2,695	$28,745	$50,003	$21,258
Ppn. Insulin Type: Bolus	0.024	0.036	$28,084	$48,345	$20,261
Cost (event history): Renal Disease	$67,666	$101,499	$38,513	$57,593	$19,080
Starting insulin dose (IU/kg)	0.210	0.530	$53,133	$35,128	$18,006

Incremental QALYs

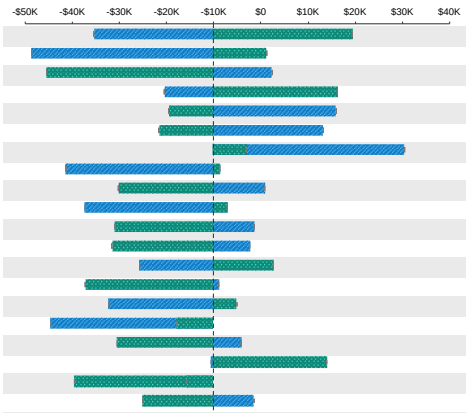


Parameter	Low Value	High Value	Low Result	High Result	Spread
Utility coefficient: Amputation event	-0.108	0.006	0.18	-0.22	0.41
MACE HR: Empagliflozin HR vs.Oral Semaglutide	0.89	1.44	0.04	0.43	0.39
Utility coefficient: Ischemic heart disease history *	-0.026	-0.006	0.25	-0.10	0.35
Ppn. Insulin Type: Basal	0.256	0.384	0.20	-0.13	0.34
Ppn. Insulin Type: Basal plus Bolus	0.024	0.036	0.30	-0.02	0.32
Utility coefficient: Blindness history	-0.075	-0.039	0.15	0.43	0.28
Utility coefficient: Current smoker	-0.066	-0.042	-0.21	0.03	0.24
Utility coefficient: Myocardial infarction history	-0.023	0.001	0.39	0.16	0.23
Utility coefficient: Hypoglycemia event	-0.056	-0.016	0.21	-0.02	0.23
Mild/Moderate Hypoglycemia (Cycles 2+): Add-on Treatr	0.264	0.396	-0.18	0.03	0.21
CHF HR: Oral Semaglutide HR vs. Background Tx	0.76	1.40	-0.01	0.20	0.21
Utility coefficient: Congestive heart failure event	-0.132	-0.046	-0.04	0.17	0.21
Utility coefficient: Stroke history	-0.117	-0.085	-0.06	0.13	0.19
Utility coefficient: Age at diagnosis (per year ≥52)	-0.003	-0.002	0.22	0.03	0.19
Annual Disutility for Tx Injection	-0.065	-0.043	0.23	0.06	0.17
Utility coefficient: Stroke event	-0.273	-0.135	0.01	0.17	0.16
Utility coefficient: Renal disease history	-0.055	0.007	0.20	0.04	0.16
Change in insulin dose (IU/kg)	0.140	0.560	0.34	0.19	0.15
Utility coefficient: Others	-0.024	0.004	0.26	0.14	0.13
Sev. Hypoglycemia: Oral Semaglutide	0.001	0.002	0.08	0.19	0.11

Results use an assumed annual net price of $6103 for oral semaglutide.

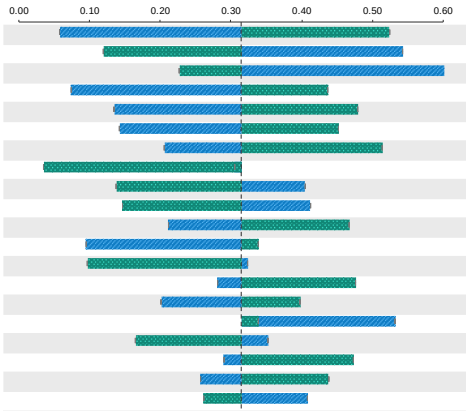
Figure E5. Tornado Diagrams for One-Way Sensitivity Analyses of Oral Semaglutide vs. Liraglutide

Incremental Cost



Parameter	Low Value	High Value	Low Result	High Result	Spread
Annual Cost: Oral Semaglutide	$4,883	$7,324	-$35,402	$19,456	$54,858
Cost (year of event): Hypoglycemia Requiring Hospitaliz	$15,548	$23,322	-$48,718	$1,214	$49,932
Annual Cost: Liraglutide (Victoza®)	$6,410	$9,615	$2,383	-$45,495	$47,877
Severe Hypoglycemia (Cycles 2+): Insulin	0.168	0.252	-$20,411	$16,276	$36,687
Cost per Insulin Unit: Bolus	$0.23	$0.34	$15,985	-$19,532	$35,516
Neph HR: Liraglutide HR vs.Oral Semaglutide	0.85	1.75	$13,221	-$21,585	$34,806
Ppn. Insulin Type: Basal	0.256	0.384	$30,484	-$3,034	$33,517
Cost (year of event): Congestive heart failure	$22,417	$33,626	-$41,441	-$8,704	$32,737
Cost (year of event): Ischemic heart disease	$20,198	$30,297	$832	-$30,149	$30,981
Cost per Insulin Unit: Premix	$0.11	$0.17	-$37,361	-$7,016	$30,345
Starting insulin dose (IU/kg)	0.210	0.530	-$1,365	-$30,997	$29,632
CHF HR: Liraglutide HR vs.Oral Semaglutide	0.59	1.21	-$2,354	-$31,564	$29,210
Cost (event history): Myocardial infarction	$1,797	$2,695	-$25,788	$2,674	$28,462
Ppn. Insulin Type: Premix	0.496	0.744	-$8,880	-$37,227	$28,347
HbA1c change: Background Tx	-0.282	-0.188	-$32,321	-$5,134	$27,187
Change in insulin dose (IU/kg)	0.140	0.560	-$44,595	-$17,856	$26,739
Cost (event history): Ischemic heart disease	$1,797	$2,695	-$4,174	-$30,537	$26,362
HbA1c change: Oral Semaglutide	-1.482	-0.988	-$10,578	$14,014	$24,591
Annual Cost: Sulfonyuria	$69	$103	-$15,742	-$39,653	$23,911
Cost (event history): Renal Disease	$67,666	$101,499	-$1,499	-$25,126	$23,626

Incremental QALYs



Parameter	Low Value	High Value	Low Result	High Result	Spread
Utility coefficient: Renal disease history	-0.055	0.007	0.06	0.52	0.47
Utility coefficient: Hispanic	-0.061	-0.029	0.54	0.12	0.42
MACE HR: Liraglutide HR vs.Oral Semaglutide	0.91	1.43	0.60	0.23	0.38
Utility coefficient: Stroke event	-0.273	-0.135	0.07	0.44	0.36
Utility coefficient: Congestive heart failure history	-0.061	-0.021	0.14	0.48	0.34
Utility coefficient: Hypoglycemia event	-0.056	-0.016	0.14	0.45	0.31
Neph HR: Oral Semaglutide HR vs. Background Tx	0.46	0.89	0.21	0.51	0.31
Utility coefficient: Congestive heart failure event	-0.132	-0.046	0.31	0.04	0.27
Utility coefficient: Amputation event	-0.108	0.006	0.41	0.14	0.27
Annual Disutility for Tx Injection	-0.065	-0.043	0.41	0.15	0.27
Utility coefficient: Ischemic heart disease history	-0.026	-0.006	0.21	0.47	0.26
Discontinuation (Cycle 1): Liraglutide	0.075	0.112	0.09	0.34	0.24
Utility coefficient: BMI (per unit ≥32)	-0.008	-0.007	0.32	0.10	0.23
Utility coefficient: Current smoker	-0.066	-0.042	0.28	0.48	0.20
CHF HR: Liraglutide HR vs.Oral Semaglutide	0.59	1.21	0.20	0.40	0.20
Sev. Hypoglycemia: Liraglutide	0.000	0.000	0.53	0.34	0.19
Severe Hypoglycemia (Cycles 2+): Insulin	0.168	0.252	0.35	0.17	0.19
Utility coefficient: Other Race	-0.024	0.004	0.29	0.47	0.18
Utility coefficient: Blindness history	-0.075	-0.039	0.26	0.44	0.18
Change in insulin dose (IU/kg)	0.140	0.560	0.41	0.26	0.15

Results use an assumed annual net price of $6103 for oral semaglutide.

Additional Scenario Analyses Results

5-year Time Horizon

Limiting the model time horizon to five years resulted in fewer incremental life years and QALYs gained between the comparators (Table 4.14). Therefore, the comparisons between oral semaglutide and the comparators resulted in higher incremental cost-effectiveness ratios due to lack of accounting for long-term patient outcomes.

Table E4. Five-year Time Horizon Results: Oral Semaglutide versus Each Comparator

Comparator	Cost per LY Gained*	Cost per MACE Avoided*	Cost per QALY Gained*
Sitagliptin (Januvia®) + background treatment	$200,000	$330,000	$200,000
Empagliflozin (Jardiance®) + background treatment	$740,000	$630,000	$730,000
Liraglutide (Victoza®) + background treatment	Cost-saving	Cost-saving	Cost-saving
Background treatment alone	$190,000	$290,000	$160,000

LY: life year; QALY: quality-adjusted life year; MACE: major adverse cardiovascular event
*Results use an assumed annual net price of $6103 for oral semaglutide.

Long-Term Duration of Incremental Outcomes

When we gradually reduced the efficacy of oral semaglutide for both MACE and renal outcomes by 5% and 10% per year, this increased the lifetime incidence of MACE and renal outcomes, which led to increased cost and decreased life years and QALYs for oral semaglutide. This also impacted the other add-on agents because MACE and renal outcomes for sitagliptin, empagliflozin, and liraglutide were calculated relative to oral semaglutide (i.e., [baseline UKPDS equation]*[oral semaglutide HR vs. placebo]*[comparator HR vs. oral semaglutide]). In general, incremental cost-effectiveness ratios tended to increase for oral semaglutide versus each comparator, with a greater increase seen in the 10% annual efficacy reduction scenario compared to the 5% annual efficacy reduction scenario. The main text in the report provides scenario analysis estimates where MACE and renal outcomes were adjusted simultaneously. Below are estimates in which MACE and renal efficacy were independently modeled.

Table E5. Annual 5% Efficacy Decline (MACE Only) for Oral Semaglutide

Treatment	Cost per LY Gained*	Cost per MACE Avoided*	Cost per QALY Gained*
Sitagliptin (Januvia®) + background treatment	$90,000	$1,550,000	$150,000
Empagliflozin (Jardiance®) + background treatment	$500,000	$10,720,000	$730,000
Liraglutide (Victoza®) + background treatment	Cost-saving	$1,380,000 (lower cost, lower effectiveness)	Cost-saving
Background treatment alone	$80,000	$1,000,000	$120,000

LY: life year; QALY: quality-adjusted life year; MACE: major adverse cardiovascular event
*Results use an assumed annual net price of $6103 for oral semaglutide.

Table E6. Annual 5% Efficacy Decline (Renal Outcomes Only) for Oral Semaglutide

Treatment	Cost per LY Gained	Cost per MACE Avoided	Cost per QALY Gained
Sitagliptin (Januvia®) + background treatment	$90,000	$740,000	$150,000
Empagliflozin (Jardiance®) + background treatment	$330,000	$950,000	$550,000
Liraglutide (Victoza®) + background treatment	Cost-saving	Cost-saving	Cost-saving
Background treatment alone	$70,000	$650,000	$120,000

LY: life year; QALY: quality-adjusted life year; MACE: major adverse cardiovascular event
*Results use an assumed annual net price of $6103 for oral semaglutide.

Table E7. Annual 10% Efficacy Decline (MACE Only) for Oral Semaglutide

Treatment	Cost per LY Gained	Cost per MACE Avoided	Cost per QALY Gained
Sitagliptin (Januvia®) + background treatment	$100,000	$4,860,000	$170,000
Empagliflozin (Jardiance®) + background treatment	$10,970,000	Dominated	$2,160,000
Liraglutide (Victoza®) + background treatment	Cost-saving	$440,000 (lower cost, lower effectiveness)	Cost-saving
Background treatment alone	$90,000	$1,840,000	$130,000

LY: life year; QALY: quality-adjusted life year; MACE: major adverse cardiovascular event
*Results use an assumed annual net price of $6103 for oral semaglutide.

Table E8. Annual 10% Efficacy Decline (Renal Outcomes Only) for Oral Semaglutide

Treatment	Cost per LY Gained	Cost per MACE Avoided	Cost per QALY Gained
Sitagliptin (Januvia®) + background treatment	$90,000	$680,000	$150,000
Empagliflozin (Jardiance®) + background treatment	$390,000	$810,000	$590,000
Liraglutide (Victoza®) + background treatment	Cost-saving	Cost-saving	Cost-saving
Background treatment alone	$80,000	$580,000	$120,000

LY: life year; QALY: quality-adjusted life year; MACE: major adverse cardiovascular event
*Results use an assumed annual net price of $6103 for oral semaglutide.

Broad Type 2 Diabetes Mellitus Population

We also simulated a broader patient population of all people with T2DM from the NHANES population (n=745), including treating people with a HbA1c below 7.0. This set of simulations indicated similar overall incremental cost-effectiveness ratios compared to the simulations that were restricted to the uncontrolled (HbA1c³7) T2DM population (Table 4.17).

Table E9. Broad Type 2 Diabetes Mellitus Patient Population (n=745) Results: Oral Semaglutide versus Each Comparator

Comparator	Cost per LY Gained*	Cost per MACE Avoided*	Cost per QALY Gained*
Sitagliptin (Januvia®) + background treatment	$80,000	$690,000	$140,000
Empagliflozin (Jardiance®) + background treatment	$320,000	$900,000	$580,000
Liraglutide (Victoza®) + background treatment	Cost-saving	Cost-saving	Cost-saving
Background treatment alone	$70,000	$620,000	$120,000

LY: life year; QALY: quality-adjusted life year; MACE: major adverse cardiovascular event

*Results use an assumed annual net price of $6103 for oral semaglutide.

Undiscounted Results

Table E10. Undiscounted Results for the Base Case for Oral Semaglutide and Comparators

Treatment	Add-On Drug Cost	Complication Cost	Total Cost	MACE*	CHF*	ESRD*	Life Years	QALYs
Oral Semaglutide + background treatment	$58,000	$263,000	$377,000	59.9%	29.4%	13.0%	10.42	4.98
Sitagliptin (Januvia®) + background treatment	$6,000	$262,000	$321,000	65.8%	27.7%	14.7%	9.65	4.57
Empagliflozin (Jardiance®) + background treatment	$21,000	$259,000	$335,000	63.7%	22.9%	12.4%	10.25	4.89
Liraglutide (Victoza®) + background treatment	$76,000	$257,000	$389,000	62.2%	23.4%	12.3%	10.25	4.61
Background treatment alone	--	$260,000	$315,000	67.2%	27.6%	14.6%	9.46	4.43

Results use an assumed annual net price of $6103 for oral semaglutide.

*Differences from the base case are due to randomness in the Monte Carlo simulation

Appendix F. Public Comments

This section includes summaries of the public comments prepared for the New England CEPAC Public Meeting on November 14, 2019, in Providence, RI. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. One speaker did not submit a summary of their public comments.

A video recording of all comments can be found here, beginning at minute 1:25:00. Each of the following speakers are full-time employees of pharmaceutical manufacturers.

Todd Hobbs, MD
Vice President, North America Chief Medical Officer – Diabetes & Obesity
Clinical, Medical, & Regulatory, Novo Nordisk Inc.

Knowing that injectable therapy is a barrier for many patients living with T2D, Novo Nordisk advanced the innovation of diabetes treatment with Rybelsus® to offer a new option for patients. As the first GLP-1RA available by oral delivery, Rybelsus® represents an innovation in peptide-based therapy. With this advancement, Novo Nordisk is able to provide the efficacy and safety of a GLP-1RA in a form that may better address the needs of many patients living with T2D.

Novo Nordisk recognizes the challenges and limitations of conducting this economic analysis, while considering the individualization of care required to treat patients with T2D and integrating all the facets of T2D population characteristics, comparators, and clinical guidelines. Cost-effectiveness, which can be modelled in many different ways, is driven by model assumptions to generate model outputs, most of which are currently highly uncertain. Novo Nordisk agrees with ICER in urging caution in interpreting findings and drawing conclusions between Rybelsus® and the other therapies in consideration.

Regarding the public narratives around the revised evidence report, ensuring accurate and balanced reporting of the limitations of the analysis is imperative to avoid misinterpretation of the conclusions. Novo Nordisk encourages ICER to develop public messaging that reflects the final report and contextualizes the uncertainty in the clinical comparisons.

Thank you for the opportunity to share in this dialogue around the clinical and economic benefits of Rybelsus® to patients, payers, and society. Novo Nordisk is dedicated to ensuring access to innovative therapies that improve quality of life such as Rybelsus®.

Swapnil Rajpathak, MD, MPH, PhD
Executive Director, Center for Observational and Real World Evidence, Merck

Merck welcomes availability of innovative therapies and supports evidence-based value frameworks developed in a transparent manner with broad stakeholder engagement.

Sitagliptin has a well-established clinical profile with real-world use in over 10 million US patients. Oral semaglutide was not cost effective vs. sitagliptin at the thresholds of $100,000 and $150,000 for the 5 year horizon. The lifetime incremental cost-effectiveness ratio (ICER) for this comparison was $140,000. Note that all analyses were conducted without accounting for loss of exclusivity for products, which may have significant impact on the results.

Adherence determines drug effectiveness in the real world. In the PIONEER program, the discontinuation rates related to AEs were higher for oral semaglutide compared to other oral anti-hyperglycemic agents. These were only accounted for in the first year after initiation of therapy. However, differential discontinuation rates may still occur well beyond the first year and could further increase the ICER. Additional scenario analysis to account for discontinuation rates beyond the first year is recommended.

Related to the issue of adherence is the ability to titrate to higher doses for oral semaglutide. In the PIONEER 7 pragmatic RCT, ~40% patients on oral semaglutide did not reach the 14 mg dose which is the dose also associated with a higher rate of GI side effects and of discontinuation. The assumption that all patients reach the 14 mg dose is unlikely in the real world. An additional analysis using the expected dose distribution of oral semaglutide based on available RCT data is recommended.

Leo Seman, MD, PhD
Full-Time Employee of Boehringer Ingelheim

Boehringer Ingelheim would like to acknowledge the effort ICER has put into constructing an economic evaluation, although some limitations and uncertainties remain.

Boehringer Ingelheim is committed to bringing value through innovation. We believe that the findings of the ICER evaluation of T2DM treatments supports the value of empagliflozin as a cost-effective therapy.

To continue to provide high value and high quality treatments to T2DM patients, we believe it is important to keep in mind three key elements of importance.

First, since T2DM is a cardio-renal metabolic disease, the robustness of the cardiovascular outcomes trials are important to consider and understand. To truly understand the value of T2DM treatments, it will be important to develop properly powered and executed clinical trials with statistical significant and an adequate time horizon to capture long-term outcomes and an adequate number of events to have confidence in the data.

Second, although it was beneficial to have clinical trials with head-to-head comparisons of treatments on market, there needs to be complete transparency on how the comparison was performed. In this case, the assumptions around imputations in generating estimated mean differences (estimands) were not fully disclosed in the publications.

Third, amputations and worsening diabetic retinopathy are outcomes of significance for T2DM patients. The manner in which the model estimates these events merit further scrutiny as they do not reflect randomized clinical trial results, which would suggest lower rates of worsening diabetic retinopathy in the empagliflozin arms than in placebo and ususal care in the Empa Reg Outcome trial. Additionally, there has been no evidence of an increase in amputations with empagliflozin in clinical trials or in ongoing monitoring by the FDA and phamacovigilence at Boehringer Ingelheim.

Boehringer Ingelheim recognizes the importance of working collaboratively with all stakeholders to identify the areas of value for patients and demonstrate the ability of treatments to deliver that value and are committed to continuing working with all stakeholders.

Appendix G. Conflict of Interest Disclosures

Tables G1 through G3 contain conflict of interest (COI) disclosures for all participants at the New England CEPAC Public Meeting on November 14, 2019, in Providence, RI.

Table G1. ICER Staff and Consultant COI Disclosures

Name	Organization	Disclosures
Pam Bradt, MD, MPH	Institute for Clinical and Economic Review	*
Eric Borrelli, PharmD, MBA	Institute for Clinical and Economic Review	*
Rick Chapman, PhD, MS	Institute for Clinical and Economic Review	*
Katherine Fazioli, BS	Institute for Clinical and Economic Review	*
Greg Guzauskas, MSPH, PhD	University of Washington	*
Ryan Hansen, PhD, PharmD	University of Washington	*
Catherine Koola, MPH	Institute for Clinical and Economic Review	*
Steve Pearson MD, MSc	Institute for Clinical and Economic Review	*
Michelle Poulin, BA	Institute for Clinical and Economic Review	*
David Rind, MD, MSc	Institute for Clinical and Economic Review	*

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table G2. New England CEPAC Panel Member COI Disclosures

Name	Organization	Disclosures
Robert Aseltine Jr, PhD*	Professor and Chair, Division of Behavioral Sciences and Community Health, UCONN Health	*
Marthe Gold, MD, MPH*	Senior Scholar, New York Academy of Medicine	*
Claudio Gualtieri, JD*	Advisor, Center to Champion Nursing in America, AARP	*
Stephen Kogut, PhD, MBA, RPh*	Professor of Pharmacy Practice, University of Rhode Island College of Pharmacy	*
Greg Low, RPh, PhD*	Program Director, MGPO Pharmacy Quality and Utilization Program	*
Eleftherios Mylonakis, MD, PhD, FIDSA*	Chief of the Infectious Diseases Division and Dean's Professor of Medicine, Warren Alpert Medical School of Brown University	*
Stephanie Nichols, PharmD, BCPS, BCPP, FCCP*	Associate Professor Pharmacy Practice, University of New England College of Pharmacy	*
Leslie Ochs, PharmD, PhD, MSPH*	Associate Professor of Social and Administrative Pharmacy, University of New England College of Pharmacy	*
Brian O'Sullivan, MD*	Professor of Pediatrics, Geisel School of Medicine at Dartmouth College	*
Jason Schwartz, PhD*	Assistant Professor, Department of Health Policy and Management, Yale School of Public Health	*
Jason Wasfy, MD, MPhil*	Director, Quality and Outcomes Research, Massachusetts General Hospital Heart Center	*
Edward Westrick, MD, PhD*	Primary Care Physician, Assistant Medical Director, Comprehensive Community Action Program	*

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table G3. Policy Roundtable Participants and COI Disclosures

Participant	Affiliation	Disclosure
Jeff Casberg, MS, RPh	Director of Clinical Pharmacy, IPD Analytics	Owns Anthem, Cigna, CVS, and McKesson stock shares
Bonnie Donato, MA, PhD	Executive Director of Primary Care, Health Economics, and Outcomes Research, Boehringer Ingelheim	Full-time employee of Boehringer Ingelheim
Todd Hobbs, MD	Vice President, Chief Medical Officer of North America, Novo Nordisk	Full-time employee of Novo Nordisk
Joanna Mitri, MD, MS	Staff Endocrinologist, Joslin Diabetes Center	Received support from the National Dairy Council, National Institutes of Health, Kowa, and the Juvenile Diabetes Research Foundation. Received <$6,000 for a one-time consultation with Novo Nordisk.
Lisa Murphy, MD, DPhil	Chief, Division of Endocrinology and Metabolism, San Francisco General Hospital, University of California, San Francisco	*
David Strutton, PhD	Vice President, Global Pharmaceuticals & Policy Research, Center for Observational and Real-World Evidence, Merck	Full-time employee of Merck
Susan Weiner, MS, RDN, CDE, FAADE	Scientific Council Member, Beyond Type 2	*

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.