The Effectiveness and Value of Oral Semaglutide for Type 2 Diabetes Mellitus

A Summary from the Institute for Clinical and Economic Review's New England Comparative Effectiveness Public Advisory Council

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In the United States, there are approximately 30 million people living with diabetes mellitus (DM), the majority (95%) of whom have type 2 DM (T2DM).¹ Patients with DM are at an increased risk of developing microvascular complications (e.g., damage to the kidneys) and macrovascular complications (e.g., cardiovascular disease). Tighter glycemic control can reduce the risk of microvascular complications and potentially macrovascular complications, particularly in those with a new diagnosis of DM.²

Metformin is generally the first-line medication for the treatment of T2DM.³ If adequate glycemic control is not achieved with metformin, additional antihyperglycemic agents can be added.³ Additional antihyperglycemic options include sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter 2 (SGLT-2) inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1 RAs), and insulin.^{3,4} Recent evidence, largely from cardiovascular outcome trials (CVOTs), has supported the use of SGLT-2 inhibitors or GLP-1 RAs as the preferred agents to be added to metformin if additional glycemic control is needed in patients with T2DM and cardiovascular disease.^{5,6}

Oral semaglutide (Rybelsus, Novo Nordisk) was approved for the treatment of T2DM in September 2019; the injectable formulation of the drug was approved in December 2017. Oral semaglutide is the first oral formulation of a GLP-1 RA approved in the United States (US). The Institute for Clinical and Economic Review (ICER) performed a systematic literature review and cost-effectiveness analysis to evaluate the health and economic outcomes of oral semaglutide for the treatment of T2DM. Here, we present the summary of our findings and highlights of the policy discussion with key stakeholders that took place at a public meeting of the New England Comparative Effectiveness Public Advisory Council (NE CEPAC) on November 14, 2019. The detailed report is available on the ICER website.⁷

Summary of Findings

Clinical Effectiveness

We compared the clinical effectiveness of oral semaglutide with liraglutide (an injectable GLP-1 RA), empagliflozin (an

SGLT-2 inhibitor), sitagliptin (a DPP-4 inhibitor), and no treatment beyond background antihyperglycemic therapy (i.e., placebo arms of clinical trials). We reviewed clinical benefits in terms of intermediate outcomes (e.g., glycated hemoglobin A1c [HbA1c]) and key benefits (e.g., cardiovascular outcomes).

We included evidence from 12 randomized controlled trials (RCTs).⁸⁻¹⁹ Eight RCTs were part of PIONEER, a phase 3 clinical development program for oral semaglutide, including 1 CVOT.^{8,10,13-18} Three RCTs were CVOTs of our selected active comparator therapies.^{9,12,19} Finally, we included the CVOT of injectable semaglutide to inform our assessment of the key benefits of semaglutide as a molecule.¹¹

Head-to-head data on intermediate outcomes were available from the PIONEER trials. Results showed that oral semaglutide reduced HbA1c more than placebo, sitagliptin, and empagliflozin and more than liraglutide at 52 weeks but not at 26 weeks. Results also showed oral semaglutide reduced body weight more than placebo, sitagliptin, and liraglutide but had similar effects compared with empagliflozin.

Because the CVOTs were placebo-controlled, we did not have head-to-head data for oral semaglutide versus active comparators on key benefits. Therefore, we conducted network meta-analyses on results from the CVOTs to obtain comparative estimates on the following outcomes: 3-point MACE (i.e., a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke); hospitalization for heart failure; and nephropathy.

We found that semaglutide (oral and injectable) reduced the risk of 3-point MACE more than sitagliptin; no significant differences were found between semaglutide and liraglutide or empagliflozin. We also found that empagliflozin reduced the risk of hospitalization for heart failure more than semaglutide. We found no differences between semaglutide and active comparators on nephropathy.

Adverse events (AEs) experienced with oral semaglutide were generally mild to moderate in severity and most commonly related to gastrointestinal effects. The rates of AEs leading to discontinuation were considerably higher for oral semaglutide versus the other comparators. In the CVOTs, both formulations of semaglutide had numerically higher rates of retinopathy events compared with placebo, with a significant risk increase reported for injectable semaglutide.

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TABLE 1 Base Case Results for Oral Semaglutide and Comparators and Incremental Cost-Effectiveness of Oral Semaglutide Versus Comparators^a

Treatment	Total Cost	LYs	QALYs	ICERs for Oral Semaglutide vs. Each Comparator	
				Per LY Gained	Per QALY Gained
Oral semaglutide + background therapy	\$295,000	8.18	4.03	–	–
Sitagliptin + background therapy	\$254,000	7.66	3.73	\$80,000	\$140,000
Empagliflozin + background therapy	\$263,000	8.07	3.97	\$290,000	\$480,000
Liraglutide + background therapy	\$305,000	8.06	3.72	Cost saving	Cost saving
Background therapy alone	\$250,000	7.55	3.63	\$70,000	\$110,000

^aResults use an assumed annual net price of \$6,103 for oral semaglutide (assuming the same average discount as injectable semaglutide).

ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

Limitations of the Clinical Evidence

The comparative clinical effectiveness of oral semaglutide on key benefits was assessed through indirect comparisons that are potentially susceptible to effect modification. Additionally, by combining results from the oral and injectable semaglutide CVOTs, we assumed that the clinical benefits of these formulations are reasonably similar. In January 2020, the U.S. Food and Drug Administration expanded the indication for injectable semaglutide for MACE risk reduction, but oral semaglutide does not currently have this expanded indication. This adds additional uncertainty as to whether these agents are comparable; however, it appears that the decision may have been because the CVOT of oral semaglutide was short in duration and showed statistical noninferiority but not superiority compared with placebo. Finally, in choosing our active comparators, we hypothesized that these comparators provided estimates for the classes they represent; however, this adds additional uncertainty when assessing the comparative clinical effectiveness of oral semaglutide and other antihyperglycemic agents.

Long-Term Cost-Effectiveness

We estimated that the lifetime cost-effectiveness of oral semaglutide added to current antihyperglycemic therapy for T2DM. We developed an adaptation of a published US-based microsimulation model,²⁰ which was based on the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model 2.²¹ Oral semaglutide was compared with 4 other options: (1) ongoing background antihyperglycemic therapy, (2) sitagliptin, (3) empagliflozin, and (4) liraglutide. Outcomes included life-years (LYs) gained, quality-adjusted life-years (QALYs) gained, and total lifetime costs. The base case used a health care sector perspective and a lifetime time horizon. A cohort of US adults with self-reported diabetes and HbA1c ≥ 7 from National Health and Nutrition Examination Survey (NHANES) program 2013-14 and 2015-16 surveys (n = 362) served as the population for our microsimulations.²² The cohort had a mean age of 61.8 years, a mean duration of diabetes of 13.1 years, and a mean HbA1c of 8.7.

Oral semaglutide had the highest LYs gained and QALYs gained (Table 1). Oral semaglutide was cost saving compared with liraglutide. Oral semaglutide was more expensive but met cost-effectiveness thresholds between \$100,000-\$150,000 per QALY when compared with background therapy alone and sitagliptin. Compared with empagliflozin, however, oral semaglutide had a much higher incremental cost-effectiveness ratio of \$480,000 per QALY (Table 1). Results from one-way sensitivity analysis showed the parameters with the greatest effect on the incremental cost-effectiveness ratio for oral semaglutide versus background therapy alone included the cost of congestive heart failure and the MACE hazard ratio. Full results from the one-way sensitivity analysis, as well as the probabilistic sensitivity analysis are available in the ICER report.⁷

Limitations of Long-Term Cost-Effectiveness

The overarching limitation of our cost-effectiveness analysis is the complexity of the clinical outcomes related to T2DM. Although this complexity was accounted for in part by using a microsimulation model, individual patient outcomes are challenging to predict. Another uncertainty arises from our reliance on effect estimates obtained through indirect treatment comparisons that may be susceptible to effect modification.

In the base case, we assumed that key benefits remained constant for a patient's lifetime because of a lack of data with longer follow-up. In a scenario analysis, we observed that gradual decreases in key benefits over time led to higher costs and decreased LYs and QALYs for oral semaglutide. Another key assumption was that patients who discontinued treatment moved on to receive insulin therapy; although this allowed for direct head-to-head comparisons of treatment with an initial therapy, this treatment pathway is not likely representative of the clinical management of all patients with T2DM.

Policy Discussion

The NE CEPAC is one of the independent appraisal committees composed of medical evidence experts convened by ICER to engage in the public deliberation of the evidence on clinical

TABLE 2 Other Contextual Considerations

<i>Are any of the following contextual considerations important in assessing the long-term value for money of oral semaglutide?</i>	
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

and cost-effectiveness of health care interventions. Their deliberation includes input from clinical experts and patient representatives specific to the condition under review, as well as formal comment from manufacturers and the public. A policy roundtable concludes each meeting during which representatives from insurers and manufacturers join clinical experts and patient representatives to discuss how best to apply the findings of the evidence to clinical practice, insurance coverage, and pricing negotiations.

The NE CEPAC voted 12-0 that there is adequate evidence to demonstrate that adding oral semaglutide to ongoing background therapy provides a positive net health benefit. The NE CEPAC also voted 12-0 that there is adequate evidence to demonstrate that the net health benefit of adding oral semaglutide is superior to that provided by adding sitagliptin. The NE CEPAC voted 11-1 that there is *not* adequate evidence to demonstrate that the net health benefit of adding oral semaglutide is superior to that provided by adding liraglutide. The NE CEPAC also voted 11-1 that there is *not* adequate evidence to distinguish the net health benefit of adding oral semaglutide from that provided by adding empagliflozin.

The NE CEPAC panel also voted on “other potential benefits” and “contextual considerations” as part of a process intended to signal to policymakers whether there are important considerations when making judgments about long-term value for money not adequately captured in analyses of clinical and/or cost-effectiveness. Results from votes on “other potential benefits” showed that the majority of the panel (9/12) agreed that oral semaglutide offers reduced complexity compared with liraglutide that will significantly improve patient outcomes. The results of the votes on “contextual considerations” are shown in Table 2.

The culminating vote of the NE CEPAC was on the overall “long-term value for money” of oral semaglutide, taking into consideration its clinical effectiveness, incremental cost-effectiveness, potential other benefits, and contextual considerations. Voting categories for long-term value for money are “low,” “intermediate,” or “high.” Of the 12 panel members, 4 voted low, 6 voted intermediate, and 2 voted high long-term value for money of oral semaglutide compared with ongoing background therapy.

The policy roundtable discussion explored how best to translate the evidence and broader perspectives discussed

into clinical practice and into pricing and insurance coverage policies. The key policy perspectives on coverage policy are as follows:

- *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-2 inhibitors or DPP-4 inhibitors 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 before 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-2 inhibitor or a GLP-1 RA, and in those cases, it would be appropriate for clinicians to pick the substantially cheaper agent (currently an SGLT-2 inhibitor), 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 before 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.

- *Other coverage criteria:* We heard from clinical experts that concurrent therapy with an SGLT-2 inhibitor and a GLP-1 RA is common. Some payers may wish to consider limiting an initial trial of oral therapy to 1 agent after metformin, but there may be considerable resistance from clinicians and patients, given the lack of previous experience with active management in this disease space.
- *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.

ICER’s potential budget impact analysis suggested that only approximately 7%-14% of eligible patients with T2DM could be

treated with oral semaglutide before passing a budget impact threshold of \$819 million per year over 5 years. During the policy discussion, clinical experts stated their belief that, because primary care providers are often uncomfortable prescribing injectable GLP-1 RAs, oral semaglutide would be an attractive alternative for up to 50% of the eligible patient population. ICER therefore issued an “Access and Affordability Alert” as part of its final report to signal to policymakers that special measures may need to be considered to ensure that the health care system can absorb the added costs from these therapies over the short term without reducing access inappropriately or contributing to rapid growth in health care insurance costs.

Conclusions

Clinical evidence shows that treatment with oral semaglutide resulted in better outcomes compared with ongoing background therapy and sitagliptin. Oral semaglutide provided better improvements in intermediate outcomes compared with liraglutide, although no significant differences in key benefits were found. Oral semaglutide reduced HbA1c but had similar effects on body weight compared with empagliflozin; no significant differences in 3-point MACE were found, but empagliflozin was found to reduce the risk for hospitalization for heart failure more than semaglutide.

Oral semaglutide was estimated to be dominant compared with liraglutide and to have incremental cost-effectiveness ratios between \$100,000 and \$150,000 per QALY versus sitagliptin and background therapy alone. But oral semaglutide is unlikely to meet commonly accepted cost-effectiveness thresholds compared with empagliflozin and, with substantial uptake, could contribute to short-term budget strains in the health system. Clinicians and policymakers should work together to ensure that this important new treatment option is brought into clinical practice in a way that maximizes its health benefits without adversely affecting access and affordability.

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REFERENCES

- Centers for Disease Control and Prevention. National Diabetes Statistics Report. 2017. Available at: <https://dev.diabetes.org/sites/default/files/2019-06/cdc-statistics-report-2017.pdf>. Accessed July 18, 2020.
- Inzucchi SE, Lupsa B. Glycemic control and vascular complications in type 2 diabetes mellitus. Mulder JE, ed. UpToDate. 2020. Retrieved July 27, 2020. Available at: <https://www.uptodate.com/contents/glycemic-control-and-vascular-complications-in-type-2-diabetes-mellitus>. Accessed July 28, 2020.
- American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(Suppl 1):S61-S70.
- 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):2669-701.
- American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(Suppl 1):S90-S102.
- 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.
- Rind D, Guzauskas G, Fazioli K, et al. Oral semaglutide for type 2 diabetes: effectiveness and value. Institute for Clinical and Economic Review. December 9, 2019. Available at: https://icer-review.org/wp-content/uploads/2019/04/ICER_Diabetes_Final-Evidence-Report_120919-1.pdf. Accessed July 18, 2020.
- 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;42(9):1724-732.
- Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373(3):232-42.
- Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381(9):841-51.
- Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-844.
- Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311-22.

13. 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):515-27.
14. 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):528-39.
15. 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.
16. 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;42(12):2272-81.
17. 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):1466-80.
18. 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;42(12):2262-71.
19. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-28.
20. 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):170-78.
21. 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):1925-33.
22. Centers for Disease Control and Prevention, National Center for Health Statistics. National Health and Nutrition Examination Survey. Survey Years: 2013-14, 2015-16. Available at: <https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes/Default.aspx?BeginYear=2015>. Accessed July 18, 2020.