

## Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value

*Final Background and Scope*

May 31, 2019

### Background

In the US, approximately 30 million individuals have diabetes mellitus, of which 95% have the Type 2 form.<sup>1</sup> Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance, a condition in which the body does not respond to insulin appropriately. Insulin is a hormone produced by beta cells in the pancreas that helps to control blood glucose levels; patients with T2DM have elevations in blood glucose (hyperglycemia). With chronic hyperglycemia, patients with T2DM 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 death.<sup>2</sup> In 2014, 7.2 million hospital discharges were reported among individuals with diabetes, including hospitalizations for major cardiovascular disease and lower-extremity amputation.<sup>1</sup> The annual cost of managing diabetes is approximately \$245 billion, including both direct medical costs and lost productivity resulting from complications.<sup>1</sup>

T2DM management includes close monitoring of blood sugar and glycated hemoglobin (HbA1c) levels – a measure of average blood sugar control over several months – as well as other aspects such as ophthalmic care, podiatric care, and managing risk factors for cardiovascular disease.<sup>2</sup> Levels of HbA1c are generally used as “glycemic targets” in patients with T2DM, with somewhat less intense control being accepted for older patients or for patients with a history of severe hypoglycemia, shorter life expectancy, established vascular complications, important comorbid conditions, or long-standing diabetes.<sup>3</sup> Improving glycemic control may reduce the risk or delay progression of microvascular complications, but the impact on macrovascular complications is less certain and may only manifest in individuals with longer life-expectancy. Healthy lifestyle changes (e.g., improved diet and increased exercise) are generally a standard part of T2DM management, and they may be sufficient to achieve healthy blood glucose levels or delay the onset of complications in some individuals. However, many individuals with T2DM will require antihyperglycemic medications to achieve and sustain glycemic control.<sup>2,4</sup>

Metformin is currently the most effective first-line medication option and has a favorable safety profile in that it does not increase weight or the risk of hypoglycemia (low blood sugar).<sup>2,4</sup> If lifestyle changes (e.g., diet and exercise) and metformin do not achieve a desired glycemic target, another glucose-lowering drug may be added.<sup>2,4</sup> Additional management options include oral administrations of sulfonylureas, thiazolidinediones, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, as well as injectable administrations of glucagon-like peptide 1 (GLP-1) receptor agonists, and insulin.<sup>2,4</sup>

The focus on glucose control has raised concerns that although some therapies may lower blood glucose, they may also increase the risk for adverse cardiovascular events which emerge more slowly. In 2008, the Food and Drug Administration (FDA) issued recommendations for the evaluation of cardiovascular risk for new antihyperglycemic therapies, which include the conduct of randomized trials that include patients at high risk for cardiovascular events.<sup>5,6</sup> Since then, several cardiovascular outcome trials have been conducted, and this evidence has allowed for greater certainty in considering the relative benefits and risks of each therapy.<sup>5</sup>

A new, oral GLP-1 receptor agonist, semaglutide (Novo Nordisk) is currently in development to treat patients with T2DM.<sup>7</sup> The manufacturer filed for FDA approval of oral semaglutide in March 2019 for two indications. A decision is expected by September 2019 for the first indication – to control blood glucose in patients with T2DM – and by January 2020 for the second indication – to reduce major cardiovascular events in adults with T2DM and established cardiovascular disease.<sup>8</sup> If approved, oral semaglutide would be the first oral formulation of a GLP-1 receptor agonist.

## **Stakeholder Input**

The draft scoping document incorporated feedback gathered during preliminary calls with clinicians and open input submissions from the public, including from manufacturers of the agents of focus in this review. This final scoping document includes additional input from clinicians, researchers, and manufacturers. Specifically, this final scope includes additional outcomes in the Clinical Effectiveness Review (estimated glomerular filtration rate, hospitalizations, heart failure) and clarifications that background treatments include metformin with or without sulfonylureas. As noted in the Comparative Value section, we will work to address concerns about the limitations of existing economic models as we develop a de novo model.

ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of oral semaglutide.

## Report Aim

This project will evaluate the health and economic outcomes of oral semaglutide for T2DM. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

## Scope of Clinical Evidence Review

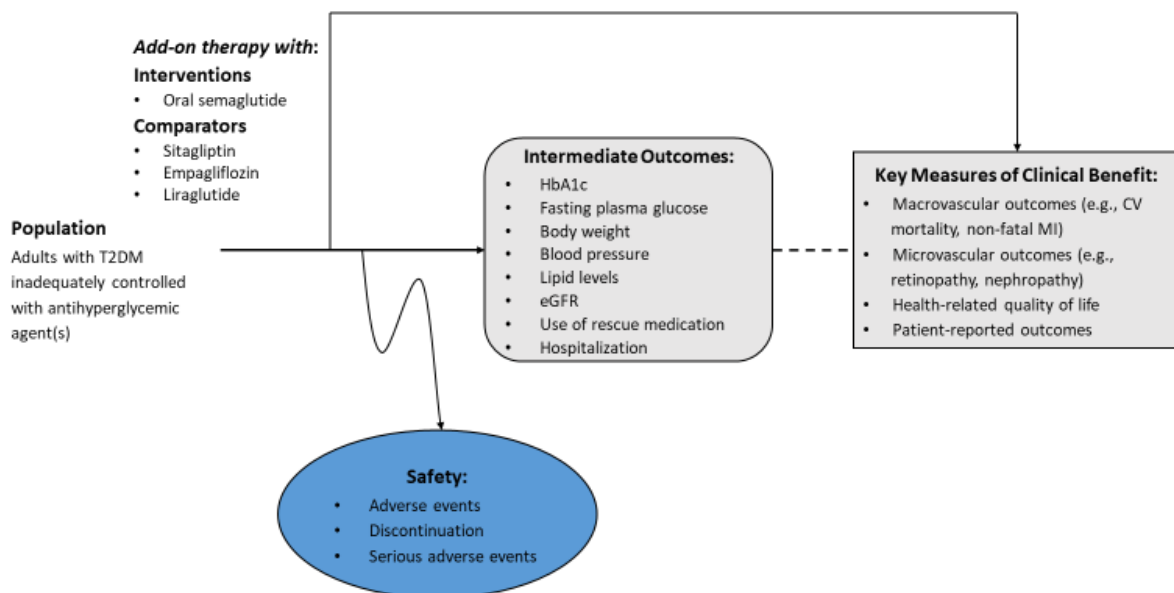
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see <https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/>).

All relevant evidence will be narratively summarized or quantitatively synthesized. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (<https://osf.io/7awvd/>).

## Analytic Framework

The general analytic framework for assessment of therapies for T2DM is depicted in Figure 1.1 below.

**Figure 1.1. Analytic Framework: Oral Semaglutide for Type 2 Diabetes Mellitus**



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

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.<sup>9</sup>

### **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 intend to examine subgroups including, but not limited to, the following:

1. Patients at high risk for cardiovascular 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)

## ***Intervention***

Our intervention of interest for this review is oral semaglutide (Novo Nordisk) added to current antihyperglycemic treatment.

## ***Comparators***

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

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

These three agents were chosen in part because they were active comparators in the trials of oral semaglutide. We will summarize recent systematic reviews of the other DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 RA receptor agonists in the appendix of our evidence report.

## ***Outcomes***

We will look for evidence for the following outcomes of interest.

### *Efficacy*

#### **Intermediate Outcomes**

- HbA1c
- Fasting plasma glucose
- Body weight
- Blood pressure
- Lipids levels
- Estimated glomerular filtration rate (eGFR)
- Use of rescue medication (e.g., additional glucose-lowering medication)
- Hospitalization

#### **Key Measures of Clinical Benefit**

- Macrovascular outcomes including:
  - All-cause mortality
  - Cardiovascular mortality
  - Stroke
  - Myocardial infarction
  - Heart failure
  - Other cardiovascular events
- Microvascular outcomes including:

- Retinopathy
- Nephropathy
- Neuropathy
- Other renal or eye events (e.g., chronic kidney disease progression, visual deterioration)
- 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
  - Renal effects
  - Cardiovascular events
  - Other events occurring in more than 5% of patients
- Discontinuation (all-cause, due to adverse events)
- Serious adverse events

### **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 in the United States.

### **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.

**Table 1.1. Potential Other Benefits and Contextual Considerations**

<b>Potential Other Benefits</b>
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
<b>Potential Other Contextual Considerations</b>
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.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

## Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a simulation model to assess the lifetime cost-effectiveness of the treatments of interest relative to relevant comparator treatments. The base case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only). Data permitting, a societal perspective analysis will be conducted, adding indirect costs including productivity losses. The target population will consist of adults with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s). We will develop a de novo model structure based in part on (a) risk equations adapted from a U.S.-based model of the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model 2 (OM2)<sup>10,11</sup> that predicts health states for the relevant microvascular and macrovascular events as well as (b) an internal review of prior published models of T2DM. Data permitting, we will also model risk reductions for the rate of kidney function decline and major adverse cardiovascular events (MACE), independent of A1C control. Of note, we are aware of the limitations of the UKPDS OM2 as they relate to the U.S. population and incorporation of independent cardiovascular and

renal function effects, and we will work to address these concerns as we develop the model. A cohort of patients based on the populations from the PIONEER program trials<sup>7,12</sup> will be simulated through the risk equations over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness may be estimated for shorter time horizons (e.g., five years), if deemed relevant.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness and safety will be estimated using results of the PIONEER program clinical trials.<sup>7,12</sup>

Health outcomes and costs will be dependent on time spent in each equation-driven health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of overall diabetes-related complications avoided, MACE avoided, life-years gained, and quality-adjusted life years (QALYs) gained. Quality of life weights will be applied to each health state, including quality of life decrements for each complication event and for serious adverse events (SAEs). The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and SAEs. In addition, productivity losses and other indirect costs will be included in a separate analysis if available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per life-year gained, and cost per MACE avoided. Data permitting, subgroup analyses will be considered for patient groups that could be of interest either clinically or economically.

In separate analyses, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: <http://icer-review.org/wp-content/uploads/2018/05/ICER-value-framework-v1-21-18.pdf>.

### ***Identification of Low-Value Services***

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see <https://icer-review.org/material/final-vaf-2017-2019/>). These services are ones that would not be directly affected by oral semaglutide (e.g., fewer



hospitalizations for cardiovascular events), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of T2DM beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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