



October 4, 2019

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

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

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide comments regarding ICER's draft evidence report titled "Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value," released September 11, 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 physicians committed to shaping a patient-centered health care system. IfPA is a 501(c)(3) public charity nonprofit organization.

Draft Evidence Report Comments

Several methodological issues in the draft evidence report for oral semaglutide are likely biasing the results toward an overly restrictive cost-effectiveness result. These issues include:

- Not adequately accounting for the additional patient benefits that a once-daily oral formulation provides
- Not adequately accounting for the co-morbidities associated with Type 2 diabetes
- Underestimating the full costs Type 2 diabetes impose on patients and their caregivers
- Not adequately accounting for the well-documented heterogeneity across Type 2 diabetes patients.

In addition, as documented in the draft evidence report, the results of the cost-effectiveness model contain an unacceptable level of uncertainty.

Each of these issues, detailed below, leads ICER's conclusions to underestimate the cost-effectiveness of oral semaglutide, potentially introducing inappropriate access obstacle for patients.

The Report Does Not Adequately Account for the Benefits of a Once-Daily Oral Formulation

Current evidence demonstrates that, as a pill rather than an injection, oral semaglutide improves patients' adherence and willingness to take the medicine that is most appropriate for them. Oral semaglutide should, therefore, improve overall health outcomes and decrease overall disease management costs.

Injectable drugs are often an obstacle to patient adherence. In describing the introduction of oral semaglutide, the *American Journal of Managed Care* noted that the entire purpose of the drug is to

... address an unmet need in patients with T2D [Type 2 diabetes] and CV [cardiovascular] risk who are overweight, as the GLP-1 receptor agonist class has been shown to help patients achieve significant weight loss. However, not all patients are willing to use an injectable drug, even one only needed once a week.

An ACC panel discussion reviewed case studies on when to prescribe GLP-1 receptor agonists or SGLT2 inhibitors, and cardiologists said there are cases in which GLP-1 receptor agonists are indicated, but patients will not take an injectable drug. In one scenario described during the ACC session, an obese female patient was prescribed an SGLT2 inhibitor instead, but the physician commented that while this would control her blood sugar, it would not provide the same weight loss benefits.¹

The draft evidence report fails to adequately incorporate these benefits, thereby underestimating the cost effectiveness of this drug.

The Report Does Not Adequately Account for Co-Morbidities

A number of serious and complex co-morbidities are associated with Type 2 diabetes. The existence of these co-morbidities significantly limits the reliability of the results derived from the cost-effectiveness model.

Cardiovascular disease, for example, is a common comorbidity of Type 2 diabetes. Cardiovascular disease imposed over \$555 billion in costs in 2015, and is projected to impose \$1.1 trillion in costs by 2035.² Oral semaglutide is associated with a lowered rate of adverse cardiovascular outcomes for patients with Type 2 diabetes who also had high cardiovascular

¹ Caffrey Mand DiGrande S (2019) "Novo Nordisk Seeks Oral Semaglutide Approval, CV Indications on New Drug and Injectable" *the American Journal of Managed Care*, March 21; <https://www.ajmc.com/newsroom/novo-nordisk-seeks-oral-semaglutide-approval-cv-indications-on-new-drug-and-injectable->.

² <https://healthmetrics.heart.org/wp-content/uploads/2017/10/Cardiovascular-Disease-A-Costly-Burden.pdf>

risks, and it improves patient adherence and patient willingness to use a GLP-1 receptor.³ Therefore, an additional benefit from oral semaglutide is that it will reduce the costs associated with cardiovascular disease. Similar benefits are derived from other co-morbidities associated with Type 2 diabetes.

While these benefits are significant, it can take years for patients or the health care system to fully realize them. In other words, it is difficult to “reliably predict” the full benefits from oral semaglutide to include the benefits gained by reducing the co-morbidities associated with Type 2 diabetes.

The draft evidence report admits that these concerns are a significant limitation to the cost-effectiveness model:

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.

Sensitivity analyses, however, do not adequately address this limitation. In reality, the public health effects of oral semaglutide cannot yet be fully understood, and accurate lifetime cost-effectiveness estimates are simply unknowable at present.

The Report Underestimates the Costs Associated with Diabetes

Diabetes was the seventh leading cause of death in the United States as of 2015.⁴ The draft evidence report notes that 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.

To get a sense of how much these costs could have grown, as of 2007, the estimated costs of diabetes were \$174 billion.⁵ Thus, the American Diabetes Association is estimating that the direct and indirect costs of diabetes grew 41 percent between 2007 and 2012.

While there are no estimates for how much these costs have increased over the past seven years, applying the past five-year growth rate over a seven-year timeframe (a conservative assumption) would imply that the direct and indirect costs of diabetes could be more than \$345 billion today.

The implications of this growth are not immaterial. A 41 percent increase in the economic costs of diabetes meaningfully changes the cost effectiveness of oral semaglutide. Without accounting

³ <https://www.nejm.org/doi/full/10.1056/NEJMoa1607141>.

⁴ <https://www.cdc.gov/diabetes/data/statistics-report/deaths-cost.html>.

⁵ <http://care.diabetesjournals.org/content/36/4/1033>.

for these higher costs, the report underestimates the economic burden that Type 2 diabetes imposes on society.

The Report Fails to Fully Account for Patient Heterogeneity

Current treatments are not effective for all patients. Given the high cost of diabetes, there is a significant value to a medicine that can effectively treat patients who have not achieved adequate control with current therapies for Type 2 diabetes. As the draft evidence report notes, oral semaglutide has properties that can make it more appropriate for many patients. Nevertheless, the report does not account for the value that is created when patients who did not have an effective option now do.

The Analysis Contains an Excessive Amount of Uncertainty

While uncertainty is inherent with all models, the base case results of the long-term cost effectiveness model are plagued with an excessive amount of uncertainty. When discussing the base case results, the draft evidence report states:

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***. (emphasis added)

The best interests of patients cannot be served when a medicine's cost effectiveness is based on "highly uncertain" findings. Due to this uncertainty, it is not possible to know whether the estimated cost-effectiveness thresholds are overly restrictive, thereby denying patients access to a medicine that would provide value to them.

Given the number of patients living with Type 2 diabetes in the United States, such errors will be excessively costly to the health care system. If the uncertainties that plague the base case model cannot be reduced, ICER should delay its analysis until such time that the results can be modeled with an acceptable level of uncertainty.

Conclusion

Comparing the efficacy of a treatment when robust post-marketing data does not yet exist is always problematic. It offers an understanding of the drug's benefits that is, by definition, constrained, increasing the uncertainty of any cost-effectiveness evaluation. The sheer number of times the draft evidence report notes "significant uncertainties" raises serious red flags regarding the accuracy of the cost-effectiveness results.

As a result, IfPA is concerned that the report provides 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,

A handwritten signature in black ink, appearing to read "B. Kennedy", written in a cursive style.

Brian Kennedy
Executive Director

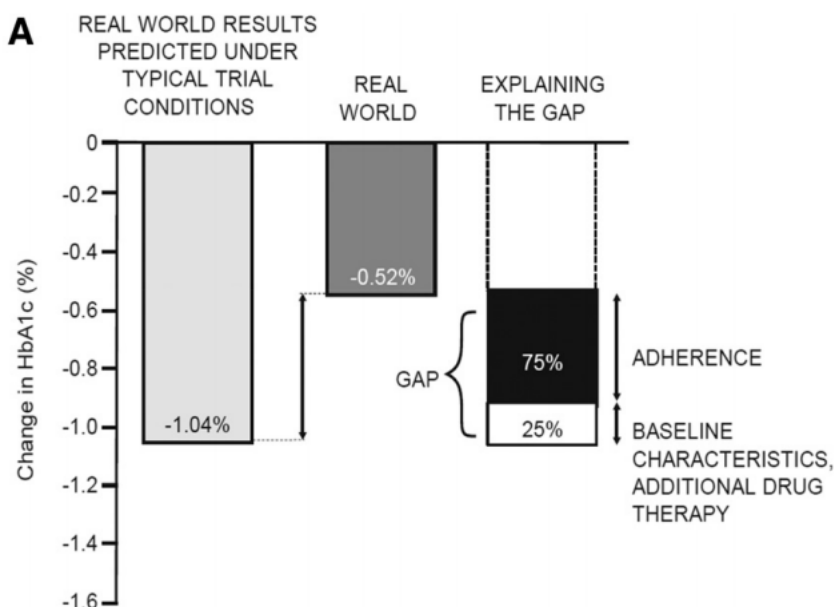
8 October 2019

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

Thank you for the opportunity to provide comments relating to the proposed ICER analysis of diabetes treatments, specifically in relationship to oral semaglutide. We would like to provide feedback on the Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value Draft Evidence Review released on 12 Sep 2019.

Over the past 15 years, more than 40 products have been approved by the FDA for the treatment of Type 2 diabetes. Nonetheless, over this same time period, there has been negligible improvement in overall rates of glycemic control based on a recently published analysis of NHANES cross-sectional data from 2005-2016. Of great concern is the proportion of patients with Hemoglobin A1c (HbA1c) values above 9, which remains above 30% of all Type 2 diabetes patients in 2016 just as it did in 2005. The authors conclude that the diabetes care cascade in the United States has not significantly improved between 2005 and 2016 and that gaps in diabetes care that were present in 2005 persist.¹

In a peer-reviewed analysis designed to assess the factors influencing glycemic control differences in the real-world relative to randomized, controlled clinical trials entitled Type 2 Diabetes in the Real World: The Elusive Nature of Glycemic Control, Drs. Edelman and Polonsky conclude that the majority of this difference is due to suboptimal adherence.²



Accordingly, there may be other relevant and important questions to consider relating to “Potential Other Benefits and Disadvantages” and “Contextual Considerations” that the New England CEPAC voting body will deliberate regarding the effectiveness and value of oral semaglutide for Type 2 diabetes. The current key points for consideration are listed in Table 5.1:

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

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

The ICER review poses the question of “whether having an oral GLP-1 receptor agonist will produce better outcomes due to many patients remaining on oral treatment who would otherwise require escalation of therapy using a once-weekly GLP-1 receptor agonist.” Although an important consideration, in the context of the challenges that all Type 2 diabetes patients face when managing their chronic metabolic control issues with advancing therapeutic options, this may not be the most relevant question. Perhaps a more appropriate question is whether oral semaglutide will produce adherence rates that meaningfully exceed rates for either once-weekly injectable GLP-1 receptor agonists such as dulaglutide (the current market leading GLP-1 RA) or SGLT-2 inhibitors (the current preferred branded oral class of anti-diabetic medicines).

No matter what the choices are for initial or combination treatments, adherence rates of type 2 diabetes therapies are far from optimal. Below are 6-month adherence rates, as measured by the Proportion of Days Covered (PDC) $\geq 80\%$, for SGLT-2 inhibitors as a group and the market leading once-weekly GLP-1 receptor agonist. The methodology used for these analyses can be found in the references to this commentary.

- SGLT-2 inhibitors 61.4%³
- Dulaglutide 54.2%⁴

In real-world clinical settings, as patients are faced with all of the complexities of managing a chronic condition such as type 2 diabetes, 4 out of 10 patients who started therapy with a SGLT-2 inhibitor and almost half of patients who began therapy with a once-weekly injectable GLP-1 RA were not adherent over a six-month period of time. The clinical implications of non-adherence include higher total medical costs and inferior glycemic control.

In a second real-world analysis of the once-weekly GLP-1 RA dulaglutide, there was a highly significant difference in glycemic efficacy as measured by the lowering of HbA1c in patients who were adherent (defined as PDC measured to be $\geq 80\%$) vs. patients who were not adherent (PDC $< 80\%$).⁵

- A1c reduction PDC $\geq 80\%$ -1.14
- A1c reduction PDC $< 80\%$ -0.53

Based on the realities of suboptimal medication adherence with oral SGLT-2 inhibitors (requiring a straight-forward once daily oral regimen) and the market-leading GLP-1 RA (utilizing an optimized once-weekly injection where the patient does not see or handle a needle and simply uncaps the delivery device, places the device on the site of administration, unlocks the safety lock and presses the autoinjector button enabling the device to automatically insert and retract the needle after delivering the necessary dose)⁶, it will be important to anticipate and track adherence rates with oral semaglutide.

Factors that could impact oral semaglutide adherence rates will likely include the following:

- Three-step titration regimen: 3 mg for 4 weeks, followed by 7 mg for 4 weeks, followed by 14 mg, as needed for additional glycemic control.
- Complexity of administration for a once-daily oral medication: To comply with dosing instructions for oral semaglutide, the patient needs to be in a fasted state for at least 6 hours; can consume no more than 4 ounces of water; must stay fasted for an additional 30 minutes without additional fluids, food or other medications. If this strict administration regimen is not followed, the bioavailability of oral semaglutide drops significantly, thereby limiting its effectiveness.⁷

- Significant GI adverse event rates: 20% nausea rate for oral semaglutide vs. 2% for empagliflozin, in the PIONEER-2 Head-To-Head trial⁸, which was likely to be a strong influence on the discontinuation rate of 11% for oral semaglutide.

At face value, one could reason that oral semaglutide might offer reduced therapeutic complexity relative to injectable GLP-1 RA products that would significantly improve patient outcomes based on its oral route of administration. However, given the real-world adherence challenges for both oral SGLT-2 inhibitors as well as the market leading once-weekly injectable GLP-1 RA dulaglutide, which one could argue would be no worse than the real-world adherence rates for oral semaglutide given the complex daily oral administration instructions and the expected gastrointestinal symptoms and tolerability challenges, it is premature to conclude that oral semaglutide will improve patient outcomes. These factors all contribute to uncertainties about the magnitude or durability of the long-term benefits of oral semaglutide. Once oral semaglutide is available to patients and has sufficient treatment experience, it will be important to conduct real-world analysis with oral semaglutide, including relevant comparisons to oral SGLT-2 inhibitors and injectable once-weekly GLP-1 RAs, in order to assess its clinical and economic value.

Sincerely,

Fred T. Fiedorek, MD
Chief Medical Officer & Head of Global Regulatory Affairs
Intarcia Therapeutics, Inc.
One Marina Park Drive, Suite 1300
Boston, MA 02210

References:

¹ Evaluation of the Cascade of Diabetes Care in the United States, 2005-2016. Pooyan Kazemian, PhD; Fatma M. Shebl, MD, PhD; Nicole McCann, BA; Rochelle P. Walensky, MD, MPH; Deborah J. Wexler, MD, MSc; *JAMA Intern Med.* doi:10.1001/jamainternmed.2019. 2396 Published online August 12, 2019.

² Type 2 Diabetes in the Real World: The Elusive Nature of Glycemic Control. Steven V. Edelman, William H. Polonsky; *Diabetes Care.* 2017, 40(11):1425-1432.

³ Comparing Medication Adherence and Persistence Among Patients with Type 2 Diabetes Using Sodium-Glucose Cotransporter 2 Inhibitors or Sulfonylureas. Kelly F. Bell, PharmD, MSPhr, MS, Katherine Cappell, PhD, Michael Liang, MS, and Amanda M. Kong, MPH; *Am Health Drug Benefits.* 2017, 10(4): 165–174.

⁴ Treatment patterns in patients with type 2 diabetes mellitus treated with glucagon-like peptide-1 receptor agonists: Higher adherence and persistence with dulaglutide compared with once-weekly exenatide and liraglutide. Carlos Alatorre MBA, PhD, Laura Fernández Landó MD. Maria Yu MS, Katelyn Brown Pharm D, Leslie Montejano MA, CCRP, Paul Juneau MS, Reema Mody MBA, PhD, Ralph Swindle PhD. Diabetes, Obesity and Metabolism. 2017, 19(7):953-961

⁵ Real-world effectiveness, adherence and persistence among patients with type 2 diabetes mellitus initiating dulaglutide treatment. Reema Mody, Michael Grabner, Maria Yu, Ralph Turner, Anita Y. M. Kwan, Whitney York & Laura Fernández Landó; Current Medical Research and Opinion 2018, 34(6):995–1003.

⁶ Trulicity US Prescribing Information Instructions for Use, September 2018.

⁷ Rybelsus US Prescribing Information, September 2019.

⁸ Oral Semaglutide versus Empagliflozin in Patients with Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. Rodbard HW, Rosenstock J, Canani LH, Deerochanawong C, Gumprecht J, Lindberg SØ, Lingvay I, Søndergaard AL, Treppendahl MB, Montanya E; PIONEER 2 investigators. Diabetes Care. 2019 Sep 17. pii: dc190883. doi: 10.2337/dc19-0883. [Epub ahead of print] PubMed PMID:31530666.



INSTITUTE FOR
**PATIENT ACCESS
& AFFORDABILITY**

October 8, 2019

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Oral Semaglutide for Type 2 Diabetes: Draft Evidence Report

Dear Dr. Pearson:

Institute for Patient Access & Affordability is a new program division of Patients Rising with the mission to provide patient-powered pathways to help both public and private payers as they make critical coverage decisions for patients with rare and chronic diseases. As scientific innovation advances and evolves, it is imperative that we look beyond the one-size fits all approach to identify ways to promote access and maintain affordability. IPAA evaluates the various frameworks and protocols used to access and demonstrate the value of new treatments to ensure that the patient is kept at the center of these decisions. To support our work, we engage stakeholders to foster realistic, people-centered, solution-oriented discussions to create balanced, truthful and equitable dialogues around health care access and affordability issues.

We appreciate the opportunity to provide our comments on ICER's September 12th Draft Evidence Report about "Oral Semaglutide for Type 2 Diabetes." As you know, people with diabetes also often have other related conditions (such as obesity, high blood pressure and high cholesterol), and thus may be taking medicines and other treatments for those conditions – including biopharmaceuticals, devices, surgeries, and lifestyle changes – which can make their overall health care and self-care regimens complicated. We point this out at the beginning of our comments to highlight the importance of communications and collaboration between a patient and their clinical team, and the very personal nature of the process for making individualized treatment decisions. Therefore, we urge ICER to recognize that policy makers need to have people-centered perspectives that focus on treatment and care plans for the person, and not siloed onto specific treatments, diseases or conditions – and that people are much more than the sum of their diseases and health conditions.

Our specific people-focused comments about the draft report are organized below into sections about People-Centered Perspectives; Timing of Report; Individualized Treatment Approaches for Diabetes; Data Uncertainty; Other Analytical and Methodological Concerns; and Additional Points. And **within those sections we have identified specific questions or points for ICER to respond to with this symbol ».**

People-Centered Perspectives

The draft report does a good job of describing the complexity of type-2 diabetes, and presents a reasonable although limited overview of the range of possible treatment options. For example, it would be good to note that weight loss for people with T2DM – which may be achieved with

“nutrition therapy and physical activity (“lifestyle changes”)”¹ – can help reduce the significance of the disease and lessen a person’s need for medicines.² As good clinicians know, support for such life style changes requires a variety of resources and skills within the care team, such as cognitive behavioral therapy. It has also been proposed that gastric bypass surgery (or similar interventions) may be reasonable treatment options for obese people with diabetes since it may lead to remission or a cure for their diabetes.³ We point out these treatment options for people with diabetes and urge ICER to consider and evaluate the full spectrum of treatment options in their analyses – including all the associated cost, benefits, risks, and people-centered factors.

In the report, we believe ICER could use more patient friendly language, such as specifying that “hospitalizations for major cardiovascular disease (CVD)”⁴ means heart attacks and strokes. We note this because the hospitalizations are actually for sequela from the underlying CVD, such as a heart attack or stroke. That is, if someone has stable CVD they would likely not be hospitalized simply because they have CVD. Using those terms for CV events requiring hospitalization is akin to the military using the term “collateral damage” to refer to civilian deaths.

We appreciate ICER noting that costs of medicines are a concern for patients, and citing the CDC’s survey about the impact of those costs for people with diabetes and how it effects their adherence to medications.⁵ »Related to that point, it would appropriate for the draft report to note that the July 17, 2019 notice from the IRS that enables high deductible health insurance plans starting in 2020 to cover treatments for diabetes (“Insulin and other glucose lowering agents”) before a person has met their deductible amount.⁶

In the past, we have commented on ICER’s limited use of focus groups – including its inclusion of information about a focus “group” that only included three people.⁷ In the same vein, we note that the current draft report cites information from a single patient.⁸ Since an anecdote is not data, we continue to urge ICER to work with patient groups on real data collection through responsible methodologies such as well constructed surveys and focus groups.⁹

Timing of Report

¹ Draft report p. 9

² <https://www.medicalnewstoday.com/articles/322662.php>

³ <https://www.webmd.com/diabetes/news/20190207/gastric-bypass-means-diabetes-remission-for-many#1>

⁴ Draft report p. 9

⁵ Draft report p. 9

⁶ IRS NOTICE 2019-45, Additional Preventive Care Benefits Permitted to be Provided by a High Deductible Health Plan Under § 223, <https://www.irs.gov/pub/irs-drop/n-19-45.pdf>

⁷ ICER Draft Evidence Report ““Esketamine for the Treatment of Treatment-Resistant Depression” March 21, 2019

⁸ Draft report p. 16

⁹ We note that in ICER’s proposal for updating its Value Assessment Framework process that greater work in this area is being considered.

»Because on September 20th the FDA approved oral semaglutide (brand name Rybelsus¹⁰), and that the price will reportedly be \$772 per 30 tablets across all doses,¹¹ the report’s text, tables and analyses at a minimum should be updated with that information. However, we believe it would be more appropriate to revise and reissue the draft report with updated information.

Further supporting our rationale for ICER to put forth a revised draft report rather than a final version is that ICER has modeled a variety of scenarios beyond the base case and plans on including a modified societal perspective in a future version of the report.¹² We read this to mean that ICER is withholding other modeling and analysis. We are particularly troubled that a societal perspective is considered an after-thought to be completed later, or has been done and is being withheld. If ICER simply did not have the time to complete that analysis, that would be another reason why a revised draft report rather than a final report should be issued. »ICER needs to explain those statements in greater detail and justify its decisions for not including such modeling – whether completed or not.

»Because CV events (i.e., Major Adverse Cardiovascular Events or MACEs) is the “Key Measure of Benefit”¹³ chosen by ICER for the draft report (with HgA1c and renal function considered as “Intermediate Outcomes” of “Clinical Benefit”¹⁴), wouldn’t it be more useful and responsible for ICER to withhold a final report and instead issue an updated draft report after the FDA acts (or not) concerning the indication for CVD, which is expected in early 2020?¹⁵ We particularly think this is warranted since ICER has stated in its proposal for updating its framework assessment process¹⁶ that it will only review and update its reports a year after the date of its final reports – which means that ICER might not update the final report for oral semaglutide until a year after the FDA has acted on the CVD indication. Of course, if ICER were to state that its 12-month timeline for potentially updating reports is only a guidance and that it will update this report after the FDA acts on the CVD indication, that would be a reasonable approach too. (We also note that the Preamble to the draft report ICER leaves itself that option by stating – without a specific timeframe – that it “may revisit its analyses in a formal update to this report in the future.”¹⁷)

Individualized Treatment Approaches for Diabetes

»In the section on Clinical Guidelines,¹⁸ we are curious why ICER did not mention the 2019 guidance and algorithm from the American Association of Clinical Endocrinologists and the

¹⁰ <https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-glp-1-treatment-type-2-diabetes>

¹¹ <https://www.fiercepharma.com/marketing/novo-prices-oral-rybelsus-par-injectables-ending-investor-discounting-fears>

¹² Draft report p. 54 and p. 66

¹³ Draft report p. 39

¹⁴ Draft report p. 30

¹⁵ Draft report p. 10

¹⁶ <https://icer-review.org/meeting/2020-value-assessment-framework/>

¹⁷ Draft report p. iii

¹⁸ Section 2.2 of Draft Report pp. 19-20

American College of Endocrinology.¹⁹ We recognize that the AACE/ACE publication may not be as deep and granular an exploration of treatment options for type-2 diabetes as some of the other guidelines cited, but it does present a prioritized treatment approach and algorithm that is consistent with the recommendations from the other sources cited. Since the primary audience for ICER’s work is in the United States, would it not make sense to cite the recommendations from the two leading groups of clinicians for people with diabetes in the U.S.?

»The draft report notes that “oral semaglutide is administered on an empty stomach, which may affect adherence and acceptability”²⁰ but does not pair that notion with the similar concept that patients might prefer swallowing a pill once a day rather than a subcutaneous injection once a week – particularly in a population that is likely already taking other oral medications. We note that this concept is raised later in the report: “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.”²¹ We also note that an additional advantage of the oral form of semaglutide is that unlike the injection formulation, it does not have to be refrigerated prior to initial use,²² which could be a factor for use for people without access to adequate refrigeration. Such adherence factors should be discussed together rather than separated.

Data Uncertainty

There are a variety of ways ICER embraces uncertainty in the draft report, and Institute for Patient Access & Affordability believes ICER should highlight statements where it declares such uncertainties in **bold type** and declare them up front in the preamble to the report much like the FDA does with **Black Box Warnings**. And of course, such important caveats should also be prominent in the Conclusions section. For example:

- **“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.”**²³
- “While the similar point estimates for overall MACE for oral and injectable semaglutide provide additional support for this benefit, **s concern affected decisions below about how quantitative analyses used for comparative clinical effectiveness and economic modeling were performed.**”²⁴ »In this discussion, ICER should also include perspectives about why validated markers (such as HbA1c) are so important because long-term clinical trials demonstrating clinical outcomes before FDA approval are impractical and unethical since they would result in denial of beneficial treatments for many years. Such delays and unscientific rationale (i.e., demanding final clinical outcomes) runs counter to FDA’s

¹⁹ AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM (2019)
<https://www.aace.com/disease-state-resources/diabetes/clinical-practice-guidelines-treatment-algorithms/comprehensive>

²⁰ Draft report p. 50

²¹ Draft report p. 76

²² FDA label for Ozempic, Section 16 “How Supplied/Storage and Handling”

²³ Draft report p. 43

²⁴ Draft report p. 40

evidence-based standards and the individual and collective interests of patients, and the United States as a society.

- **“we urge caution when interpreting these findings as they are highly uncertain.”²⁵**
- **“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.”²⁶**
- **“All of these incremental value estimates are coupled with high levels of uncertainty. This uncertainty is a combination statistical variance from model parameters and additional uncertainty in the NMA results from which MACE benefits for oral semaglutide are derived. Therefore, it is difficult to draw strong conclusions between oral semaglutide and the other add-on treatments.”²⁷**

»The draft report cites data about increased risk for retinopathy with oral semaglutide, but the FDA approved label states “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.”²⁸ This should be cited and noted in the report, particularly since ICER seems so enamored with projecting long-term outcomes without data.

»What is ICER’s justification for developing and using an unvalidated model, e.g., “To our knowledge, ours is the first and currently only microsimulation model to undertake such a novel approach to predict these long-term events in T2DM.”²⁹

Other Analytical and Methodological Concerns

»In the Base Case Analysis, Table 4.1 indicates that 33.3% of the population are current smokers. This is a much higher percentage than the overall U.S. adult population (14%) – particularly those over age 64 (8.2%).³⁰ Does ICER have data to indicate that the target population for the draft report’s analysis (i.e., “adults with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s)”) actually have such a high rate of smoking? That is, is the data source for this base case population appropriately representative of the target population in the U.S.? This is a critical point since smoking is an independent risk factor for vascular disease.

»In the Utilities section of the draft report it is stated that the “annual disutility for daily injection of insulin (for patients who discontinue treatment) and liraglutide based on Boye et al., who used

²⁵ Draft report p. 66

²⁶ Draft Report p. 68

²⁷ Draft report p. 73

²⁸ FDA label for Rybelsus, Section 5.3 “Diabetic Retinopathy Complications”

²⁹ Draft report p. 72

³⁰ https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm

standard gamble interviews of T2DM patients in Scotland to estimate the utility values for injection-related attributes.”³¹ Does ICER have any evidence that the utility values derived from interviewing patients in Scotland represent the same utility perspectives as in the United States?

»For the Budget Impact Analysis, it seems that ICER is assuming that oral semaglutide would completely replace other medicines in the other classes.³² »Please explain how that is any way a realistic assumption – even for patients who are not adequately controlled on their current regimen? »How can ICER assume that other interventions – including non-pharmacological such as lifestyle changes or surgery – would not be used by some of those patients, or that they would just continue to have their diabetes suboptimally managed and with inadequate glycemic control?

Additional Points

- »What is the purpose of ICER analyzing and reporting on health plan coverage since it does not seem to factor into its analysis for the rest of the report? Since health plans and insurance companies know their own coverage policies and can benchmark themselves against their peers and competitors, what is the “value” of including that information in the draft report?
- »Similarly, since it is well known to ICER that health plans do not have coverage policies for unapproved compounds (except under their experimental treatment policies and protocols), what is the point of “looking” for such coverage policies – or in the case of oral semaglutide – using the injection form of the same compound as a surrogate even though there is no evidence that coverage policies may translate to the yet to be approved medicine?
- »Why did ICER look for economic models for something that hasn’t been approved and for which there wasn’t a price (until after September 20, 2019), or any sales or utilization data?³³ If ICER is concerned about using its resources to provide useful information and analyses, searching for things that are known to not exist seems like an extreme waste of time and resources. Please explain the rationale for conducting such pointless activities.
- On page 37 (last sentence of first paragraph under “Adherence and Use of Rescue Medicine”) there seems to be a typo since the description of Table 3.7 and the table’s data seem to contradict each other, i.e., the table indicates a **higher** rate of rescue medicine use for people taking placebo compared to oral semaglutide in the PIONEER 1 and 8 studies (15.2% v. 1.1-2.3% and 31% v. 15.5-16.5%).
- Because the analysis of the subgroup with moderate renal impairment³⁴ had a mean age of 70 years old it would seem appropriate to analyze this group within the context of Medicare as a payer rather than continue to view ICER’s analyses as applying to the entire U.S. health care system, population, and all payers and insurance plans.

Conclusions

³¹ Draft report p. 62

³² “We assumed in our analysis of potential budget impact among the prevalent population that oral semaglutide as a potential ADD for switching would replace entirely the market share of drugs in these other classes, represented by sitagliptin (DPP-4 inhibitor), liraglutide (GLP-1 receptor agonist) and empagliflozin (SGLT-2 inhibitor.” Draft report pp. 78-9

³³ “In our review of the literature, we found no cost-effectiveness model that compared oral semaglutide to other T2DM treatment strategies.” Draft report p. 71

³⁴ Draft Report p. 48

Institute for Patient Access & Affordability is very excited that people with diabetes now have a new treatment option. However, we are very concerned that ICER's actions will embolden health insurance plans to restrict access for patients, increase administrative barriers for clinicians, and ultimately harm patients and increase costs for patients and employers in the U.S.

Sincerely,

A handwritten signature in cursive script that reads "Terry M. Wilcox". The signature is written in dark ink and is positioned below a short horizontal line.

Terry Wilcox

Co-Founder & Executive Director, Patients Rising & Patients Rising Now

Response Comments to ICER Draft Evidence Report “Oral Semaglutide for Type 2 Diabetes”

Ronald Carico Jr, Pharm.D., M.P.H.
Clinical Pharmacist, Marshall Health

Karrie Murphy, Pharm.D, BCGP, CDE
Assistant Professor University of Charleston School of Pharmacy

October 8th, 2019

Greetings,

We are writing in response to ICER’s request for public comment on the Draft Evidence Report (DER) titled “Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value.” One of the authors (KM) is a professor in a school of pharmacy and a clinical pharmacist who practices in a free and charitable clinic in central West Virginia. This author is a certified diabetes educator who helps patients manage their diabetes each week; many of these patients are of lower socioeconomic status and may have limited means of payment. In addition, she serves on the West Virginia Medicaid Pharmaceutical and Therapeutics Committee. The other author (RC) is a clinical pharmacist and observational researcher with experience leading national quality assessment initiatives with the Department of Veterans Affairs. This report is of interest because of the high prevalence of type 2 diabetes in West Virginia. According to the most recent Behavioral Risk Factor Surveillance System (BRFSS) data, as of September 2019, West Virginia has the highest rate of diabetes in the United States (16.2%).¹ We are thus intrigued by the therapeutic potential of an oral GLP-1 agonist in diabetes care, but are concerned that such a medication may be too expensive for both individual patients and healthcare systems. We therefore reviewed the DER with great interest and discussed ICER’s cost effectiveness model in detail, combining our respective areas of expertise.

In opening, we deeply appreciate ICER’s continued dedication to patient-oriented outcomes, such as cardiovascular events and length of life. We feel that the comparisons with empagliflozin and liraglutide are fair, and give oral semaglutide a chance to distinguish itself from other agents with proven cardiovascular benefits. We also value the use of comparative-effectiveness and long-term studies whenever they are available. Analyses that use patient-oriented outcomes and comparative effectiveness research provide vital “real world” perspectives.

Our first concern about the applicability of the model to our patients centers on adherence. As discussed in the DER’s limitations, data on the impact of partial adherence to many of the treatments are limited. We often serve rural Appalachian patient populations who may have limited access to primary care providers or endocrinology specialists. Our patients therefore face many geographic and financial barriers to continuous medication access. We encourage ICER and other interested entities to continue to investigate the relevant costs and benefits, and to incorporate any resulting findings to real-world, patient-oriented models.

We have other concerns related to external validity. While published data on patients with diabetes in our region are limited, our patients may differ from the simulated patients used in ICER’s model in key ways. The NHANES-derived patients used in ICER’s base case are often older (mean age of approximately 63 years) and may have a lower A1c (mean value 7.4%) than many of our patients. By contrast, BRFSS-derived analyses have found that residents of economically-distressed Appalachian counties are more likely to be diagnosed with diabetes at a younger age than residents of other parts of the United States². This finding is concordant with data that we extracted from the 2017 BRFSS results showing that more than half of patients who self-report a history of diabetes diagnosis in West Virginia are under the age of 45 (Table 1

below). As economically vulnerable populations, we believe our rural patients may be of special interest to ICER, and we will want to use ICER's models to advise our healthcare systems on treatments that provide a good balance of quality and cost. Our patients may be followed by the healthcare system for decades; we believe they will have a great deal of time to accumulate benefits, costs, and risks of treatment. As the data permit, we would be interested in sensitivity analyses (or possibly forthcoming scenario analyses) that combine younger patient population with a higher baseline A1c.

Thank you again for your consideration and your efforts. We eagerly await ICER's evidence report on oral semaglutide in type 2 diabetes.

Sincerely,

A handwritten signature in black ink, reading "Ronald Carico Jr." in a cursive script.

Ronald Carico Jr, Pharm.D., M.P.H.

A handwritten signature in black ink, reading "Karrie Murphy" in a cursive script.

Karrie Murphy, Pharm.D, BCGP, CDE

References

1. Diabetes in the United States. The State of Obesity. <https://www.stateofobesity.org/diabetes/>. Accessed October 6, 2019.
2. Barker L, Gerzoff R, Crespo R, Shrewsberry M. Age at diagnosis of diabetes in Appalachia. *Popul Health Metr.* 2011;9:54. Published 2011 Sep 30. doi:10.1186/1478-7954-9-54

Table 1: Age Distribution of Patients in West Virginia by Self-Reported Diabetes History, 2017 BRFSS

Age	Have you ever been told you have diabetes?				
	Yes	Yes, but only in pregnancy	No	No, but borderline	Total
Total (n)	1027	31	4275	126	5459
Age 18 to 24 (n)	0	1	211	1	213
Age 25 to 44 (n)	68	17	992	12	1089
Age 45 to 64 (n)	451	8	1720	60	2239
Age ≥ 65 (n)	508	5	1352	53	1918

Oct 7, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Value Assessment for Type 2 Diabetes – comments on draft evidence report

Dear Dr. Pearson:

Thank you for the opportunity to continue providing comments on the ongoing ICER assessment of diabetes therapies.

In addition to the draft evidence report released on September 11 2019, we also received the actual model from the University of Washington (UW) on September 11 first, with another updated version on September 15, as well as a second update on September 30. Based on our model review on the September 15 version, we sent several comments to UW on September 17, 2019 (we had shared a copy with the ICER team). Importantly, several of our identified issues on the model raised some concerns on the validity of the model. In fact, UW acknowledged some of these issues in the Sept 30 version of the model which now provides dramatically different results than what is included in the draft evidence report (more information below). **We recommend that ICER send out a public announcement to create awareness that the results in the draft evidence report are no longer valid.**

Please find below our comments on the draft report as well as some critical issues on the model.

1. Life Years and QALY calculations

As shown in table 4.10, the life years gained range from 3.13 to 3.50 years and QALYs range from 1.76 to 1.95. These seem very low and overall unreasonable from the lifetime perspective. Given that average baseline age of patients is 62.7 years in the cohort, it does not seem plausible that patients would only gain another 3 years. This further doesn't benchmark against other published studies including those referenced in the draft evidence report (Laiteerapong 2018, Neslusan 2018, Shah 2018). While the methods section (4.2) report mentions that the numbers were compared to other publications, it is not clear what publications had similar numbers.

Recommendation:

- This is a major issue and questions the technical validity of the model. If the reported LYs and QALYs are validated, please provide information on what was used for the validation.

2. Rates of comorbid conditions

The proportion of patients with certain comorbidities seem very high and much higher compared to published literature. For example:

- The incidence of end-stage renal disease (ESRD) estimated from the model is very high (approx. 50%). In essence, this means that every second patient would be hemodialysis dependent which is clearly not the case in the real world.
- Given that the baseline ESRD rate was not reported and only renal complications rates were mentioned, it is unclear why the results suggest such high ESRD rates.
- The representative Neslusan 2018 cost-effectiveness analysis of canagliflozin vs. dapagliflozin found a cumulative ESRD rate of 6.75% (no baseline value reported).

Recommendation

- Similar to the first concern identified, this is another major issue that warrants confirmation of the technical validity of the applied model.

NOTE: Please note that the above two issues were communicated to UW on Sept 17, and they sent an updated model on September 30 which produced different results than what is reported in the draft report. Some of the key changes include:

- Based on the new model, the information in tables 4.10 and 4.11 are no longer valid (range of LY changed from 3.13-3.53 years to 7.49-8.11 years and QALYS changed from 1.76-1.99 to 3.71-4.09).
- Similarly, there was significant change in rates of some of the comorbidities. For example, ESRD rate changed from 44.8-48.5% to 12.5-14.8%
- Previously, in terms of QALYs gained, sitagliptin therapy was no better than the background therapy – which is no longer the case in the latest model.
- For the willingness-to-pay threshold of \$100,000 per QALY gained, oral semaglutide is no longer cost-effective when compared to sitagliptin (Cost per QALY gained changed from \$80K to \$140K).
- There are also important changes for other comparisons in the latest model

3. Price assumption for sitagliptin:

As mentioned in earlier communications, the analysis should account for the price of sitagliptin after patent expiration. The price of sitagliptin is expected to decline significantly with the entry of generic competition by end of 2022. The use of the branded price for the result in a significant over-estimation of potential treatment cost for patients on the sitagliptin over both short-term (3-5 year) and lifetime model time horizons.

Recommendation: We recommend of incorporation of the expected price decrease of sitagliptin at time of patent expiry in the analysis. In fact, when we calculated cost-effectiveness of oral semaglutide vs. sitagliptin using anticipated LoE price change

using the new model that UW shared on Sept 30, as expected the results further dramatically change in terms of costs per QALYs gained.

4. Patient cohort selection

The analysis uses the entire NHANES population for cohort development without use of appropriate selection criteria. The NHANES population does not represent individuals from which clinical efficacy data (PIONEER studies) were drawn. For example, the treatment effects for oral semaglutide were based on higher baseline HbA1c but applied to NHANES population with much lower HbA1c; this is not appropriate or realistic. For example, the proportion of patients with HbA1c below 7% was 51.4% and those with eGFR less than 45 were 11.8%. These patients would either not require an intensification in therapy or may not be eligible to receive SGLT-2i based on renal function. Furthermore, due to lack of availability of amputation, blindness, foot ulcer, and hypoglycemia data in NHANES, all patients are assumed to enter the model with no prior history of these events. Also, it is not clear why GE Centricity data was not used throughout the analysis rather than using different sources of data for different model inputs.

Recommendation: The analysis using NHANES population should use appropriate criteria based on information of population included in the PIONEER trials for cohort selection process. Also useful to use one source of data is possible (Perhaps, GE Centricity database could have been used without the need to use NHANES).

5. Combining data for injectable and oral semaglutide

- In the analysis, the model inputs included hazard ratios for MACE and renal HR which included data from both oral as well as injectable semaglutide. This was justified by noting that a phase 2 dose finding trial showed similarities of effect between various oral and injectable formulations. This approach could overestimate the effects of oral semaglutide.
- Based on our review, injectable semaglutide had possibly better HbA1c effect compared to oral formulation in (-1.1% with lower dose and -1.6% with the higher dose of injectable vs. -0.9%, -1.2% and -1.4% for oral semaglutide) [Pratley 2018 and Aroda 2019]
- There could be differences in other outcomes as well – for example, in table 3.9, injectable semaglutide had numerically lower hazard ratio for the 3-point MACE effect compared to oral semaglutide.

Recommendation: Consider the use of only oral semaglutide data or run a sensitivity analysis excluding the data for injectable semaglutide to evaluate how results change with this exclusion.

6. Adherence and effect of treatment:

As mentioned in our earlier correspondence and as also pointed out on page 50 of the report in the section on “Controversies and Uncertainties”, adherence is an important factor that determines effectiveness in the real world for different drug classes. In this context, a US study comparing real world efficacy of injectable GLP-1 receptor agonists

to DPP4 inhibitors, the investigators reported a similar reduction at the end of 12 months (-0.52% for GLP-1 receptor agonists and -0.51% for DPP4 inhibitors) [Rosenstock 2019]. There have also been differential discontinuation rates of different therapies, given the different safety and tolerability profiles, in the PIONEER program; In PIONEER 3, the adverse event related discontinuation rate in the semaglutide arm was 11.6%. However, the analysis did not account for these differences.

Recommendation: We propose a sensitivity analysis to help compare results of the model while adhering to the clinical trial efficacy data and of a model reflecting the clinical trial discontinuation data and/or documented real-world effectiveness for the different drug classes when available.

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,



Swapnil Rajpathak, MD, MPH, DrPH
Executive Director, Cardiometabolic
Center for Observational and Real-world Evidence (CORE)
351 N Sumneytown Pike, North Wales, PA 19454
Swapnil.rajpathak@merck.com
Tel: 267 305 3134

References:

1. Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes. *Diabetes Care*. 2019 Sep;42(9):1724-1732.]
2. 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.
3. 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 Apr;9(2):565-581. doi: 10.1007/s13300-018-0371-y. Epub 2018 Feb 6.
4. Pratley RE, Aroda VR, Lingvay, I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes & Endocrinology* 2018;6(4):275-286]

5. 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. *JAMA* 2019;321(15):1466-1480.
6. 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. *Clinical Outcomes Research*. 2018;10:791-803.

Institute for Clinical and Economic Review
2 Liberty Square
Boston, MA 02109

October 8, 2019

NOVO NORDISK PUBLIC RESPONSE TO ICER DRAFT EVIDENCE REPORT RELEASED ON SEPTEMBER 11, 2019

Novo Nordisk appreciates the continued opportunity to participate in ICER's review of oral semaglutide (Rybelsus®) for type 2 diabetes (T2D), and to provide a public response to the Draft Evidence Report released by ICER on September 11, 2019. Novo Nordisk recognizes the challenges and limitations of conducting this economic analysis, while also considering the individualization of care required to treat patients with T2D.

Recognizing that injectable therapy is a barrier for many patients living with T2D, Novo Nordisk was able to advance the innovation of diabetes treatment with Rybelsus® to offer a new option for patients. Peptide-based drugs, such as GLP-1 receptor agonists, typically must be administered via injection due to very low bioavailability when administered orally due to extensive degradation by acidic pH and gastric enzymes, as well as poor absorption across the gastrointestinal mucosa. Rybelsus® represents an innovation in peptide-based therapy by being the first GLP-1 receptor agonist available by oral delivery. With this advancement, Novo Nordisk was able to provide the efficacy and safety of a GLP-1 receptor agonist in a form that may better address the needs of many patients living with T2D.

Timely and effective treatment of T2D is needed to reduce the risk of developing long term, complications, yet even with numerous treatment options available, many patients do not achieve their individual HbA_{1c} targets. GLP-1RAs provide effective glycemic control along with weight reduction and low risk of hypoglycemia.^{1,2} Rybelsus® offers an innovative solution that can help patients meet T2D treatment goals through an oral mode of administration where previous GLP-1 RA formulations were only available by injection. The American Diabetes Association (ADA) has stated that patient-centered care should be a focus and a priority when selecting a treatment regimen for a patient.³ The latest 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, along with key patient factors, such as hypoglycemia risk, body weight, costs and patient preference. Therefore, drug classes should be considered carefully when applying this patient-centric approach considering both efficacy and key patient factors when choosing an appropriate pharmacological treatment.

Novo Nordisk recognizes the challenge of optimally integrating all the facets of T2D population characteristics, comparators, and clinical evidence into an economic analysis. Constructing an evidence network of connected treatments creates considerable heterogeneity with respect to study characteristics (including eligibility criteria and duration of follow-up), patient characteristics as identified in the NHANES population dataset (including gender, weight, diabetes duration, HbA_{1c} levels, prior CVD, and renal function), concomitant medications (specifically insulin use), and outcomes definitions. Novo Nordisk appreciates ICER's recognition of these limitations throughout the draft report and agrees with ICER's statements of "*it is difficult to draw strong conclusions*

between oral semaglutide and the other add-on treatments” and ICER urges “caution when interpreting these findings as they are highly uncertain.”

Novo Nordisk appreciates ICER noting that *“the overarching limitation of this model is the complexity of T2DM, its large number of co-morbidities, and its patient-specific clinical management.”* To add to this complexity, the report additionally states that *“people with T2DM are treated based on clinical guidelines, which have been muted for this modeling exercise.”*

Throughout the Draft Report, ICER has highlighted these uncertainties. ICER notes in the Draft Report that:

“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 [ICER’s] analysis. We [ICER] acknowledge these limitations and emphasize the need to interpret the results with caution.”

As noted in the Draft Report, this uncertainty extends particularly to the following product comparisons:

- Rybelsus® and liraglutide 1.8 mg (Victoza®) as *“promising but inconclusive”*
- Rybelsus® and empagliflozin (Jardiance®) as *“insufficient evidence”*

These uncertainties are further noted in the base-case and sensitivity analysis results where ICER notes:

“results represent averages over sufficient simulations to achieve statistical convergence; nonetheless, we urge caution when interpreting these findings as they are highly uncertain.”

“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.”

“Therefore, it is difficult to draw strong conclusions between oral semaglutide and the other add-on treatments.”

Novo Nordisk appreciates ICER’s acknowledgment of study limitations and inherent uncertainty of the analyses and recommends the continued consistent and transparent reporting of these uncertainties where conclusions or findings are discussed.

CONCLUSION

Novo Nordisk recognizes that a comprehensive economic analysis is difficult to conduct and extrapolate. Novo Nordisk encourages all members of the panel to consider the full extent of benefits and harms within each medication class and their impact on patients, including but not limited to those mentioned in the ICER report. We appreciate this opportunity to provide feedback and look forward to the final analysis.



Todd M. Hobbs, MD

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

REFERENCES:

1. DeFronzo RA, Ferrannini E, Groop L, et al. Type 2 diabetes mellitus. *Nat Rev Dis Primers*. Jul 23 2015;1:15019.
2. DeFronzo RA. Combination therapy with GLP-1 receptor agonist and SGLT2 inhibitor. *Diabetes Obes Metab*. Oct 2017;19(10):1353-1362.
3. American Diabetes Association. Standards of medical care in diabetes—2019. *Diabetes Care*. 2019;42(suppl 1): S1-S193.

October 8, 2019

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

On behalf of the Partnership to Improve Patient Care (PIPC), we are writing to provide comments on the Institute for Clinical and Economic Review's (ICER) draft evidence report on treatments for Type 2 Diabetes. 1.5 million Americans are diagnosed with diabetes each year, and it is the seventh leading cause of death in the United States.¹ Given these alarming statistics, it is vitally important we find effective treatments for diabetes patients and that evaluations of these treatments are conducted in a scientifically sound, patient-centric manner. Unfortunately, ICER's report contains significant methodological flaws: it continues to omit quality of life data patients deem valuable; uses a flawed data set that underestimates risk, burden, and treatment effect; and uses negative utilities, which imply there are health states worse than death.

We would like to highlight the following concerns with ICER's report:

ICER Continues to Omit Quality of Life Data Deemed Valuable by Patients, Instead Relying on Faulty Data That Claims Health States Worse Than Death

In this report, as in previous reports, ICER assumes the only impact a new therapy has on quality of life are movement between specific, clinical health states. In reality, there is a growing body of evidence that successful treatment of cardiovascular disease risk factors in patients, including those suffering from diabetes, have had strong effects on psychological wellbeing and quality of life beyond gains associated purely with their event risk effects or movements across health states.

For example, a recent study in long-term statin users showed lower depression, anxiety, and hostility after adjustment for the propensity for statin use and potential confounders. The beneficial psychological effects of the statins appeared to be independent of the drugs' cholesterol-lowering effects.² Similar results have been seen in drugs used to treat high blood pressure.³

¹ American Diabetes Association. Statistics About Diabetes. Accessed September 18, 2019.

² Young-Xu Y, Chan KA, Liao JK, Ravid S, Blatt CM. Long-term statin use and psychological well-being. *Journal of the American College of Cardiology*. 2003 Aug 20;42(4):690-7.

³ Croog SH, Levine S, Testa MA, Brown B, Bulpitt CJ, Jenkins CD, Klerman GL, Williams GH. The effects of antihypertensive therapy on the quality of life. *New England Journal of Medicine*. 1986 Jun 26;314(26):1657-64.

We are especially concerned about ICER's use of utility data. It is unacceptable that ICER continues to use negative utility values, which imply there are health states worse than death. ICER has used negative utilities in previous reports and has been heavily criticized for it. The academic literature has also shown negative utilities to not really exist.⁴ We cannot stress enough the ethical ramifications - and irrational consequences - of using such methods to attribute a value to treatments that may then be used by payers to determine whether to cover a new treatment.

We also take serious issue with the source of the utility data. The utilities used for baseline Type 2 Diabetes, and various complications of Type 2 Diabetes are the most significant drivers of variance in the model. The source of these weights is cross-walked from unrelated studies, rather than waiting for actual data from ongoing trials, bringing into question the longer-term validity of the base case results. ICER even goes on to state in its report that;

" ... 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". (Page 73)

It is difficult to understand how ICER can justify reporting findings based on this data and approach given what is stated above.

ICER Ignores the Heterogeneity of Type 2 Diabetes Patients

A glaring limitation of ICER's analysis is its reporting of a single ratio of cost effectiveness of oral semaglutide against each comparator. Theoretically, the shift to microsimulation models should give outputs on an infinite number of potential patient types, but instead of taking advantage of this, ICER has retained a base case that gives just one set of cost-effectiveness ratios.

Type 2 Diabetes is particularly difficult and sensitive to treat, given the complexity of co-morbidities. This means that prescribing and prognosis are particularly heterogeneous and specific to individual patients. ICER admits this itself when describing the model:

"The overarching limitation of this model is the complexity of T2DM, its large number of co-morbidities, and its patient-specific clinical management." (Page 72)

ICER also notes that the primary aim of the report will be to evaluate the new drug in four very specific subgroups:

⁴ Bernfort L, Gerdle B, Husberg M, Levin LA. People in states worse than dead according to the EQ-5D UK value set: would they rather be dead?. *Quality of Life Research*. 2018 Jul 1;27(7):1827-33.

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)

Despite this nod to the fact that patients are heterogeneous and react differently to different treatments, there are no more references to these essential subgroup classifications in the section on cost-effectiveness. This exemplifies ICER's tendency to oversimplify and its unwillingness to accept that it is impossible to determine whether a treatment is "cost-effective" for the general population when patients are heterogeneous with different comorbidities and treatment needs.

Healthcare is becoming more and more complex, and more and more specific to individuals with particular sets of diseases, complications, and co-morbidities. A continued reliance on a population perspective in reporting value statements is likely to become more and more misguided⁵ and less and less beneficial to decision makers.^{6,7}

ICER Again Uses Artificially Narrow Definition of Major Adverse Cardiovascular Event

As in ICER's assessment of treatments for cardiovascular disease, ICER chooses to use an incredibly narrow definition of Major Adverse Cardiovascular Event (MACE). The definition of MACE in the base case is a shorthand version including only MI, stroke, and CVD death. More common and more comprehensive definitions of MACE include revascularizations and other events such as severe angina and heart failure.

Exactly how MACE is defined and what events are included is known to have a significant impact on outcomes.⁸ It is concerning that, with this knowledge, ICER selected a less comprehensive measure of MACE.

The Source of Risk Equations for Patient Underestimates Value of Therapies

The risk equations ICER has chosen to use may artificially underestimate the value of therapies.

⁵ Kravitz RL, Duan N, Braslow J. Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages. *The Milbank Quarterly* 2006; 84(4): 759.

⁶ Basu A. Economics of individualization in comparative effectiveness research and a basis for a patient-centered healthcare. *Journal of Health Economics* 2011; 30(3): 549-559.

⁷ 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.

⁸ Kip KE, Hollabaugh K, Marroquin OC, Williams DO. The problem with composite end points in cardiovascular studies: the story of major adverse cardiac events and percutaneous coronary intervention. *Journal of the American College of Cardiology*. 2008 Feb 19;51(7):701-7.

The model used is based on data from a United Kingdom-based sample.⁹ Metabolic syndrome conditions and diabetes itself are more prevalent in the population of the United States, so using a United Kingdom data set may underestimate risk of cardiovascular events in the population of need, hence underestimating absolute benefits from successful treatment.

It is also worth pointing out that the risk algorithms generated from the United Kingdom Prospective Diabetes Study (UKPDS) are less reliable generally, and for an American population specifically, than those generated more recently by the RECODE study using data from the Action to Control Cardiovascular Risk in Diabetes study (ACCORD; 2001–09).¹⁰ Nevertheless, both sets of risk equations suffer from the fact they are generated on a very narrow selection of participants, as they rely on data from clinical trials rather than being taken from a real world population that is likely to be more representative of the actual population that could benefit from the treatment under investigation. A number of studies have highlighted the limitations of trial data only in generating risk equations for models that will ultimately make decisions about actual populations of need, and all suggest that both risk and event rates are underestimated as a result.^{11, 12, 13}

ICER's Budget Impact Model Continues to be Concerning as it is Equivalent to Budget Capping in Health Care.

We continue to be concerned with ICER's problematic tactic of budget capping in healthcare. Following ICER's disturbing pattern, this report assumes that only a little over 4% of eligible patients could be treated with oral semaglutide in a given year without crossing ICER's arbitrary budget threshold.

As we described at length in our recent comments on cardiovascular disease, budget capping both presents a significant ethical problem and is also illogical. This concept tells us we can only give a new, effective drug to a certain number of people who could benefit from it. Since the goal of the healthcare system is ultimately better health, this premise does not make sense.

⁹ 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 Sep 1;56(9):1925-33.

¹⁰ Basu S, Sussman JB, Berkowitz SA, Hayward RA, Yudkin JS. Development and validation of Risk Equations for Complications Of type 2 Diabetes (RECODE) using individual participant data from randomised trials. *The Lancet Diabetes & Endocrinology*. 2017 Oct 1;5(10):788-98.

¹¹ Franklin JM, Schneeweiss S. When and how can real world data analyses substitute for randomized controlled trials?. *Clinical Pharmacology & Therapeutics*. 2017 Dec;102(6):924-33.

¹² Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *European heart journal*. 2015 Jan 13;36(19):1163-70.

¹³ Finegold JA, Raphael CE, Levy WC, Whinnett Z, Francis DP. Quantification of survival gain from cardiac resynchronization therapy: nonlinear growth with time, and greater gain in low-risk patients, make raw trial data an underestimate of real-world behavior. *Journal of the American College of Cardiology*. 2013 Dec 24;62(25):2406-13.

The model itself is also not sound. ICER's budget impact model assumes a take-up rate of 100% over five years for these new drugs, which assumes that every single person that could theoretically benefit from these interventions will ultimately receive it. This is illogical and have been proven incorrect time and time again, yet ICER persists in making this assumption. A prime example of this is ICER's budget impact model for PCSK9i drugs in 2015.¹⁴ That report also relied on the unrealistic assumption of full take-up over five years. Four years later the take-up rate of PCSK9 inhibitors is estimate at less than 1%.¹⁵

Conclusion

ICER continues to use a flawed methodology, ignoring the reality of heterogeneous patient populations and quality of life outcomes that matter to patients in favor of data that easily crosswalks into the discriminatory QALY metric. We urge ICER to consider alternative methodologies that will foster improved health care decisions for individual patients.

Sincerely,



Tony Coelho
Chairman, Partnership to Improve Patient Care

¹⁴ <https://icer-review.org/wp-content/uploads/2016/01/Final-Report-for-Posting-11-24-15-1.pdf>

¹⁵ Chamberlain AM, Gong Y, Shaw KM, Bian J, Song WL, Linton MF, Fonseca V, Price-Haywood E, Guhl E, King JB, Shah RU. PCSK9 Inhibitor Use in the Real World: Data From the National Patient-Centered Research Network. Journal of the American Heart Association. 2019 May 7;8(9):e011246.

Boehringer Ingelheim (BI) Response to the Draft Evidence Report – October 8, 2019**Primary contact:** Bonnie MK Donato, PhD (Bonnie.Donato@Boehringer-Ingelheim.com)

Boehringer Ingelheim (BI) appreciates the opportunity to comment on the Draft Evidence Report for the treatment of type 2 diabetes mellitus (T2DM). BI would like to acknowledge the effort ICER has put into constructing an economic evaluation reflective of current evidence for the treatments under consideration, as well as current understanding of and clinical practice regarding T2DM. Although limitations remain in the approach, BI believes that ICER has made its best attempt at conducting a robust assessment, given data availability.

BI recognizes the concerted focus by ICER to capture cardiovascular (CV) and renal outcomes, particularly with the addition of heart failure as a key outcome. This approach reflects the understanding of T2DM as a cardiorenal metabolic disease,¹ affecting key CV outcomes, such as 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, relative to patients without diabetes.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 extend further than glycemic control, and consider CVD, HF, and kidney health, when selecting treatment.¹¹ ICER's approach to capturing the full CV and renal benefits of the treatment under evaluation is limited by the data and models available. BI believes that ICER has produced a plausible estimate of these benefits given availability of models and data, while noting the limitations.

Empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor approved for the treatment of T2DM, indicated specifically to reduce the risk of CV death in adult patients with T2DM and established CVD. Empagliflozin has been approved for treatment of T2DM since 2014, with its first clinical trial published in 2013.¹² Empagliflozin has an established record of effective glucose control management, and a reduction in CV and renal adverse outcomes. We acknowledge that ICER's evaluation of empagliflozin has appropriately assessed its superior clinical and economic value.

Nevertheless, BI would like to provide the following feedback, regarding the assessment:

Real-World Evidence

While clinical trials remain the gold standard for determining treatment efficacy, real world studies provide additional information that is important for stakeholders. Treatment effectiveness in the real world can differ substantially from treatment efficacy, as measured in clinical trials. There are a number of reasons for this 'efficacy-effectiveness gap', including disparate patient populations, and sizeable differences in adherence outside of the highly controlled clinical trial setting.¹³ This difference is even more problematic for chronic diseases where the duration of treatment in the real world may vastly surpass the treatment period allotted to a clinical trial; even in an open label extension trial.¹⁴ Evidence of long-term effectiveness and sustainability are of

great importance to patients and payers. BI suggests that ICER note the importance of relevant RWE in decision making criteria for treatment, as leveraged by healthcare providers and stakeholders.

Contextual Considerations

There are a number of treatment characteristics of high importance to patients and providers, such as tolerability, adherence, and productivity impacts. BI would suggest including in the section on contextual considerations, treatment burden and mode of administration. Oral semaglutide has to be taken at least 30 minutes before first food, beverage, or other medications with no more than 4 ounces of plain water.¹⁷ Additionally, oral semaglutide must be titrated after 30 days from 3 mg to 7 mg, and can optimally be titrated up again, after an additional 30 days.¹⁷ Oral semaglutide also requires titration over 2 months to determine the optimal dose. In comparison, treatment administration for empagliflozin has significantly less restrictions: to be taken once daily in the morning with or without food.¹⁸ Treatment burden is an important consideration, as the relationship of treatment burden to adherence and persistence has been well documented for both T2DM and other disease areas.¹⁹⁻²² In addition to mode of administration and number of doses, treatment complexity was found to be a key factor in treatment adherence in a survey of T2DM patients.²³

Given the importance of treatment burden and complexity to adherence and real world effectiveness, BI believes these are important treatment characteristics to highlight as additional contextual considerations for the treatments under evaluation.

Furthermore, in the contextual considerations, BI encourages ICER to include treatment characteristics that may be as important as clinical safety and efficacy to patients, caregivers, and providers. Treatment characteristics to consider include robustness of clinical evidence, uncertainty introduced by clinical trial design, and subgroups of interest for whom efficacy evidence may be available.

Model Transparency

BI commends ICER for providing a version of the model for review (for a nominal transaction fee), along with the model information included in the appendix of the report. However, the model is not entirely transparent, making it difficult to review the accuracy of results, and to provide recommendations for model adjustments. As an example, it is difficult to interpret the cost per MACE and cost per heart failure results as the inputs to the underlying calculations are not clear. Specifically, it is difficult to determine what cost was used in the calculation, whether it was total cost or only cost associated with the outcome. Further, in reviewing the calculations of 3-point MACE in the model shared, BI was only able to confirm the inclusion of first MI, subsequent MI, first stroke, and subsequent stroke in the calculation, not CV death, as described in the report. Additionally, it would be important for ICER to clarify how CV death was calculated, as it is not an outcome that was included in the original OM2 model.

BI recommends including the calculations underlying the model either in the report or with the model when delivered. Increasing the transparency of the economic assessment, will only serve to improve the quality of both models and outputs.

Overall Report Approach

Lastly, BI urges ICER to provide further explanation regarding model inputs and calculations, as well as detailed interpretations for all figures and tables contained in the report. Without sufficient explanation and context, the data contained in the figures and tables could be easily misinterpreted or mischaracterized. For example, the legend in Figure E1 is cut-off, and the probabilistic sensitivity analyses do not have written interpretations. Additionally, as part of this effort, BI encourages ICER to perform a thorough quality check of all data and results in the report. As an example of an error that should be corrected, the cost per MACE averted for empagliflozin is listed as \$940,000 in the top paragraph on page 67, but as \$1,170,000 in Table 4.11 on page 67, which also differ from the values in Appendix Table E3. Since BI was unable to view the detailed calculation steps, BI was unable to confirm which number ought to be the correct value or why there might be a discrepancy between text and table. BI suggests ICER provide additional detail on the inputs and calculations as well as interpretations of the presented figures and tables.

References

1. Das SR, Everett BM, Birtcher KK, et al. 2018 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *Journal of the American College of Cardiology*. 2018;72(24):3200-3223.
2. Giorgino F, Home PD, Tuomilehto J. Glucose control and vascular outcomes in type 2 diabetes: is the picture clear? *Diabetes Care*. 2016;39(Supplement 2):S187-S195.
3. Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. *European heart journal*. 2016;37(19):1526-1534.
4. CDC. National diabetes fact sheet. In: National Center for Chronic Disease Prevention and Health Promotion; 2011.
5. Franco OH, Steyerberg EW, Hu FB, Mackenbach J, Nusselder W. Associations of diabetes mellitus with total life expectancy and life expectancy with and without cardiovascular disease. *Arch Intern Med*. 2007;167(11):1145-1151.
6. Willey JZ, Moon YP, Kahn E, et al. Population attributable risks of hypertension and diabetes for cardiovascular disease and stroke in the northern Manhattan study. *Journal of the American Heart Association*. 2014;3(5):e001106.
7. Shahbazian H, Rezaii I. Diabetic kidney disease; review of the current knowledge. *Journal of renal injury prevention*. 2013;2(2):73-80.
8. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. *Jama*. 2016;316(6):602-610.
9. Parving HH, Lewis JB, Ravid M, Remuzzi G, Hunsicker LG, investigators D. Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. *Kidney Int*. 2006;69(11):2057-2063.
10. Sarafidis P, Ferro C, Morales E, et al. *SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA*. Vol 342019.
11. American Diabetes Association. Standards of Medical Care in Diabetes --- 2019. *Diabetes Care*. 2018;42(Suppl. 1):S1-S194.
12. Roden M, Weng J, Eilbracht J, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. *The lancet Diabetes & endocrinology*. 2013;1(3):208-219.
13. Carls GS, Tuttle E, Tan RD, et al. Understanding the Gap Between Efficacy in Randomized Controlled Trials and Effectiveness in Real-World Use of GLP-1 RA and DPP-4 Therapies in Patients With Type 2 Diabetes. *Diabetes Care*. 2017;40(11):1469-1478.
14. Davidson MH. Differences between clinical trial efficacy and real-world effectiveness. *The American journal of managed care*. 2006;12(15 Suppl):S405-411.
15. Paterno E, Pawar A, Franklin JM, et al. Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care. *Circulation*. 2019;139(25):2822-2830.

16. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Archives of internal medicine*. 2003;163(22):2716-2724.
17. NovoNordisk. Rybelsus semaglutide tablets [prescribing information]. 2019.
18. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *The New England journal of medicine*. 2015;373(22):2117-2128.
19. Barbosa CD, Balp M-M, Kulich K, Germain N, Rofail D. A literature review to explore the link between treatment satisfaction and adherence, compliance, and persistence. *Patient preference and adherence*. 2012;6:39-48.
20. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clinical therapeutics*. 2001;23(8):1296-1310.
21. Coleman CI, Limone B, Sobieraj DM, et al. Dosing frequency and medication adherence in chronic disease. *Journal of managed care pharmacy : JMCP*. 2012;18(7):527-539.
22. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence*. 2016;10:1299-1307.
23. de Vries ST, Keers JC, Visser R, et al. Medication beliefs, treatment complexity, and non-adherence to different drug classes in patients with type 2 diabetes. *Journal of psychosomatic research*. 2014;76(2):134-138.
24. Hughes DA, Bagust A, Haycox A, Walley T. The impact of non-compliance on the cost-effectiveness of pharmaceuticals: a review of the literature. *Health economics*. 2001;10(7):601-615.