

Comments: ICER Draft Scoping Document for the Assessment of Treatments for

Type 2 Diabetes

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In the last two decades, clinicians have expanded their armamentarium of drugs that can be used to manage patients with type 2 diabetes (T2D). Some of these new classes have demonstrated clear benefits in comorbidities related to diabetes that are beyond the reductions in A1c alone, such as reduction in cardiovascular events and renal failure. While the clinical benefits are obvious, a major limitation of these new drugs has been their high costs.

We are in support of the ICER process that addresses both the health as well as the economic outcomes of oral semaglutide for T2D in comparison to conventional drugs. Multiple GLP1 agonists have demonstrated reductions in cardiovascular events and mortality. In particular, once weekly subcutaneous semaglutide has been shown to reduce CV events by 26% in high CV risk subjects with T2D. However, their limitation have been that they are injectables and costly. Oral semaglutide, a GLP1- agonist currently in phase 3 clinical trials, has the potential to overcome both of these limitations. Therefore, this Draft Scoping Document is important in reviewing the comparative clinical as well as economic effectiveness of oral semaglutide. Moreover, ICER also attempts to incorporate innovation, public health effects, reduction in disparities and unmet medical needs. These factors, which are critical to adoption in clinical practice, are often underrepresented in traditional reviews that result in guidelines and treatment algorithms.

Specifically, this analysis will compare oral semaglutide, a GLP-1 agonist currently in phase 3 clinical trials, to three products currently on market: liraglutide (Victoza®, Novo Nordisk), another GLP-1 agonist; empagliflozin (Jardiance®, Boehringer Ingelheim and Eli Lilly), a SGLT-2 inhibitor; and sitagliptin (Januvia®, Merck), a DPP-4 inhibitor.

However, we do have several suggestions for consideration. The first is the selection of the drugs chosen as comparators. It would be very useful to include two other older and much less costly classes, metformin and sulfonylureas as they still very commonly used. Additionally, it is not clear why a once daily GLP1-RA injection (liraglutide) was chosen as a comparison as opposed to once weekly formulation (dulaglutide, semaglutide weekly, exenatide weekly) which may be of more clinical pertinence for efficacy, side effects and patient adherence.

In reviewing the proposed populations of interest, it would also be important to include age as subgroups. In particular, disparities in the elderly would be of particular interest

both clinically and economically, where comorbidities and side effects as well medical costs are more pervasive and challenging.

For the safety comparison, one known complication of GLP1-RA therapy is missing which is cholelithiasis which may require additional more costly medical therapy such as hospitalization, imaging surgery, etc. Additionally, there is some concern for neoplasms which may also be included. In fact, oral semaglutide has been published to have increased incidence of various types of neoplasms.¹

With respect to the timing of the intervention effectiveness, realizing that most of the clinical trials are on average 6 months of duration, some of the outcomes sought in this review (microvascular and macrovascular complications, economic, public health, QALY, etc.) would like require much long than the proposed limit of three months duration. Consideration should be given to at least 6 months of duration for the intended outcomes. In terms of the settings, most of the data pertinent to these clinical outcomes is relevant to outpatient settings. If other settings such as inpatient were to be included, this should be a subgroup analysis.

Finally, the comparative value analysis is critical section of this review as mentioned early in this comment. While the clinical benefits are clear, the costs of the drugs to patients as well as the health care system are the elephant in the room at this time. Will the reductions in clinical outcomes and their associated cost savings, as well as the QALY negate the current high costs of these drugs? This analysis and discussion would add great value to this document and influence further adoption into clinical practice much beyond a clinical review. It would be ideal if a traditional drug such as metformin and/or sulfonylurea were added to the comparator group. However, even an obvious cost analysis of oral versus subcutaneous therapy would be useful.²

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1. Ahmann AJ, et al. Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial. *Diabetes Care* 2018 Feb; 41(2): 258-266
2. Quantifying the value of orally delivered biologic therapies: A cost-effectiveness analysis of oral semaglutide. *J Pharm Sci*. 2019 Apr 26. pii: S0022-3549(19)30255-2. doi: 10.1016/j.xphs.2019.04.022. [Epub ahead of print]

Boehringer Ingelheim (BI) Response to Draft Scoping Document - May 2, 2019
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Thank you for the opportunity to provide comments to the Draft Scoping Document. The following are concerns and considerations, from BI, as ICER refines their approach to evaluate oral semaglutide for type 2 diabetes mellitus (T2DM).

The Draft Scoping Document positions T2DM as a glucose-related disease, despite the fact that chronic hyperglycemia has an impact on both macro and microvasculature, affecting the entire cardiovascular (CV) and renal systems. T2DM is a cardiorenal metabolic disease¹ with implications for a wide range of CV outcomes, including heart failure (HF) and renal outcomes that go beyond glucose control.^{2,3} Evidence has demonstrated the relationship between T2DM and CV disease (CVD) risk, with diabetes patients experiencing higher rates of CVD, major adverse cardiac events (MACE), and mortality due to heart disease.⁴⁻⁶ Diabetes is also the leading cause of chronic kidney disease (CKD),^{7,8} accounting for 30-50% of end stage renal disease (ESRD) in western countries.^{9,10} The American Diabetes Association (ADA) guidelines recommend T2DM treatment based on goals that go beyond glycemic control and to consider CVD, HF and kidney health, when selecting treatment.¹¹

Given the systemic impact of T2DM on the vascular system, any value assessment of T2DM treatments must include CV and renal outcomes.^{12,13} ICER's approach includes the use of the UKPDS OM2 (OM2), which models CV outcomes only as a function of glucose and related risk factors, rather than as standalone outcomes. This model will underestimate the magnitude of potential CV clinical and economic benefits from treatments such as SGLT-2 inhibitors and GLP-1s, receptor agonists, by neglecting CV benefit beyond the result of improvement in risk factors contained in the OM2. BI has published a simulation of OM2 with the EMPA-REG OUTCOME data, in which OM2 only accounted for 12.75–15% of the overall CV benefit of empagliflozin.¹⁴ BI believes that the value of empagliflozin, if evaluated with the OM2, will be severely underestimated. BI is concerned that ICER's microsimulation model of choice, the OM2, is not adequate for a holistic evaluation of oral semaglutide versus DPP4, GLP-1 and SGLT-2 inhibitors.

BI would like to highlight the following Draft Scoping Document Comments:

1. **Macrovascular Outcomes:** Include HF as a key measure of clinical benefit; model HF and other CV outcomes independently of glucose and other risk factors
2. **Microvascular Outcomes:** Include delay in CKD progression and CKD staging as primary renal outcomes
3. **Data Source:** Leverage existing CV outcomes trials, in addition to the PIONEER program, for population characteristics and key measures of clinical benefit data
4. **Model Framework:** There are limitations with the UKPDS data and the risk equations used for OM2
5. **Model Inputs:** Health state utility estimates should reflect the target treatment population and disease

Proposed actions to address comments:

1. **Macrovascular Outcomes:** The OM2 can model ischaemic heart disease, congestive HF, stroke, and myocardial infarction as risk equations calculated using risk factors and patient characteristics. We recommend ICER leverage these existing risk equations (albeit with risk adjustments or as a new model as described in the Model Framework Section below) and include HF as an outcome.
2. **Microvascular Outcome:** Nephropathy is included as a microvascular outcome. We recommend the following specific renal outcome measures: progression to macroalbuminuria, doubling of the serum creatinine level, initiation of dialysis, or death from renal disease. Furthermore, to capture the pleiotropic effects of T2DM therapies, risk factors of nephropathy must be captured by the risk equations utilized in the model. These include eGFR, creatinine, albumin, and albumin/creatinine ratio. If ICER must use the OM2 (see our model suggestion in Model Framework), we recommend that ICER adapt the OM2, which currently only includes renal failure, to include the additional renal outcomes.
3. **Data Source:** To improve the generalizability and accuracy of the assessment, ICER should conduct a network meta-analysis (NMA) to leverage the publically available data from a breadth of CV outcomes trials

(CVOT) (e.g. EMPA-REG OUTCOME, TECOS, LEADER). In addition, ICER should leverage all available CVOTs, to determine appropriate baseline patient characteristics for the desired population.

- 4. Model Framework:** The Draft Scoping Document notes that if data permits, rate of kidney function decline and MACE will be modeled independent of A1C control. We recommend this approach be applied to all CV outcomes. If OM2 is selected, we recommend comparing the rate reduction of CV outcomes from the OM2 to clinical trial outcomes for the comparator treatments of interest and applying an additional hazard to CV and renal outcomes, including HF, to account for the effects that are unobservable in the OM2. After our review of available models and use of OM2, BI recommends ICER develop a de-novo model reflective of the multi-systemic impact of diabetes and clinical and economic value of T2DM treatment.
- 5. Model Inputs:** We recommend Lindgren 2007, Gandy 2012 and Sullivan 2016 for input utilities, as they are the most recent literature reviews capturing utility estimates for the patient population of interest.¹⁵⁻¹⁷

Macrovascular Outcomes: Include HF as a key measure of clinical benefit. HF is not listed as an outcome in the current scope, though the OM2 includes HF. Without HF, ICER's model would fail to capture a major macrovascular outcome with significant clinical and economic impacts for patients, payers, and society.¹⁸⁻²³ The importance of HF is supported by a breadth of T2DM studies that include hospitalization for HF (HHF) as an endpoint.^{3,24-30} Including HF in its current form in the OM2 would suffer from the same limitations as described above for other CV outcomes, with the exception that in the OM2, glucose is not a risk factor for HF. If ICER proceeds with the OM2, we recommend the inclusion of HF, but suggest that ICER assess the need to apply an additional hazard after comparing OM2 outcomes to clinical trial outcomes. Not doing so would potentially undervalue current T2DM treatments. For example, in EMPA-REG OUTCOMES, a study of empagliflozin versus placebo, empagliflozin demonstrated a beneficial impact on HHF compared to placebo.¹⁹ In addition, SGLT2 inhibitors, are being studied in patients with HF (with or without T2D), with a primary endpoint of time to first event of adjudicated CV death or adjudicated HHF (EMPEROR).^{31,32} There are also ongoing studies on the effect of empagliflozin on functional outcomes and quality of life measures (EMPERIAL).^{33,34}

Microvascular Outcomes: Specify delay in CKD progression and CKD staging as primary renal outcomes. Diabetes is the most common cause of ESRD and CKD in the world, with a prevalence of 20-30%.⁷ Progression of diabetic nephropathy is associated with high costs and clinical burden, especially as patients develop ESRD and ultimately require dialysis. The OM2 only includes renal failure as a renal outcome, the risk for which is determined by eGFR, hemoglobin, LDL, white blood cells, and presence of micro/macro albuminuria, therefore missing important renal disease progression and outcomes.^{12,13,35-42} Neither the OM2 nor any other existing diabetes model has an adequate CKD module. If OM2 is chosen, we recommend building a separate renal module to capture progression to macroalbuminuria, doubling of the serum creatinine level, initiation of dialysis, or death from renal disease to capture the full spectrum of renal clinical benefits for treatments (see our suggestion in Model Framework). For example, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal nephropathy when added to standard care compared to placebo.⁴² Patients on empagliflozin had 61% risk reduction of renal progression nephropathy.⁴³

Data Source: Leverage existing CV outcomes trials, in addition to the PIONEER program, for population characteristics and key measures of clinical benefit data. ICER has indicated that they will be using data from the PIONEER trials. BI would like to caution ICER, as there are prominent gaps in data provided by PIONEER that have the potential to bias results of ICER's review. Focusing on the comparison with empagliflozin, PIONEER 2 trial was an open label and short duration trial in a second line treatment on top of metformin. This study cannot inform comparison in three out of four specified subgroups.⁴⁴⁻⁴⁶ PIONEER 6 trial was underpowered for the 20% reduction in the primary end-point of time to first 3-point MACE (the combination of non-fatal MI, non-fatal stroke, and cardiovascular death, hazard ratio [HR]=0.8, p=not significant [NS]).⁴⁵ The PIONEER studies do not include sufficient information on patients at increased risk of CVD or impaired renal function, which are central and pervasive characteristics of the T2DM burden of disease. Underrepresentation of

these groups introduces omission bias to ICER's assessment.⁴⁷ Additionally, the PIONEER 6 trial had a much shorter duration of follow-up compared to available CVOTs (e.g. EMPA-REG OUTCOME, TECOS, LEADER) and will provide a less comprehensive data set for deriving new sets of risk equations.

6. **Model Framework: Limitations of the UKPDS and the risk equations from the UKPDS OM2.** UKPDS was a randomized, multicenter trial of glycemic therapies in 5,102 patients with newly diagnosed T2DM conducted in 1977–1997. The UKPDS is a well-published study, on which validated models have been developed, including the OM2. However, there are limitations to using the OM2 to evaluate T2DM treatments. 1) The initial UKPDS population is UK-based newly diagnosed T2DM patients from 1977 to 1997. This population differs fundamentally from ICER's US-based target population. Additionally, diagnosis and treatment patterns of clinical outcomes have evolved substantially over the past 20 years.⁴⁸⁻⁵¹ Using data from a study population that differs from the target may lead to inaccurate results. 2) UKPDS does not adequately capture pleiotropic CV or renal outcomes, and therefore does not assess positive health impacts of T2DM treatments outside of glucose levels. This will underestimate the effect of T2DM treatments, such as empagliflozin. 3) A model using the UKPDS may not be able to represent the benefit of a ketogenic state, reductions in glomerular pressures with preservation of renal function, and lower left ventricular filling pressures that are independent of BP lowering and volume contraction. 4) UKPDS includes newly diagnosed T2DM individuals,⁴⁰ and risk equations derived for this cohort are not representative of the risk of CV and renal events for patient populations from CVOTs with an average T2DM duration of over 10 years.^{22,36} CVOTs like EMPA-REG OUTCOME enrolled around 7000 patients, with an average follow-up more than three years. Risk equations derived for patients at high risk of CV events will yield more accuracy in projection of CV and renal events. Thus, they should be used in a cost-effectiveness analysis for patients with increased CV risk or prevalent CKD, instead of UKPDS.⁴⁴⁻⁴⁶ Given these limitations, BI recommends a de novo model, which is structured to model T2DM as a cardiorenal metabolic disorder. **Model Inputs:** We recommend Lindgren 2007, Gandy 2012 and Sullivan 2016 for input utilities, as they are the most recent literature reviews capturing utility estimates for the patient population of interest.¹⁵⁻¹⁷

Model inputs: Utility Values. We recommend using utility and disutility estimates based on literature representative of the modeled patient population. Lindgren 2007, Gandy 2012 and Sullivan 2016 are recent papers capturing health state utilities for the patient population of interest.¹⁵⁻¹⁷

Additional Modeling Considerations:

- Dosing regimen for oral semaglutide is associated with a treatment burden that should be captured in the assessment. Oral semaglutide requires that patients are in a fasting state, take dose with up to half a glass of water, and then wait at least 30 minutes before eating, drinking, or taking other oral medication, including metformin.⁴⁴ Oral semaglutide requires titration over 2 months to determine optimal dose. Research has linked treatment burden to adherence and persistence;⁵³ this should be reflected in the model.
- The 14mg dose of oral semaglutide may cause nausea and vomiting severe enough to result in discontinuation. The model should include the impact of these events on discontinuation and quality of life as well as on treatment adherence, persistence, and effectiveness - particularly at lower dosages.⁵⁴
- The impact of treatment on all-cause hospitalization is an important cost savings driver, particularly under the Hospital Readmissions Reduction Program (HRRP). HRRP is a Medicare value-based purchasing program that reduces payments to hospitals with excess readmissions for six conditions, including heart failure.⁵⁵ Given the importance to payers and patients, this outcome should also be captured and valued.

Areas Meriting Further Clarification and Sensitivity Analyses

- How will third-line treatment be modeled?
- Assumptions on sustainability of body weight reduction beyond the study follow up.
- Impact on quality of life values for range of BMI needs to be carefully explored in sensitivity analyses.

- The background section describes metformin as most efficacious. We would suggest using the terminology as “most commonly used for glycemic control.”

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May 22, 2019

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Re: Draft Scoping Document on Oral Semaglutide for Type 2 Diabetes

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide comments regarding ICER's draft background and scope document, "Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value," dated May 2, 2019.

About the Institute for Patient Access

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality health care. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about patient access to approved therapies and appropriate clinical care. IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of more than 800 physician advocates committed to patient access. IfPA is a 501(c)(3) public charity non-profit organization.

Draft Scoping Document Comments

The Institute for Patient Access urges you to account for several important patient considerations in your analysis of oral semaglutide.

First, ICER's evaluation should explicitly account for the value created by the fact that this therapy is the first oral formulation of a GLP-1 receptor agonist. As an oral formulation, semaglutide creates convenience benefits for patients that could save time and increase their overall productivity. Specifically, oral semaglutide provides a less complex mode of administration, one that may work better for patients who dislike injections or for whom the cadence of a daily medication is more natural and simpler to maintain than the weekly injection required by the current GLP-1 formulations.

These factors may improve overall adherence rates. Of particular value, the administrative convenience of oral semaglutide may also improve accessibility for under-treated socio-

economic and geographic patient populations, increasing their adherence to treatment. The benefits from increased adherence and accessibility cannot be underestimated. They will likely improve overall health outcomes while also decreasing overall disease management costs. It is imperative that ICER fully incorporate these considerations in its analysis.

Second, when evaluating the health and economic outcomes of oral semaglutide for T2DM, it is imperative that ICER account for the high health and economic costs that Type 2 diabetes imposes on society. Diabetes was the seventh leading cause of death in the U.S. as of 2015 (the crude death rate was 24.7 per 100,000 persons).¹ As the scoping document notes, the estimated total direct and indirect costs of diabetes were \$245 billion; on a per-patient basis, there were \$7,900 in annual health expenditures directly attributable to diabetes. These cost estimates are as of 2012, however. The costs are undoubtedly higher today.

As a point of reference, the American Diabetes Association noted a 41 percent increase in the costs of diabetes between 2007, when costs totaled \$174 billion,² and 2012. While there are no estimates for costs increases over the past seven years, the growth pattern between 2007 and 2012 suggests that the direct and indirect costs of diabetes today could be more than \$345 billion. ICER should account for the likely increase in the cost that diabetes imposes on society when making its cost-effectiveness evaluations.

Third, it is imperative that ICER recognize that current treatments are not effective for all patients. In light of the high costs of diabetes, there is significant value in a medicine that can effectively treat patients for whom current therapies do not adequately control Type 2 diabetes. Global phase 3a trials have demonstrated that oral semaglutide may be more efficacious for these patients.³ It is imperative that ICER's analysis explicitly incorporate the value created when patients who did not have an efficacious medicine now do.

Fourth, patients living with diabetes have an increased risk for cardiovascular disease and stroke, which is even higher if they also struggle with obesity. Cardiovascular disease imposed over \$555 billion in costs in 2015, and it is projected to increase to \$1.1 trillion in 2035.⁴ To improve the health outcomes for patients, and lower overall health care costs, the health care system must employ a team-based, whole-patient approach to caring for people with both diabetes and cardiovascular disease. Toward this goal, medicines that can help patients control their diabetes *and* reduce their cardiovascular risks hold great promise.

It is, consequently, imperative to incorporate the long-term impact of oral semaglutide on cardiovascular disease in order to accurately assess the therapy's lifetime cost effectiveness. Based on current initial research, semaglutide may be associated with a lowered rate of adverse cardiovascular outcomes for patients with type 2 diabetes who also had high cardiovascular

¹ <https://www.cdc.gov/diabetes/data/statistics-report/deaths-cost.html>.

² <http://care.diabetesjournals.org/content/36/4/1033>.

³ <https://www.pharmacytimes.com/resource-centers/diabetes/oral-semaglutide-demonstrates-benefits-for-patients-with-type-2-diabetes>

⁴ <https://healthmetrics.heart.org/wp-content/uploads/2017/10/Cardiovascular-Disease-A-Costly-Burden.pdf>

risks.⁵ Excluding oral semaglutide’s potential cardiovascular benefits will undervalue the therapy, in turn leading to coverage and access barriers that leave patients unnecessarily at risk.

Fifth, the “Report Aim” section of the scoping document states that ICER intends to capture important “public health effects” related to oral semaglutide. However, broader, longer-term, public health effects are difficult to extrapolate from clinical trial data. Inappropriate extrapolations could lead to unwarranted conclusions.

As the aforementioned connection between diabetes and cardiovascular disease illustrates, the broader public health benefits that oral semaglutide may create can be material, even if the evidence is still preliminary or not yet available. The unavailability of the data does not justify excluding (or undervaluing) these benefits. The still developing public health effects of oral semaglutide also warrant caution regarding ICER’s intention to run a “simulation model to assess the lifetime cost-effectiveness of the treatment.” Since the public health effects cannot yet be fully understood, accurate lifetime cost-effectiveness estimates are unknowable at present. Consequently, judgements regarding the lifetime value of the treatment, given the limited nature of the clinical trial data, will simply be quantitative speculation.

Should there be insufficient evidence, particularly because only phase 3 data are available, IfPA urges caution regarding any cost-effectiveness determination. Unsupported conclusions could inappropriately jeopardize patients’ access to these medicines once a fuller understanding of the broader public health benefits is better understood.

Finally, there are always concerns when studies compare the efficacy of a treatment that has not yet been approved by the FDA to approved treatments that have been in use for years. Treatments that have not yet been approved will not have any post-marketing data (by definition). As a result, any understanding of the drug’s benefits and side-effects will be less robust than an understanding of treatments that have been available for years. Caution is warranted before any sweeping conclusions are reached regarding relative efficacy.

Conclusion

IfPA urges ICER to account for these considerations when performing its analysis, lest the clinical evidence review provide an inaccurate picture of the benefits that oral semaglutide could offer patients living with Type 2 diabetes. If IfPA can provide further detail or aid the Institute for Clinical and Economic Review in incorporating any of the above recommendations into its final draft, please contact us at 202-499-4114.

Sincerely,



Brian Kennedy
Executive Director

⁵ <https://www.nejm.org/doi/full/10.1056/NEJMoa1607141>.



May 22, 2019

Steven D. Pearson, MD, MSc, FRCP
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RE: Value Assessment for Type 2 Diabetes

Dear Dr. Pearson:

Thank you again for the continued opportunity to provide comments on the proposed ICER analysis of diabetes treatments. At this time, we would like to provide feedback on the scoping document released on May 2, 2019.

Thank you also for the phone meeting on May 17, 2019 which has helped us shape some of our comments and we hope that you find them useful as you initiate this assessment. As discussed, use of OM2 model, sitagliptin pricing/loss of exclusivity, heterogeneity of diabetes cardiovascular outcome trials (CVOTs), generalizability of these trial data to all patients with diabetes, differences in methods used to assess efficacy in clinical trials, and real world adherence to diabetes medications should also be considered in this report. Please note that given that several of the points we raised in the open input period are still relevant for the scoping period, we have also included them below. Below we provide additional information on a few selected issues:

1. Selection of United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model 2 (OM2)

From Mount Hood challenges for diabetes model, several issues with OM2 were identified. Cardiovascular outcomes results:

OM2 model has been shown to overestimate rates of fatal and non-fatal CV events as well as ESRD from the EMPAREG study. Consequently, over estimation of baseline risk of CV and renal events could overestimate the potential value of more efficacious products versus less efficacious products. (based on 9th Mount Hood Challenges meeting in Oct 2018)

- Quality Adjusted Life Years (QALYs) and total costs:
For transparency challenge by reproducing UKPDS 72, OM2 did overestimate the differences in total cost and underestimated the differences in total QALYs (based on 8th Mount Hood Challenges meeting report [1])

Not accounting for these limitations from OM2 model could easily bias the findings and favor one intervention more than other. It would be useful to understand the reasons of choosing OM2 and a clear explanation how ICER will correct and calibrate these model limitations. Merck looks forward to further engagement with ICER regarding model selection in the next phase of this review.

2. Sitagliptin price to be used in the model

Loss of Exclusivity: The current patent for sitagliptin (Januvia®) is expected to end in 2022 with eligibility for a 6-month pediatric extension. After patent expiration, the cost of sitagliptin is expected to decline with the entry of generic competition. We recommend ICER discuss this important information in the review because of its implication to near-future decisions by ICER's stakeholders. Merck hopes to work with ICER to identify methods for creating meaningful budget impact and cost-effectiveness comparisons which reflect system costs more accurately.

List Price vs. Net Price: Any potential analysis using the list price does not consider the varying discounting rates for sitagliptin offered to different US payers (several commercial plans, Medicare, Medicaid, etc.). Hence, a base case analysis that utilizes the list price is not relevant for most payers in the US. While each individual payer is aware of its actual (net) price for sitagliptin, this information may not be available for oral semaglutide. If use of the net price is not feasible, another option is to consider use of relative price difference to evaluate cost-effectiveness. If this is not possible for all products being reviewed, ICER should discuss this as a significant limitation of this review.

3. Generalizability and heterogeneity of CVOT data

Available CVOT data for most SGLT-2i and some GLP-1 receptor agonist (GLP-1 RA) therapies have shown significant cardiovascular/mortality benefits among type 2 diabetes patients with established CVD (~20% of total type 2 diabetes population) [1-4]. However, this benefit is not documented among those without established CVD (remaining 80% of the type 2 diabetes population). This should be accounted for when ICER is conducting this review.

In addition to generalizability, it is important to note that there is considerable heterogeneity between diabetes CVOTs in terms of study population and other study design-related factors. For example, the CVOT for sitagliptin (TECOS) was designed as a glycemic equipoise study and the average difference in HbA1c for the active vs. placebo arm was 0.3%. In comparison, in the CVOT for injectable semaglutide (SUSTAIN-6), this difference was much larger between the two study arms (0.7% for 0.5 mg dose and 1.0% for 1 mg dose) [5,6]. Not accounting for these differences while using the data as model inputs would be a limitation and could bias findings towards those products where equipoise was not achieved.

4. Adherence to medications

In the real world, medication adherence is an important factor that determines the benefits of any diabetes therapy. Real-world studies have suggested that adherence to injectable GLP-1 RA therapy is lower than that of DPP-4i therapy. [7,8,9]

In addition to an injectable route of administration, lower adherence may also be related to other factors including tolerability, such as gastrointestinal (GI) disturbances, complexity of dosing regimen, and patient out-of-pocket costs. While data on real-world adherence for oral semaglutide are not yet available, known tolerability issues and regimen

complexity may result in lower adherence compared to other oral medications for diabetes. For example, the PIONEER 3 trial demonstrated a substantially higher rate of GI side effects for oral semaglutide 14 mg/d compared with sitagliptin 100 mg/d (nausea 15.1% vs. 6.9%; diarrhea 12.3% vs. 7.9%; vomiting 9.0% vs. 4.1%). [10]

Adherence to medication may directly translate into effectiveness in the real world. While RCT data demonstrate higher HbA1c efficacy for injectable GLP-1 RA vs. DPP-4i, real-world effectiveness was similar (-0.52% for GLP-1 RA vs. -0.51% for DPP-4i at the end of one year) [9]. Furthermore, the real-world effectiveness of GLP-1 RA will also be dependent on the dose distribution in the population (i.e., not all patients will be on high doses, which have demonstrated higher efficacy than lower doses in RCTs).

We recommend that these limitations be considered in the ICER review; for example, conducting sensitivity analyses to take real-world medication adherence into consideration when evaluating cost-effectiveness.

5. Selection of Subgroups for the Cost Effectiveness Model

The draft scoping document does not state the characteristics of a high-risk cardiovascular population. In general, the diabetic population is at high risk of cardiovascular risk. Please also note that majority of the patients included in the CVOTs for diabetes drugs included patients with established CVD. In addition, there are several antihyperglycemic agent that can be used as a third-line therapy for patients. The draft scoping document does not specify the background therapy for triple therapy. Due to the large number of potential combinations for triple antihyperglycemic therapy it is unlikely that sufficient clinical data exist to evaluate some triple therapy treatment pathways.

Thank you again for this opportunity to provide comments and we look forward to continuing this engagement throughout the evaluation period. If you have any questions, please feel free to contact me.

Sincerely,



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May 22, 2019

NOVO NORDISK PUBLIC RESPONSE TO ICER DRAFT SCOPING DOCUMENT: ORAL SEMAGLUTIDE FOR TYPE 2 DIABETES: EFFECTIVENESS AND VALUE

Novo Nordisk appreciates the opportunity to participate in ICER's review of oral semaglutide for type 2 diabetes (T2D). Timely treatment of T2D is needed to reduce the risk of developing complications, yet even with numerous treatment options available, many patients do not achieve current HbA_{1c} targets. GLP-1RAs provide effective glycemic control along with weight reduction and low risk of hypoglycemia.^{1,2} Oral semaglutide offers an innovative solution that can help patients meet T2D treatment goals through an oral mode of administration where previous formulations were only by injection. The American Diabetes Association (ADA) has stated that patient-centered care is the focus and priority.³ The updated ADA-EASD Consensus Report significantly updated recommendations for pharmacologic treatment of T2D to specifically consider important comorbidities such as ASCVD, chronic kidney disease and heart failure and key patient factors, such as hypoglycemia risk, body weight, costs and patient preference.⁴ Novo Nordisk would like to highlight certain considerations for the scope of ICER's review:

RECOMMENDATIONS

1. Consider importance of weight management and cardiovascular risk factors, treatment inertia and reluctance to intensify therapy with injectable agents in evaluation.

T2D is a progressive disease⁵ and the goal of treatment is to prevent or delay complications and maintain health-related quality of life, which requires achievement and maintenance of glycemic control and management of cardiovascular (CV) risk factors.⁶ The 2019 ADA Standards of Medical Care recommend early consideration of a patient's history of cardiovascular disease (CVD) as well as factors such as body weight, hypoglycemic risk, and treatment cost, when selecting treatment for T2D.⁴ Two critical unmet needs (appropriate weight management and treatment inertia) exist among T2D patients, physicians, and health systems, requiring further consideration in the review of oral semaglutide.

Weight Management

As a critical CV risk factor, weight gain contributes to worsening glycemic control as well as increased risks for other comorbidities including but not limited to CVD, dyslipidemia,⁷ obstructive sleep apnea,⁷ renal disease,⁸ depression¹⁹ and cancer,¹⁰ independent of HbA_{1c} reduction.¹¹ The ADA states that a moderate weight loss of 5-10% of initial body weight can improve insulin sensitivity, glycemic control, blood pressure and reduce the need for glucose-lowering medication.⁴ Additionally, weight gain increases the risk of CVD even in the absence of other metabolic abnormalities,¹² and increases the risk of CVD mortality.¹³ Excess weight gain in people with T2D increases the cost for an inpatient or outpatient department visit by nearly 15x times when compared to people with T2D and normal weight.¹⁴

Treatment Inertia

Due to the progressive nature of T2D, most patients require treatment intensification to maintain adequate control of HbA_{1c} levels.⁵ Though treatment intensification from oral to injectable anti-diabetic agents is often required to maintain glycemic control, treatment inertia poses a significant barrier.^{15,16} Treatment inertia is the failure to initiate or intensify therapy despite inadequate glycemic control.^{17,18} Research demonstrated that 70.4–72.8% of patients in a US managed care setting received no intensification of treatment in the 6 months following above-target HbA_{1c} values.¹⁷ Treatment inertia can occur at any stage of T2D, but delays in intensification are generally greater when insulin or other injectable therapies are needed.¹⁵

Patients are often reluctant to intensify treatment or progress to injectable therapies which can result in intensification delay and poor glycemic control.¹⁹ Physician factors are reported to have the biggest influence on treatment inertia, including lack of prescribing confidence, fear of hypoglycemia, time constraints, and perceived patient opposition.^{15,16,20} Reliance on specialists for intensification to injectable therapies, where consultation costs are typically higher,^{21,22} may also increase the economic burden of diabetes.

Prolonged poor glycemic control increases health care costs due to insufficiently effective treatments, and an increased risk of costly diabetes complications.^{23,24} A 1-year delay in receiving treatment intensification in people with HbA_{1c} ≥7.0% is associated with a significantly increased risk of myocardial infarction (67%), heart failure (64%), composite CV events (62%), and stroke (51%) versus patients with HbA_{1c} <7.0%.²⁵ To avoid therapeutic inertia, it is recommended that treatment is re-assessed and modified every 3-6 months.⁶

2. Weight management (either gain or loss) and CV outcomes should also be modeled, both independent of HbA_{1c}.

Antihyperglycemic therapies can have considerable effects on patient weight, prompting careful consideration of weight-loss or weight-neutral therapies for patients with T2D.^{26,27} As such, weight management (gain / loss) should be considered and modeled independent of A1c. For example, the SCALE Diabetes randomized clinical trial demonstrated that cardiovascular endpoints were improved when additional weight loss occurred in the context of comparable A1c reductions.²⁸ A US retrospective cohort study found that, after accounting for glycemic control, weight loss was associated with significant reductions in total cost of care and T2D-related annual total health care costs.²⁹ In addition, weight change is associated with changes in health-related quality of life.^{30,31}

CV outcomes should also be considered and modeled independent of A1c. The LEADER trial demonstrated that patients treated with liraglutide had lower risk of the primary composite outcome — first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the time-to-event analysis — and lower risks of death from cardiovascular causes, death from any cause, and microvascular events, and LEADER demonstrated improved CV related outcomes independent of A1c.³²

3. Considering inclusion of all major adverse events recorded within approved prescribing information and the time course of events to assess overall benefit and risk.

Novo Nordisk suggests that ICER consider inclusion of clinically significant adverse events within approved prescribing information and not only those identified in clinical trials for oral semaglutide. Prescribing information provides a more comprehensive assessment of risk given the different trial populations used for products.

Additionally, when evaluating adverse events, it is important to consider the occurrence of adverse events over time. For example, risk for nausea seen with all GLP-1RAs, including Victoza® and oral semaglutide, occurs early during dose initiation and escalation, typically within the first 3 months, and then dissipates over time. In contrast, the risk for many other adverse events may increase over time.

4. Subpopulation comparison of interest should be focused on overweight / obese patients and patients with renal impairment.

Overweight / Obese patients

As stated above, weight management plays a significant role in glycemic control and other T2D risk factors. The ADA guidelines state that in patients with T2D who are overweight or obese, modest and sustained weight loss has been shown to improve glycemic control and to reduce the need for glucose-lowering medications.⁴ Obesity should be analyzed as an important sub-population to evaluate the economic benefits of the treatments being studied.

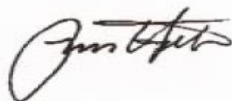
Patients with renal impairment

SGLT-2i's are not appropriate for use in patients with moderate to severe renal impairment to improve glycemic control, and as such should not be evaluated in that subpopulation for this review. According to the Prescribing Information for JARDIANCE®:

- “JARDIANCE® should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m². No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m². JARDIANCE® should be discontinued if eGFR is less than 45 mL/min/1.73 m².”

CONCLUSION

Novo Nordisk would like to thank ICER for their consideration. We recognize a comprehensive economic analysis will be difficult to conduct and extrapolate. Limitations of the analysis may include: modeling MACE, kidney function decline and body weight in addition to HbA1c; economic comparisons made across drug classes and not within classes; the extrapolation of results to all products within each class without evaluating all products within a class; and factoring in the impact of treatment inertia and innovation of oral semaglutide. We look forward to the analysis and appreciate the opportunity to provide feedback.



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The SCORE-IT study has recently completed an international consensus exercise to identify which health outcomes are the most important to people with type 2 diabetes, healthcare professionals, researchers and healthcare policymakers, and should be included in a core outcome set (COS) for research.

The development of the SCORE-IT COS has included input from all stakeholders through an international Delphi process [1] to score outcomes identified from systematic review of the clinical trials and patient perspectives literature [2, 3]. The main report has been submitted for publication and is currently under review.

The scope of the SCORE-IT COS is for use in clinical trials of non-surgical therapeutic interventions for the treatment of hyperglycaemia in adults with type 2 diabetes mellitus (T2DM). We would consider a clinical trial of the oral GLP-1 receptor agonist Semaglutide (Novo Nordisk) to be included within this scope, specifically when used for the indication to control blood glucose in patients with T2DM with inadequate glycaemic control.

We have reviewed the proposed outcomes in the draft scope against the outcomes included in the COS (Table 1). The COS does not preclude other outcomes being measured but rather recommends the minimum that should be measured and reported. With this in mind we would like to propose the following amendments to the ICER guidance:

1) That the following additional outcomes are included

- Visual deterioration or blindness
- How often someone is admitted to hospital because of their diabetes.
- Hyperglycaemia - how often someone has high blood glucose.
- Hyperglycaemic emergencies (to include diabetic ketoacidosis and hyperosmolar hyperglycaemic state).

2) That the following outcomes are specified within the included outcome “other cardiovascular complications” :

- Having gangrene or having an amputation of the leg, foot or toe.
- Heart failure

3) That the outcome “health related quality of life” also specifically includes and reports:

- Activities of daily living - being able to complete usual everyday tasks and activities including those related to personal care; house hold tasks or community based tasks.

Including the full COS in future comparative effectiveness trials, including trials of oral Semaglutide, will facilitate the comparison of results across trials and will ensure that they are relevant to all stakeholders.

Submitted on behalf of the SCORE-IT study team

Dr Nicola Harman	Core outcome set developer, University of Liverpool
Professor Paula Williamson (PI)	Professor of Medical Statistics/ Core Outcome Measures for Effectiveness Trials lead, University of Liverpool
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Table 1 Comparison of outcomes between ICER scoping document and SCORE-IT COS

SCORE-IT Outcome	ICER scoping document outcome
Glycaemic control - how well someone's blood glucose is controlled.	HbA1c
Global quality of life - someone's overall quality of life including physical, mental and social wellbeing.	Health-related quality of life
Activities of daily living - being able to complete usual everyday tasks and activities including those related to personal care; house hold tasks or community based tasks.	
Body weight - how much someone weighs.	Safety -Weight gain
Kidney function - how well someone's kidneys are working.	Nephropathy
Hyperglycaemia - how often someone has high blood glucose.	
Hypoglycaemia - how often someone has low blood glucose levels.	Safety- Hypoglycemia
Visual deterioration or blindness - if someone's eyesight gets worse or if they have loss of vision including blindness.	
Neuropathy - damage to the nerves caused by high glucose. This can lead to tingling and pain or numbness in the feet or legs. It can also affect bowel control; stomach emptying and sexual function.	Neuropathy
Having gangrene or having an amputation of the leg, foot or toe.	
Nonfatal myocardial infarction - having a heart attack that is not fatal.	Macrovascular outcomes including: All-cause mortality, Cardiovascular mortality, Stroke, Myocardial infarction, Other cardiovascular complications
Heart failure	
Cerebrovascular disease - including stroke, subarachnoid haemorrhage, transient ischaemic attack and vascular dementia.	Macrovascular outcomes including: All-cause mortality, Cardiovascular mortality, Stroke, Myocardial infarction, Other cardiovascular complications
How often someone is admitted to hospital because of their diabetes.	
Hyperglycaemic emergencies (to include diabetic ketoacidosis and hyperosmolar hyperglycaemic state).	
Side effects of treatment- any unwanted effects of the treatment.	Safety - adverse events, discontinuation due to adverse events, serious adverse events
Overall survival - how long someone lives.	Macrovascular outcomes including: All-cause mortality, Cardiovascular mortality, Stroke, Myocardial infarction, Other cardiovascular complications
Death from a diabetes related cause such as heart disease.	Macrovascular outcomes including: All-cause mortality, Cardiovascular mortality, Stroke, Myocardial infarction, Other cardiovascular complications