Boehringer Ingelheim (BI) Response to Draft Report – December 8, 2021

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 assessment of tirzepatide, for type 2 diabetes mellitus (T2DM). BI acknowledges the effort ICER has put into conducting this assessment reflective of available evidence for the treatments under consideration. However, BI believes that ICER has not been able to sufficiently address either the parameter uncertainty for the clinical inputs or the model uncertainty in the underlying disease model, weakening the strength and confidence in ICER's findings. The response document presents our concerns with ICER's approach, focusing on two critical areas, along with recommendations: (1) the clinical effectiveness comparison with empagliflozin given the limited existing evidence base; and 2) limitations in modeling the important outcomes related to T2DM as a cardiorenal metabolic disease.

1. Concerns related to the comparative clinical effectiveness with empagliflozin

BI respectfully disagrees with the comparative clinical effectiveness rating of "C++" based on the assessment of net health benefit of tirzepatide compared to empagliflozin. The net health benefit assessment is based on extremely limited indirect comparison data and does not take into consideration well-established clinical outcomes that are relevant to T2DM treatments, thereby resulting in low certainty for the findings. BI recommends that the comparative clinical effectiveness rating should be "I" (insufficient), which is consistent with ICER's definition ("any situation in which certainty in the evidence is low"). BI provides the following reasons in support of the recommendation:

A. Wide confidence intervals of the NMA estimates
B. Limitations of the biomarkers used in representing the full range of T2DM treatment benefits
C. Exclusion of cardiorenal metabolic benefits in NMA underestimates the value of empagliflozin

A. Limited indirect comparative data increases the uncertainty of NMA based treatment effects

There are no head-to-head trials comparing tirzepatide and empagliflozin. For the assessment of net health benefit of tirzepatide versus empagliflozin, ICER developed quantitative, indirect comparisons using a Bayesian NMA for outcomes of change in HbA1c, weight, LDL, and SBP at 40 weeks in adults with T2DM. Estimating the relative treatment effects on HbA1c, weight, LDL, and SBP without head-to-head evidence impacts the precision of the estimates and increases the uncertainty of the comparative evidence. While the NMA leveraged available data, only 410 patients who received empagliflozin 25 mg (PIONEER 2, see Table 3.2 in the Draft Evidence Report), were included in the analysis. This is a significant underrepresentation of the population in the evidence base for empagliflozin, as this is approximately 2% (over 12,000 subjects in trial settings) of the overall empagliflozin population and does not take into consideration treatment with 10 mg empagliflozin.

ICER acknowledges concerns with the scarcity of data and the resulting uncertainty surrounding the estimates/results in its Draft Evidence Report, for example on pages ES2, ES3, 18, 19, and 33. Describing the NMA, ICER states that *"we have only moderate certainty about the results from the indirect comparison through the NMA, as tirzepatide and empagliflozin are compared through trials of three other drugs."*(page 19) BI urges ICER to also emphasize that until additional and longer-term data is available, any assessment will not accurately capture the comparative value of tirzepatide and empagliflozin. The conclusion should therefore reflect these critical limitations with a low certainty in the evidence and result in a rating of "I", in line with ICER's own definition of the ratings.

B. HbA1C and body weight alone do not capture key treatment benefits in T2DM

ICER's evaluation assesses T2DM treatments based on glucose-lowering and weight modification therapies. These traditional biomarkers for health in the T2DM population do not correlate with the overall benefit demonstrated in studies of the SGLT2 inhibitor class, such as empagliflozin. Evaluating empagliflozin solely on its merits of a glucose lowering T2DM agent without accounting for its established CV benefits, underestimates the value of empagliflozin, undermining the integrity of the review.

Empagliflozin has demonstrated efficacy and safety in clinical trials for the treatment of T2DM via glucose lowering and weight loss. However, the overarching value of empagliflozin extends beyond these intermediate measures of clinical outcomes. Modeling the relative value of empagliflozin based on a narrow set of biomarkers such as HbA1c and body weight does not provide assurance that its well-established clinical benefits are accurately reflected, especially given availability of long-term data. To conduct a fair and comprehensive comparative clinical assessment of T2DM treatments including empagliflozin, one should take into consideration each therapeutic agent's complete, proven vector of benefits.

Despite diabetes being characterized by hyperglycemia, there are many dysmetabolic factors that lead to the multitude of comorbidities associated with T2DM. Among the most notable is CV disease, which is particularly diffuse in the T2DM population. This particular comorbidity is thought to relate to lipid metabolism which often precedes hyperglycemia by 5-10 years[3]. The normalization of glucose levels in patients with T2DM and CVD has not successfully demonstrated a benefit in reversing or reducing CV events. In particular, two major T2DM trials, ACCORD and ADVANCE, failed to demonstrate that lowering HbA1c and blood glucose would reduce mortality[3-5] Changes in HbA1c and body weight do not adequately demonstrate an overall benefit to a multi-morbid T2DM population with regards to overall mortality, and major comorbid outcomes such as CV events, renal decline, and heart failure (HF), that determine survival and quality of life in the diabetes population[6].

Conducting a comparative clinical assessment within this narrow view, as approached by the ICER evaluation, does not accurately portray the complete clinical value of T2DM treatments, and in particular does not allow for a robust comparison with empagliflozin, given its established benefits in comorbid conditions of T2DM[7]. BI emphasizes that given these limitations, certainty in the assessment for comparative clinical effectiveness of tirzepatide and empagliflozin is low, and therefore the rating should be "I".

C. CV and renal benefits are not adequately represented in ICER's evidence assessment

CVD and chronic kidney disease (CKD) are common comorbid conditions with T2DM[8]. Evaluating the effect of T2DM treatment must consider the impact on comorbid conditions, such as CVD and renal disease. The T2DM population is at a 2-5-fold increased risk of experiencing HF and approximately 45% of all HF patients have underlying T2DM[9,10]. The risk of morbidity and mortality for T2DM patients increases with the presence of CVD[11] and is compounded with the presence of renal disease[12]. A systematic review of 57 global studies, covering more than 4.5 million T2DM individuals, documented that CVD had an overall prevalence of 32.2% and accounted for 50.3% of all deaths in this population[13]. Additionally, an estimated 70% of healthcare costs in T2DM population is driven from macrovascular disease[14]. A study in the NHANES adult T2DM population from 1999 to 2012 documented that the overall prevalence of CKD was 43.5% (95% CI, 41.6%-45.4%) based on estimated glomerular filtration rate (eGFR)[15].

Empagliflozin, an SGLT2 inhibitor, has demonstrated efficacy in CV and renal outcomes. Empagliflozin is indicated to reduce the risk of CV death plus hospitalization for heart failure (HHF) in adults with HF and reduced ejection fraction (HFrEF); to reduce the risk of CV death in adults with T2DM and established CV disease; and as an adjunct to diet and exercise to improve glycemic control in adults with T2DM[16]. BI has submitted an application to FDA seeking a new indication based on the HFpEF data and, in September 2021, was granted FDA

breakthrough therapy designation for HFpEF[17]. Additional research is underway to assess its impact on both chronic kidney disease (CKD) and kidney function decline.

EMPA-REG OUTCOME offers data on outcomes for T2DM comorbid conditions such as CVD and renal complications, HHF and total hospitalizations, for up to 5 years of exposure to empagliflozin. The study, which examined the effect of empagliflozin as a treatment for T2DM patients at high risk for CV events receiving standard care, provides scientifically robust data for a mean of 3.1 years and over 780 outcomes (or events)[6]. In EMPA-REG OUTCOME, empagliflozin demonstrated a significant (14%) reduction in 3-point major adverse CV events (MACE), a 38% reduction in CV death, a reduction in the decline of glomerular filtration rate by 1.5ml/min/1.073m^2/year, a 35% reduction in HHF, and a 39% reduction in renal end points[6]. This was achieved in a study designed to maintain glucose equipoise, which in the end demonstrated less than a 0.5% reduction in HbA1c over 3.1 years and a modest blood pressure reduction of approximately 3 mmHg SBP, while maintaining no change in heart rate, unlike the GLP-1RAs, which have been shown to increase heart rate in clinical trials[18]. GLP-1RAs (such as liraglutide, and to a lesser extent semaglutide) have demonstrated CV benefit, but only have a minor impact on renal benefit and no effect on HF, despite greater glucose lowering and weight loss. Additionally, in EMPA-REG OUTCOME, time to CV benefit (a decrease in CVD and HHF) was observed within weeks of treatment initiation of empagliflozin, as compared to 12 months for GLP-1RAs, suggesting not just broader CV benefits for SGLT2 inhibitors, but also faster occurrence[19].

Tirzepatide, a dual GIP and GLP-1RA, has only demonstrated efficacy as an antihyperglycemic agent[6,20-22]. Regardless of data limitations for tirzepatide, the multitude of well-established and documented benefits of empagliflozin should be recognized and taken into consideration for a robust comparative analysis.

BI recognizes that there is an ongoing CVOT for tirzepatide, which will provide robust data for a future comparison. However, for the current analysis, the Draft Evidence Report concludes that, *"the cardiovascular outcomes trial for tirzepatide is ongoing and less mature; however, a meta-analysis of cardiovascular events for safety across the SURPASS trials showed no increase in cardiovascular events and a trend towards cardiovascular benefit."* ICER also repeatedly notes low levels of confidence in the overall clinical comparison: *"Since tirzepatide and empagliflozin have completely different mechanisms of action, without a direct comparison, it is difficult to judge whether tirzepatide may represent a substantial improvement over empagliflozin, particularly in patients with established or at high risk of ASCVD, CKD, or heart failure; three common co-morbid conditions"*[23].

Due to lack of evidence on CV and renal outcomes for tirzepatide and lack of consideration for corresponding data available for empagliflozin, the evidence base for this clinical assessment is incomplete and does not allow for a definitive rating of tirzepatide's net health benefit compared to empagliflozin. BI recognizes that ICER acknowledges the lack of long-term evidence on cardiorenal metabolic effects of tirzepatide, but urges ICER to reflect the considerable uncertainty inherent in this assessment by revising its comparative evidence rating to "I".

2. Concerns related to ICER's overall modeling approach

In addition to our comments on the comparative effectiveness rating for tirzepatide compared to empagliflozin, BI would like to point-out several concerns regarding ICER's overall cost effectiveness (CE) modeling approach. BI commends ICER for providing a version of the CE model for review, but would like to highlight three important concerns that lead to high model and parameter uncertainties and limit our confidence in the results:

A. UKPDS OM2 risk engine is not well-suited to represent current treatments for T2DM

B. Assumptions regarding treatment discontinuation are not reflective of clinical practice

C. The model does not adequately represent empagliflozin's adverse event rates observed in clinical trials.

A. *The UKPDS risk engine does not reflect cardiorenal metabolic aspects of T2DM and does not represent current population dynamics*

The initial UKPDS population is based on newly diagnosed T2DM patients in the UK from 1977 - 1997. This population fundamentally differs from ICER's US-based target population with respect to demographic and health characteristics, available medications and dietary preferences. Moreover, diagnosis and treatment patterns have evolved substantially over the past 20 years, which likely have changed underlying risk relationships described in the UKPDS OM2[24-27]. The UKPDS includes 5,102 newly diagnosed patients with T2DM[28], 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 7,000 patients, with an average follow-up of more than three years. Risk equations derived for patients at high risk of CV events will yield greater accuracy in projection of CV and renal events. Thus, they should be used in a CE analysis for patients with increased CV risk or prevalent CKD, instead of UKPDS[29-31].

A model relying on the UKPDS risk equations will not 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. It is these pleiotropic effects that mostly touch the comorbidities that account for the greatest morbidity and healthcare utilization of patients with T2DM, yet are unaccounted for in available risk engines such as OM2 or BRAVO.

To further illustrate this shortcoming of the UKPDS OM2 risk engine, a simulation of the OM2 with the EMPA-REG OUTCOME data revealed that the OM2 only accounted for 12.75–15% of the overall CV benefit of empagliflozin[32,33]. The documented limitations of available T2DM risk engines such as BRAVO[34] and the OM2[32,33] in representing benefits of SGLT2 class, introduce substantial model-based uncertainty to ICER's assessment, on top of the aforementioned data-based uncertainty inherent in the indirect comparison approach.

To reflect this magnified level of model uncertainty, BI reiterates its request that ICER revise the evidence rating to "I", and to state explicitly in the main text of the evaluation the documented shortcomings of the UKPDS OM2 in accounting for the CV benefit of empagliflozin.

B. *Assumption around treatment discontinuation in ICER's model does not reflect clinical practice guidelines*

In the model, treatment discontinuation occurs if HbA1c exceeds 8.5% (see Table 4.1). In clinical practice, patients with HbA1c exceeding 8.5% would receive additional glucose lowering agent and not discontinue their SGLT2 inhibitor. The 2021 ADA guidelines recommend SGLT2 inhibitors be continued for cardio-renal protection, irrespective of how effective they are for patients achieving their HbA1c goal[36]. In the 2019 T2DM evaluation, ICER assumed that following the first model cycle, "*oral semaglutide, empagliflozin, and liraglutide patients added insulin therapy while remaining on their current treatment if their HbA1c reached 8.5 or above"*[35].

EMPA-REG EXTEND is referenced as ICER's central data source for treatment discontinuation of each treatment under review. However, this trial was a safety extension of the EMPA-REG 26 week clinical trial which, in order to observe patients with a longer exposure without rescue, introduced a discontinuation mechanism as a safety precaution for patients not achieving goal of HbA1c ≤8.5%[37]. This threshold is not reflected in the ADA guideline issue and was specifically introduced for the conduct of this FDA-mandated safety study to increase exposure of at least 400 patients to 2 years of exposure.

The discontinuation rate in EMPA-REG EXTEND should therefore not be used to mimic real world use of empagliflozin. BI recommends that ICER's model consider continuous use of treatment, rather than discontinuation based on HbA1c levels, as was done in the 2019 T2DM assessment of oral semaglutide.

C. *Adverse event rates are not representative of empagliflozin's clinical trial data, even after ICER's adjustments for CV event rates*

ICER notes *"because no long-term cardiovascular outcomes trial data exist for tirzepatide, health benefits were informed by intermediate outcomes and were unadjusted. Modeled cardiovascular and renal outcomes for therapies with existing long-term trials were adjusted to trial data using hazard ratios."* ICER used inputs from the NMA for efficacy at reducing HbA1c, weight, SBP, and LDL for all treatments, and then applied event reduction hazard ratios from the CVOTs (in addition to benefits treatments garnered from reductions in intermediate outcomes) to both empagliflozin and semaglutide. The incidence rates of key cardiorenal metabolic outcomes such as CHF, composite MACE, CV death and renal death, observed for patients treated with empagliflozin in EMPA-REG OUTCOME differed substantially from outcomes projected in ICER's model[6]. Even after ICER's calibration, adverse event rates for empagliflozin are overestimated compared to its published data, which, in consequence, leads to an underestimation of key benefits in the model, including LYs and QALYs. Additionally, it remains unclear how various aspects of the comparison such as HbA1c and weight loss are weighted relative to other model inputs, thereby operating as a "black box". While ICER performed a calibration exercise, the calibration process and end results are lacking in both clarity and transparency.

BI recommends ICER's calibration more closely align with EMPA-REG OUTCOME data, in order to adequately represent the full range of value that empagliflozin provides for T2DM patients.

Additional analyses would enhance ICER's model and provide clarity around model assumptions:

- BI recommends including a scenario of life-long treatment, given the CV benefit of EMPA irrespective of HbA1c and ADA guidelines. See discussion above within treatment discontinuation.
- ICER assumption of a constant BMI post-treatment discontinuation impacts LY and QALYs. ICER should model the impact of this assumption on outcomes, including patient's BMI reverting to the original level, post treatment discontinuation.
- For model transparency, BI recommends including the calculations underlying the model either in the report or with the model when delivered.

BI recognizes ICER's effort to conduct a robust clinical and CE assessment for tirzepatide as treatment for T2DM. However, the inclusion of empagliflozin as a comparator has sufficiently large limitations and drawbacks, that undermines the confidence in the analysis. The restriction of empagliflozin's benefit to only the areas where tirzepatide has collected and available evidence, biases the evaluation. The approach focuses on outcomes where tirzepatide has shown value and underestimates the demonstrated value of empagliflozin. Given the high level of model-based and data-based uncertainty, BI urges ICER to revise its comparative clinical evidence rating to "I" and underscore the uncertainty and major limitations of the resultant economic evaluation comparing tirzepatide to empagliflozin.

References

1. Sacristán JA, Abellán-Perpiñán J-M, Dilla T, Soto J, Oliva J. Some reflections on the use of inappropriate comparators in CEA. *Cost Effectiveness and Resource Allocation.* 2020;18(1):1-6.
2. Díaz-Trastoy O, Villar-Taibo R, Sifontes-Dubón M, et al. GLP1 Receptor Agonist and SGLT2 Inhibitor Combination: An Effective Approach in Real-world Clinical Practice. *Clinical therapeutics.* 2020;42(2):e1-e12.
3. Group AS. Effects of combination lipid therapy in type 2 diabetes mellitus. *New England Journal of Medicine.* 2010;362(17):1563-1574.
4. Group AtCCRiDS. Effects of intensive glucose lowering in type 2 diabetes. *New England journal of medicine.* 2008;358(24):2545-2559.
5. Heller SR, Group AC. A summary of the ADVANCE Trial. *Diabetes care.* 2009;32(suppl 2):S357-S361.
6. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *New England Journal of Medicine.* 2015;373(22):2117-2128.
7. Association AD. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes—2021. *Diabetes Care.* 2021;44(Supplement 1):S111-S124.
8. Kalra S, Aydin H, Sahay M, et al. Cardiorenal Syndrome in Type 2 Diabetes Mellitus–Rational Use of Sodium–glucose Cotransporter-2 Inhibitors. *European endocrinology.* 2020;16(2):113.
9. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *The American journal of cardiology.* 1974;34(1):29-34.
10. Lehrke M, Marx N. Diabetes mellitus and heart failure. *The American journal of cardiology.* 2017;120(1):S37-S47.
11. Di Angelantonio E, Kaptoge S, Wormser D, et al. Association of cardiometabolic multimorbidity with mortality. *Jama.* 2015;314(1):52-60.
12. Wan EYF, Chin WY, Yu EYT, et al. The impact of cardiovascular disease and chronic kidney disease on life expectancy and direct medical cost in a 10-year diabetes cohort study. *Diabetes Care.* 2020;43(8):1750-1758.
13. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. *Cardiovascular diabetology.* 2018;17(1):1-19.
14. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *New England journal of medicine.* 2009;360(2):129-139.
15. Bailey RA, Wang Y, Zhu V, Rupnow MF. Chronic kidney disease in US adults with type 2 diabetes: an updated national estimate of prevalence based on Kidney Disease: Improving Global Outcomes (KDIGO) staging. *BMC research notes.* 2014;7(1):1-7.
16. *Jardiance (empagliflozin)[package insert].* Ridgefield, CT: Boehringer Ingelheim International GmbH; 2021.
17. Eli Lilly and Company Press Release. FDA grants Jardiance Breakthrough Therapy designation for heart failure with preserved ejection fraction. 2021; https://investor.lilly.com/news-releases/news-release-details/fda-grants-jardiancer-breakthrough-therapy-designation-heart.
18. Nakatani Y, Kawabe A, Matsumura M, et al. Effects of GLP-1 receptor agonists on heart rate and the autonomic nervous system using Holter electrocardiography and power spectrum analysis of heart rate variability. *Diabetes Care.* 2016;39(2):e22-e23.
19. Verma S, Leiter LA, Zinman B, et al. Time to cardiovascular benefits of empagliflozin: a post hoc observation from the EMPA-REG OUTCOME trial. *ESC Heart Failure.* 2021.
20. Packer M, Anker SD, Butler J, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. *Circulation.* 2021;143(4):326-336.

21. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *New England Journal of Medicine.* 2021.
22. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *New England Journal of Medicine.* 2020;383(15):1413-1424.
23. Lin GA BE, Nikitin D, Moradi A, Chen Y, Herron-Smith S, Hansen RN, Pearson SD, Campbell JD. *Tirzepatide for Type 2 Diabetes; Draft Evidence Report.* Institute for Clinical and Economic Review;2021.
24. United Kingdom Prospective Diabetes Study Group. United Kingdom prospective diabetes study (UKPDS) 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *BMJ: British Medical Journal.* 1995:83-88.
25. Centers for Disease Control and Prevention. National diabetes statistics report, 2017. In: Atlanta, GA: Centers for Disease Control and Prevention; 2017.
26. UK Prospective Diabetes Study Group. UK Prospective Diabetes Study XII: differences between Asian, Afro-Caribbean and white Caucasian type 2 diabetic patients at diagnosis of diabetes. *Diabetic Medicine.* 1994;11(7):670-677.
27. Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. *Diabetologia.* 2013;56(9):1925-1933.
28. Chalmers J, Cooper ME. UKPDS and the legacy effect. *New England Journal of Medicine.* 2008;359(15):1618.
29. Bain SC, Mosenzon O, Arechavaleta R, et al. Cardiovascular safety of oral semaglutide in patients with type 2 diabetes: Rationale, design and patient baseline characteristics for the PIONEER 6 trial. *Diabetes, Obesity and Metabolism.* 2019;21(3):499-508.
30. Oral semaglutide demonstrates favourable cardiovascular safety profile and significant reduction in cardiovascular death and all-cause mortality in people with type 2 diabetes in the PIONEER 6 trial [press release]. 2018.
31. Oral semaglutide shows superior improvement in HbA1c vs empagliflozin in the PIONEER 2 trial [press release]. 2018.
32. Coleman R, Gray A, Broedl U, et al. Are the cardiovascular risk reductions seen with empagliflozin in the EMPA-REG OUTCOME trial explained by conventional cardiovascular risk factors? 2017.
33. Coleman RL, Gray AM, Broedl MD UC, et al. Can the cardiovascular risk reductions observed with empagliflozin in the EMPA-REG OUTCOME trial be explained by concomitant changes seen in conventional cardiovascular risk factor levels? *Diabetes, Obesity and Metabolism.* 2020;22(7):1151-1156.
34. Shao H, Shi L, Fonseca VA. Using the BRAVO Risk Engine to Predict Cardiovascular Outcomes in Clinical Trials With Sodium–Glucose Transporter 2 Inhibitors. *Diabetes care.* 2020;43(7):1530-1536.
35. Fazioli KT, Rind DM, Guzauskas GF, Hansen RN, Pearson SD. The Effectiveness and Value of Oral Semaglutide for Type 2 Diabetes Mellitus: A Summary from the Institute for Clinical and Economic Review's New England Comparative Effectiveness Public Advisory Council. *Journal of Managed Care & Specialty Pharmacy.* 2020;26(9):1072-1076.
36. American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care.* 2021;44.
37. Haering H-U, Merker L, Christiansen AV, et al. Empagliflozin as add-on to metformin plus sulphonylurea in patients with type 2 diabetes. *Diabetes research and clinical practice.* 2015;110(1):82-90.

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.
www.lilly.com

December 8, 2021

RE: Lilly's Public Comments for ICER's Draft Evidence Report for Type 2 Diabetes

Eli Lilly and Company ("Lilly") appreciates the opportunity to provide public comments on the draft evidence report for ICER's assessment of tirzepatide in type 2 diabetes (T2D). We have outlined several important considerations, as well as some references to support these considerations within this assessment.

ICER's base-case analysis should use a cardiovascular (CV) event hazard ratio (HR) for tirzepatide from either the SURPASS-4 clinical trial or the CV safety meta-analysis of tirzepatide clinical trials. ICER should also conduct a scenario analysis with NO adjustment for CV outcomes using CV event HRs.

In the draft evidence report, ICER applies an adjustment for semaglutide and empagliflozin based on the CV event HRs from their CV outcome trials (CVOTs) but assumes a CV event HR of 1.0 (i.e., no adjusted CV benefit) for tirzepatide. This is a flawed assumption as there is early evidence suggesting that tirzepatide has a potential CV benefit and contradicts International Society for Pharmacoeconomics and Outcomes Research (ISPOR)'s good research practices as reported by the ISPOR Modeling Good Research Practices Task Force (Briggs 2012, Caro 2012, Eddy 2012). By applying adjustments to semaglutide and empagliflozin but not to tirzepatide, ICER is creating an uneven comparison by potentially double-counting benefit for semaglutide and empagliflozin and assuming no adjusted benefit for tirzepatide.

Lilly recommends revising the base-case analysis so that an empirically supported adjustment is applied to tirzepatide's estimated CV outcomes. Given that ICER acknowledges that "a meta-analysis of cardiovascular events for safety across the SURPASS trials showed no increase in cardiovascular events and a trend toward cardiovascular benefit," the base-case CV event HR should reflect the best current estimate of the potential benefit for tirzepatide. ICER should use a HR for tirzepatide from either the SURPASS-4 clinical trial or the CV safety meta-analysis of tirzepatide clinical trials. Although tirzepatide's CVOT is currently ongoing, peer-reviewed data from SURPASS-4 (which enrolled a high-risk CV population) is available (Del Prato 2021). Results found adjudicated 4-point major adverse CV events (MACE-4; CV death, myocardial infarction, stroke, hospitalization for unstable angina) occurred in 109 participants and were not increased on tirzepatide compared with insulin glargine. Lilly also conducted a CV safety meta-analysis across the tirzepatide clinical program once the predefined number of MACE occurred (Lilly 2021). The meta-analysis consisted of 116 participants with adjudicated CV events contributing to the MACE-4 outcome, the majority of which came from SURPASS-4 (Lilly 2021). This recommended base-case analysis should be conducted not only for comparison of tirzepatide vs background therapy but also comparison of tirzepatide vs active comparators (semaglutide and empagliflozin).

Additionally, ICER should conduct a scenario analysis with no additional adjustment for CV outcomes for tirzepatide, semaglutide, and empagliflozin based on CV event HRs. Because the UKPDS risk equations are intended to model CV outcomes without adjustment using CV event HRs, applying a CV event HR on top of the risk equations could result in double-counting of CV benefit. Therefore, it is important to include a scenario analysis with no HRs for any treatments to illustrate the impact of adjustments to the model.

The uncertainties and limitations of the cost-effectiveness analysis when interpreting the results and discussing conclusions should be clearly described in the report.
ICER acknowledges that there is a "wide range of plausible cost-effectiveness estimates for tirzepatide" (ES3), with cost-effectiveness ratios for tirzepatide vs semaglutide ranging from -$1,469,000/quality-adjusted life-year (QALY) to $1,541,000/QALY and for tirzepatide vs empagliflozin ranging from -$408,000/QALY to $594,000/QALY. The significant overlap in the credible intervals for tirzepatide and semaglutide in costs and QALYs indicate that there is not a conclusive difference in cost-effectiveness between the 2 drugs, as small changes in costs or QALYs could completely change the cost-effectiveness ratios. Given the uncertainties in the model results due to wide ranges of estimates, ICER should make it very clear that results and conclusions are based on many uncertainties and assumptions when discussing the interpretation and conclusions of the cost-effectiveness analysis. Making conclusive statements regarding cost-effectiveness without acknowledging the limitations and uncertainties of the analysis could impact access to valuable treatments for T2D patients.

As Tirzepatide is not currently approved and does not have a published price, Lilly recommends a threshold analysis of tirzepatide that uses the assumption of price parity to semaglutide 1.0mg to determine the HR required to reach cost-effectiveness to each of the agents.
ICER should also conduct a threshold analysis of tirzepatide that uses the assumption of price parity to semaglutide 1.0mg to determine the CV event HR required to reach cost-effectiveness compared to semaglutide, empagliflozin, and background therapy. Given that the price of tirzepatide is currently unknown and there is a level of uncertainty on the long-term CV outcomes of tirzepatide, conducting a threshold analysis to determine the HR required to reach cost-effectiveness for tirzepatide would provide readers more information about the cost-effectiveness of tirzepatide once there is pricing available and the long-term CVOT for tirzepatide is completed.

ICER should include the difference in device preference utilities between tirzepatide and semaglutide in a scenario analysis of the cost-effectiveness model.
Patient preference is an important consideration when choosing a diabetes treatment, as route of administration, frequency of administration, and injection device can affect adherence and quality of life. Lilly was pleased that ICER acknowledged differences in patient preferences for diabetes treatment by including an annual disutility for daily injection of insulin (for patients who discontinued treatment) based on a publication by Boye et al. (2011). In addition to an injection disutility for insulin (a non-active comparator), ICER should consider including quality of life data for active comparators as well, for which there is recent published and peer-reviewed data. There is a well-established difference in device preference between the injection devices for semaglutide and tirzepatide (which is the same as the dulaglutide injection device). Results from a recent study (Boye 2019) of the semaglutide and dulaglutide injection devices showed a mean (SD) utility difference between the injection device health states of 0.007 (0.019). ICER should include this difference in device preference utility between the tirzepatide and semaglutide devices in a scenario analysis of tirzepatide compared to semaglutide.

Since ICER used the UKPDS model rather than the BRAVO model despite known limitations, more detail should be provided on its limitations, the impact these limitations have on the interpretation and accuracy of the model outcomes, and the process followed to select UKPDS OM2 for use in the assessment model over other non-BRAVO risk engines.
ICER indicated that the BRAVO risk engine would be used in the model analysis plan, so more details should be provided on the difficulties implementing the BRAVO risk equations, what additional models were considered when BRAVO was deemed infeasible for use in the assessment, and why the best alternative was then determined to be the UKPDS OM2 given the known limitations of UKPDS-OM2.

ICER states that "the UKPDS-OM2 risk equations are widely used in diabetes simulation models and have been shown to accurately predict results for the population in which it was developed as well as other diabetes

populations" (page E4). While ICER is correct that the UKPDS-OM2 risk equations predict results for the United Kingdom (UK) population as well as populations similar to the UK (e.g., Ireland, Scotland, etc.), it has not been shown to accurately predict results among United States (US) populations. Evidence from the last two Mount Hood Meetings provide little evidence to support the use of the UKPDS OM2 in the US due to differences in racial and ethnic characteristics between the 2 populations, along with differences in diabetes characteristics, such as a great proportion of obese individuals, higher body mass index (BMI), younger age of diagnosis and diagnosis at a lower baseline HbA1c level for US patients (Palmer 2018, Si 2020). There is a paucity of published validation evidence supporting the use of UKPDS OM2 risk equations in populations taking newer treatments for type 2 diabetes (T2D), particularly for interventions associated with weight loss. Evidence from Mount Hood indicated that the risk equations needed re-calibration to provide plausible estimates of outcomes from CVOTs (Palmer 2018). Additionally, UKPDS OM2 is based on patient-level data for T2D patients who were recruited between 1977 and 1991 and were followed until 1997 (Hayes 2013), making this a very outdated population. ICER should provide additional details on the limitations of the UKPDS OM2, including that it is outdated and not validated in a US population, and that the risk equations have been demonstrated to poorly predict CV outcomes, as well as the impact these limitations have on the interpretation and accuracy of the model outcomes

Given the considerable uncertainty in results, ICER should conduct additional sensitivity analyses on key parameters driving model uncertainty.

Given this considerable uncertainty in results described above, ICER should conduct additional sensitivity analyses for the revised evidence report, including conducting sensitivity analyses on risk factor progression assumptions, device utility, and different weight gain utility approaches, different QALY estimation approaches, and CV event HRs. Any of these factors could considerably change cost-effectiveness results, so it is important to demonstrate the impact of each factor on these results.

ICER indicates that efficacy inputs were derived from the network meta-analysis (NMA); however, given that there is head-to-head trial data for tirzepatide vs semaglutide from SURPASS-2, ICER should use these inputs instead or provide clear rationale for why the NMA-derived data were deemed more appropriate for the comparison of tirzepatide to semaglutide than the SURPASS-2 data provided by Lilly.

On page 23, ICER states that the "effects of each included therapy, such as change in HbA1c after the first cycle, were included depending on data availability from the NMA." ICER also states on page 27, "clinical inputs regarding the efficacy of tirzepatide, injectable semaglutide, and empagliflozin as compared to background therapy alone on intermediate outcomes such as changes in HbA1c, lipid levels, blood pressure, and body weight were derived from the NMA described in Chapter 3." ICER should use efficacy inputs from the head-to-head (SURPASS-2) trial data for tirzepatide and semaglutide instead of the data from the NMA, as direct head-to-head data is preferred to indirect treatment comparisons (such as from an NMA) in the hierarchy of strength of evidence. ICER should also provide a clear rationale for why the NMA-derived data were deemed more appropriate for the comparison of tirzepatide to semaglutide than the SURPASS-2 data provided by Lilly.

Lilly recommends that ICER quality check the data inputs in their NMA and economic model to ensure the use of the tirzepatide 15 mg dose data.

On Page 11, ICER comments that there is a mean HbA1c difference in tirzepatide from background therapy of -1.7% from the NMA. In Table D2.2, the data inputs for the NMA report the change from baseline from the SURPASS-2 study (tirzepatide = -2.3%; semaglutide = -1.86%) and HARMONY-3 (background therapy = 0%; sitagliptin = -0.5%). Table 2.4 shows the results of the NMA and reports a difference of -1.72% between tirzepatide and background therapy. When Lilly ran an NMA using the same inputs, there was a difference in HbA1c of -2.0% between tirzepatide and background therapy. If the NMA is re-run using the 5 mg result for tirzepatide (-2.01%), the outcome from the NMA for tirzepatide vs background therapy matches the value reported in Table D2.4 (-1.7%). We believe that the NMA for HbA1c has incorrectly used the 5 mg tirzepatide

result as the input instead of using the 15mg tirzepatide result. We recommend that ICER quality check the data inputs in their NMA and economic model to ensure the use of the tirzepatide 15 mg dose data. Similar changes will need to be made to the difference between tirzepatide and semaglutide or empagliflozin if the 5 mg result has been incorrectly used in the NMA.

Tirzepatide's clinical evidence rating vs semaglutide should be changed from a C+ to a B+ or C++.
Tirzepatide was given a comparative clinical effectiveness grade of C+ (comparable or incremental) in comparison to semaglutide despite substantial improvements in nearly all outcomes of interest. Tirzepatide showed an improvement of 0.45% in HbA1c, an additional 5.5 kg weight loss, and an additional decrease of 2.9 mmHg in systolic blood pressure in comparison to semaglutide. Despite the lack of long-term CV outcomes, early intermediate outcomes suggest a trend toward a strong CV benefit. This was acknowledged by ICER as well. As a result, ICER should consider changing tirzepatide's clinical evidence rating from C+ (comparable or incremental) to a B+ (incremental or better) or C++ (comparable or better) in comparison to semaglutide.

In addition to the above recommendations, some additional information/data is needed to interpret the results of the cost-effectiveness model, including:

- Additional information from the NMA output, including 95% credible intervals and results from the different models run, along with deviance information criterion (DIC) values and residual deviance values so that readers may assess the models' goodness of fit data
- Results of ICER's model validation where ICER varied the model input parameters to evaluate the face validity of changes to those inputs on the results
- Clinical event rates and risk factor progression over time to aid in interpretation of cost-effectiveness results
- State diagrams to allow readers to see patient progression across the different model comparators
- Rationale for using an additive approach to combining QALY disutilities when the coefficients described by Shao et al. (2019) were designed to be combined in a regression formula (eg, OLS regression)
- Scenario analyses exploring the impact of using an additive approach vs regression formula for QALY disutilities
- Full disaggregated results with costs and outcomes stratified across all available categories (eg, AEs, CV outcomes, renal outcomes, insulin, etc.) to help assess what is occurring in the model per modeling best practices and many health economics and outcomes research guidelines from around the world
- One-way sensitivity analysis (OWSA) results for tirzepatide compared to semaglutide and empagliflozin
- Undiscounted results from the cost-effectiveness analysis so that the budget impact analysis can be validated

Furthermore, there are several areas that lack sufficient information to evaluate and replicate (for those with modeling expertise) ICER's cost-effectiveness model. ICER should include clear details in the report on the following areas:

- How treatment discontinuation is applied throughout the model
- How HRs are being applied in the model to adjust the CV and renal outcomes
- Clinical inputs and the risk factor progression
    - The report indicates that time varying values of HbA1c and weight were calculated using additional published equations from Willis 2017, but this publication only provides regression functions for changes in HbA1c and body weight on insulin initiation and does not provide estimates of risk factor progression over time. Moreover, information on insulin doses and insulin types are needed for these equations described in Willis 2017 and these are not provided.

    - Risk factor progression is critical in terms of understanding the analysis, particularly with respect to the timing and impact of discontinuation, HbA1c difference between treatment arms, and the influence of BMI over time on quality of life.
- Explanation for why high and low parameter estimates both results in higher incremental QALYs than the implied base-case value when parameters are varied in Figure 4.3
    - For example, varying the tirzepatide HR for nephropathy yields incremental QALYs of approximately 0.68 for the high estimate and 0.62 for the low estimate, whereas the base-case QALY appears to be around 0.59. This anomaly applies to the majority of the parameters. It should be clearly explained how and why both the low and high estimates would be higher than the base-case estimate.
- Limitations of using the NHANES cohort for ICER's base-case model cohort
    - Approximately 32 million people in the US have T2D (Dugani 2021). However, ICER used a cohort of only 387 patients, which is a small sample of patients to be representative of the entire US T2D population.
    - The proportion of smokers in the US general population has been estimated at around 14% (Cornelius 2020), so ICER's estimate of 36.7% in the base-case model cohort seems high.
    - Similarly, estimates of concomitant medication use (100% on metformin and 42.9% on sulfonylurea) seem high.
    - Additionally, "renal disease" appears to be costed in Table E.4 as end-stage renal disease (ESRD), but it seems implausible that 15.8% of the population has ESRD at baseline. For comparison, the population in the Yang 2020 population (used for costing) has this estimate at 0.54%.

Given ICER's commitment to open and transparent engagement with stakeholders in their reviews, ICER should allow stakeholders the ability to provide input on results and analyses that were not presented as part of the draft evidence report.

Lilly has identified several inconsistencies and errors in the data inputs, which are listed in the Appendix, that ICER should correct.

We appreciate the opportunity to provide Public Comments on the draft evidence report and believe that the points made in this letter will support a scientifically sound evaluation for tirzepatide.

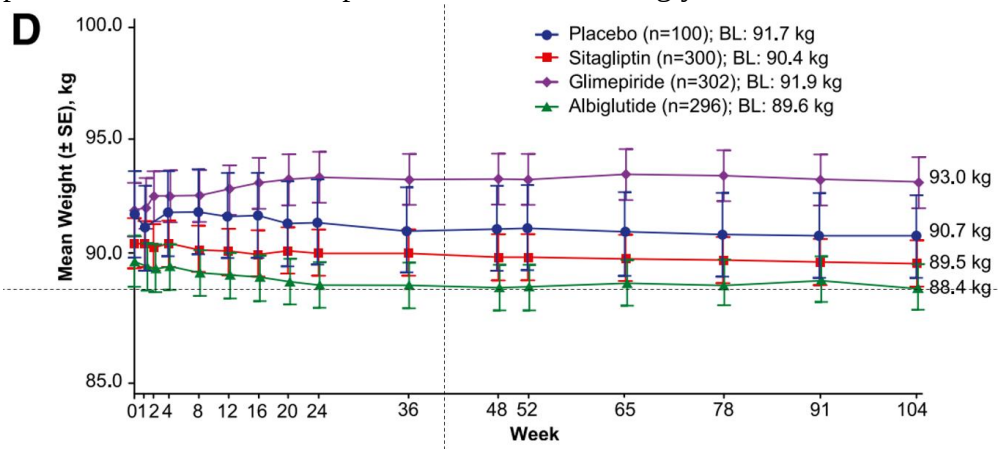
Sincerely,

Christian Nguyen
Vice President, Global Patient Outcomes & Real World Evidence
Eli Lilly and Company
nguyen_christian_t@lilly.com

Appendix: Additional Comments, Clarifications, and Corrections

Based on our detailed review, Lilly identified the following clarifications or inaccuracies in the draft evidence report that we would like for ICER to address as they incorporate changes to the revised evidence report:

1. On **Pages 16 and D31, Table D4.6**, ICER indicates that adverse events resulting in the discontinuation of the trial occurred in 8.5% (15 mg tirzepatide) and 4.1% (1 mg semaglutide) of participants; however, these rates are adverse events that resulted in discontinuation of the active treatment (tirzepatide or semaglutide), but these patients may remain enrolled in the trial on a different treatment. Can ICER please change the description on **Pages 16 and D31, Table D4.6** to say "discontinuation from study drug due to AE" in the evidence report?
2. On **Page 29**, **Table 4.4**, the incremental difference in total costs for tirzepatide ($284,000) and background therapy ($263,000) is $21,000; however, on Page 31, Figure 4.2, it appears that the base-case difference is approximately $13,000. Can ICER please correct this inconsistency in the evidence report?
3. On **Page 29**, **Table 4.4**, the incremental difference in QALYs between tirzepatide (4.69) and background therapy (4.14) is 0.55; however, on **Page 31, Figure 4.3**, it appears that the incremental difference is approximately 0.59 QALYs. Can ICER please correct this inconsistency in the evidence report?
4. On **Page 30**, **Table 4.5**, the incremental cost-effectiveness ratio for tirzepatide vs background therapy is $38,000/QALY gained, but based on **Page 31, Figures 4.2 and 4.3**, the implied ICER from the OWSA is approximately $22,000/QALY gained. Can ICER please correct this inconsistency in the evidence report?
5. On **Page D8**, ICER should add more details to **Figure D1.1**, including the list of studies that were removed and the reasons why these studies were removed. For example, there is no explanation of the decrease from 15 total references and 10 RCTs to 5 included references in the NMA. Additionally, the numbers in the flowchart do not add up, as it states that 813 references were assessed for eligibility in full text; of these, 802 citations were excluded, but another 5 references were identified through additional sources. This total should be 16 references; however, the flowchart only lists 15 total references in the next step.
6. On **Page D12**, **Table D2.2**, the body weight loss data used for HARMONY-3 in the ICER NMA does not match the HARMONY-3 publication (Ahren 2014: Figure 2D). ICER indicates a decrease in body weight by 2.2 kg at Week 40; however, the mean body weight at Week 40 appears greater than the value for body weight at Week 104 (88.4 kg). Given that baseline mean body weight is less than 90.0 kg, an estimate of 2.2 kg for body weight loss at Week 40 does not seem accurate and should be closer to 1.0 kg. Can ICER please correct the NMA inputs and model accordingly?



7. On **Page D12**, **Table D2.3**, the low-density lipoprotein (LDL) cholesterol data used for HARMONY-3 in the ICER NMA does not match the HARMONY-3 publication (Ahren 2014: Supplementary Table 3).

The LDL cholesterol data should be -0.03 instead of -1.2 for placebo and should be -0.05 instead of -1.9 for sitagliptin. Can ICER please correct these NMA inputs and model accordingly?

Supplementary Table 3. *Cardiovascular parameters at baseline and week 104.*

Mean (SD)	Placebo + Metformin (n=101)	Sitagliptin + Metformin (n=302)	Glimepiride + Metformin (n=307)	Albiglutide + Metformin (n=302)
Blood Lipids (mmol/L)				
Total Cholesterol				
Baseline	4.7 (1.0)	4.8 (1.0)	4.8 (1.0)	4.8 (1.2)
Change from baseline	-0.05 (0.8)	-0.09 (0.7)	0.07 (0.9)	-0.07 (0.9)
HDL Cholesterol				
Baseline	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
Change from baseline	0.03 (0.2)	0.03 (0.2)	0.004 (0.2)	0.04 (0.2)
LDL Cholesterol				
Baseline	2.5 (0.8)	2.6 (0.9)	2.6 (0.9)	2.6 (0.9)
Change from baseline	-0.03 (0.7)	-0.05 (0.6)	0.08 (0.7)	-0.03 (0.8)
Triglycerides				
Baseline	2.2 (1.1)	2.2 (1.2)	2.3 (1.3)	2.4 (1.6)
Change from baseline	-0.04 (1.0)	-0.15 (1.2)	-0.01 (1.9)	-0.20 (1.3)
Blood Pressure/ Heart Rate				
SBP (mmHg)				
Baseline	128.1 (13.2)	127.4 (13.6)	127.9 (14.3)	128.4 (13.9)
Change from baseline	2.2 (14.0)	0.2 (14.7)	1.5 (14.1)	-1.0 (14.2)
DBP (mmHg)				
Baseline	78.0 (8.8)	78.5 (8.6)	78.0 (8.9)	78.0 (9.3)
Change from baseline	0	0.2 (10.4)	1.0 (10.3)	-0.7 (9.3)
HR (bpm)				
Baseline	72.0 (11.2)	73.1 (10.2)	72.0 (9.5)	73.1 (10.2)
Change from baseline	2.3 (9.5)	0.8 (10.7)	-0.5 (9.6)	1.3 (10.3)

bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate. SBP, systolic blood pressure.

8. On **Page E5**, ICER describes how hypoglycemia was modeled. Can ICER confirm whether hypoglycemia rates were assumed to be the same in all treatment arms?

References

Ahren B, Johnson SL, Stewart M, et al. HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. *Diabetes Care.* 2014;37(8):2141-2148.

Boye KS, Matza LS, Stewart KD, et al. Patient preferences and health state utilities associated with dulaglutide and semaglutide injection devices among patients with type 2 diabetes in Italy. *J Med Econ.* 2019;22(8):806-813.

Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. *Eur J Health Econ.* 2011;12(3):219-230.

Briggs AH, Weinstein MC, Fenwick E, et al. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM modeling good research practices task force-6. *Value Health.* 2012;15(5):835-842.

Caro JJ, Briggs AH, Siebert U, et al. Modeling good research practices—overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. *Value Health.* 2012;15(5):796-803.

Cornelius ME, Wang TW, Jamal A, Loretan CG, Neff LJ. Tobacco product use among adults—United States, 2019. *MMWR Morb Mortal Wkly Rep.* 2020;69:1736–1742.

Del Prato S, Kahn SE, Pavo I, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet.* 2021;398(10313):1811-1824.

Dugani SB, Mielke MM, Vella A. Burden and management of type 2 diabetes in rural United States. *Diabetes Metab Res.* 2021;37(5):e3410.

Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-4. *Value Health.* 2012;15(5):843-850.

Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS Outcomes Model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. *Diabetologia.* 2013;56: 1925-1933.

Lilly Press Release. Lilly's tirzepatide achieves all primary and key secondary study outcomes against insulin glargine in adults with type 2 diabetes and increased cardiovascular risk in SURPASS-4 trial. May 20, 2021. Accessed December 3, 2021. http://lilly.mediaroom.com/2021-05-20-Lillys-tirzepatide-achieves-all-primary-and-key-secondary-study-outcomes-against-insulin-glargine-in-adults-with-type-2-diabetes-and-increased-cardiovascular-risk-in-SURPASS-4-trial.

Palmer AJ, Si L, Tew M, et al. Computer modeling of diabetes and its transparency: a report on the eighth Mount Hood challenge. *Value Health*. 2018;21(6):724-731.

Shao H, Yang S, Fonseca V, Stoecker C, Shi L. Estimating quality of life decrements due to diabetes complications in the United States: the Health Utility Index (HUI) diabetes complication equation. *Pharmacoeconomics.* 2019;37(7):921-929.

Si L, Willis MS, Asseburg C, et al. Evaluating the ability of economic models of diabetes to simulate new Cardiovascular Outcomes Trials: a report on the ninth Mount Hood Diabetes Challenge. *Value Health*. 2020;23(9):1163-1170.

Willis M, Asseburg C, Nilsson A, Johnsson K, Kartman B. Multivariate prediction equations for HbA1c lowering, weight change, and hypoglycemic events associated with insulin rescue medication in type 2 diabetes mellitus: informing economic modeling. *Value Health*. 2017;20(3):357-371.

Dec 08, 2021

Submitted electronically to: publiccomments@icer.org
Institute for Clinical and Economic Review (ICER)
One State Street, Suite 1050
Boston MA 02109 USA

As the manufacturer of Ozempic® (semaglutide), Novo Nordisk Inc. appreciates the active engagement with ICER throughout the course of this review and the opportunity to provide comment on ICER's November 9, 2021 draft evidence report for tirzepatide for type 2 diabetes.

Ozempic® was developed as a once-weekly subcutaneous injection indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. The efficacy and safety of Ozempic® has been investigated in over 11,000 adult patients with type 2 diabetes in the SUSTAIN phase 3 clinical development program which includes a cardiovascular outcomes trial (CVOT). Ozempic® has demonstrated superiority in A1C reduction in clinical trials versus placebo and active comparators. In addition, results of the SUSTAIN-6 CVOT established the direct benefit of semaglutide for reducing the risk of major cardiovascular events such as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke among patients with type 2 diabetes and known heart disease.[1]

We have carefully reviewed the draft report and wish to offer the following comments and suggestions to refine the comparative clinical value and long-term cost-effectiveness evaluation of tirzepatide.

We would like to reinforce our agreement with ICER on the following assumptions and choices:

I. No established benefit for tirzepatide for cardiovascular outcomes

Novo Nordisk agrees with ICER that it is appropriate to not assume additional benefit for tirzepatide on cardiovascular outcomes given that there is currently no data for tirzepatide from a cardiovascular outcomes trial.

II. Insufficient data for patients with comorbid CKD to evaluate at this time

Novo Nordisk agrees with ICER that patients with type 2 diabetes and comorbid chronic kidney disease (CKD) represent an important patient population, but data is currently insufficient to conduct an evaluation in this population at this time. The FLOW trial was initiated to explore the impact of semaglutide in patients with type 2 diabetes and CKD, with results expected in 2024.[2]

We would like to provide the following suggestions that we believe will improve the findings and make the report more useful to stakeholders:

I. <u>Placeholder net price for tirzepatide likely underestimates actual net price at launch</u>

The ICER price estimate for tirzepatide is likely inaccurate and will limit the usefulness of cost-effectiveness findings for payers and other stakeholders. The assumed price as equivalent to semaglutide is unlikely to represent the net price at launch. **To rectify this, we suggest using the SSR database to assess rebates *at launch* from other GLP-1 products, and correspondingly adjusting the rebate percentage suggested for tirzepatide in the model to make the model representative of what will most likely happen in the real world.**

II. <u>Influence of serious adverse events and discontinuation due to adverse events on model outputs is unclear</u>

Although no single serious treatment related adverse events occurred in either treatment arm in ≥5% of patients (ICER's threshold) in the SURPASS-2 trial, the overall rate of serious adverse events was higher with tirzepatide 15 mg (5.7%) vs semaglutide 1 mg (2.8%). In addition, discontinuations due to adverse events were approximately double with tirzepatide 15 mg (8.5% vs 4.1%).[3] **We look forward to additional clarity on how serious adverse events and adverse events leading to discontinuation are considered within in the model, given the direct head-to-head data from the SURPASS-2 trial**.

III. <u>Long-term data is suggestive of waning glycemic durability of response for some agents</u>

If the team hasn't already considered longer term trials, such as the EMPA-REG OUTCOME trial[4], we encourage the inclusion of data pertaining to the waning impact on glycemic control over the study duration. **We feel there may be implications for specific model outcomes such as the proportion of patients at any glycemic control threshold. Based on these studies and lack of long-term comparative head-to-head data, there is considerable uncertainty around the comparative durability of response**.

We appreciate the opportunity to provide input on the draft evidence report and look forward to engaging with ICER. All correspondence should continue to be directed to Dr. Michael Radin, Executive Director, Medical Affairs, Novo Nordisk.

Sincerely,

Michael Radin, MD, FACE
Executive Director, Medical Affairs
Novo Nordisk, Inc.
mzrd@novonordisk.com

REFERENCES

1. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes (SUSTAIN-6). *N Engl J Med*. 2016;375(19):1834-1844.
2. ClinicalTrials.gov. A research study to see how semaglutide works compared to placebo in people with type 2 diabetes and chronic kidney disease (FLOW), identifier NCT03819153. https://clinicaltrials.gov/ct2/show/NCT03819153.
3. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med.* 2021;385(6):503-515.
4. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-28.

Public Comments on ICER's Draft Evidence Report on Tirzepatide for Type 2 Diabetes (dated November 9, 2021)

As researchers active in the field of health economic modeling in type 2 diabetes, including past and ongoing collaborations with Eli Lilly and Company (manufacturers of tirzepatide), we appreciate the opportunity to provide public comments on ICER's recently published Draft Evidence Report on Tirzepatide for Type 2 Diabetes. ICER's analysis will, no doubt, receive a good deal of attention from stakeholders and other interested parties in the weeks and months ahead. We would therefore take this opportunity to make some comments on the transparency and reporting standards in ICER's health economic analysis, which we hope will be taken into consideration for the next version of the report (and potentially also for future reports).

In 2018, Palmer *et al.* published the proceedings of the Eighth Mount Hood Challenge meeting where all known published diabetes modeling groups were invited to evaluate transparency in existing publications and make recommendations to improve reproducibility of health economic analyses in diabetes.[1] The authors noted that to be fit for purpose, models of diabetes need to be *clinically credible and valid for the populations and jurisdictions of interest* and that *reporting models in a transparent manner and testing their internal and external validity* can help achieve that goal. The Mount Hood authors published a checklist of reporting requirements around model inputs to provide a useful framework for researchers publishing in this area. This work built on previous recommendations on transparency, albeit more generic, such as those from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM) that highlighted the need for transparency to generate confidence and credibility around any health economic decision modeling, the Second Panel on Cost-Effectiveness in Health and Medicine, and the American Diabetes Association (ADA) with specific reference to diabetes modeling.[2,3,4]

Unfortunately, the reporting in the *Long-term Cost-effectiveness* section of the ICER Draft Evidence Report falls well short of the recommendations outlined in these publications; a shortcoming which may lead to stakeholders questioning the credibility of the modeling analysis. Moreover, it would be impossible for independent researchers to reproduce the analysis (despite it being based on a published model) as several key aspects of the modeling analysis are inadequately described or missing altogether from the report. As noted by the Mount Hood authors, reproducibility is likely to enhance the credibility of any modeling analysis.[1]

Transparency of Methodology

There are several notable omissions from the *Methods* section of the report, including a clear description of initial treatment effects on baseline biomarkers (the reference to Chapter 3 does not afford the reader any clarity on precisely which values were included in the modeling analysis). The same criticism can be leveled (either in terms of lack of clarity or complete omission) at the description of any of the following aspects of treatment taken from the Mount Hood checklist:[1]

- Trajectory of biomarkers, BMI, smoking, and any other factors that are affected by treatment
- Treatment algorithm for HbA1c evolution over time
- Treatment algorithm for other conditions (e.g., hypertension, dyslipidemia, and excess weight)
- Rules for treatment intensification (conflicting descriptions are provided in the body of the report and in the supplementary material)
- Long-term effects, adverse effects, treatment adherence and persistence, and residual effects after the discontinuation of the treatment

In addition, there are several technical aspects of the modeling analysis that are missing from the report. For example, cohort characteristics are summarized in Table 4.2 on page 27 of the report but no information is provided on how the race categories described were reconciled with the ethnic groups employed in the United Kingdom Prospective Diabetes Model Outcomes Model 2 (UKPDS OM2) risk equations, which were used to evaluate the risk of complications and mortality in the model. Descriptions of the distributions used around model parameters in probabilistic sensitivity analysis (PSA) are not provided, despite all base case and sensitivity analysis results being derived from analyses in which PSA was active. Perhaps more critical is the lack of detail regarding the implementation of hazard ratios to adjust the risk of diabetes-related complications for each intervention based on data from cardiovascular outcomes trials (CVOTs) (or assumption in the case of tirzepatide).

Whilst the report is clear (Table E.2 on page E3) on the hazard ratios for the risk of major adverse cardiovascular events (MACE), congestive heart failure and nephropathy (which we assume to correspond to renal failure in the modeling analysis), how these hazard ratios are applied in the modeling analysis is simply not described. This is a critical feature of the modeling analysis as the data presented in the report indicate that it is a key driver of outcomes. MACE is a composite endpoint that is not evaluated by the UKPDS OM2 risk equations. And whilst there are UKPDS OM2 risk equations that can be used to determine which simulated patients experience myocardial infarction and/or stroke events, there is no risk equation that is specific to cardiovascular death, typically the third endpoint included in the three-point MACE definition. We would suggest that it is critical to the credibility of the modeling analysis that transparency is improved in this area. It is perhaps worth noting that we have restricted our comments here to the issue of transparency and have left aside the

serious limitations that may be associated with applying unadjusted hazard ratios to modeled endpoints in the analysis.

Transparency of Results

Similarly, reporting of results is inadequate. We would suggest that, at a minimum, the report needs to include survival curves, descriptions of the incidence of diabetes-related complications over time for each of the interventions and a breakdown of costs for each simulation arm. This would allow readers to better understand how the changes in risk factors associated with the different interventions in this review influence complication rates, and the role that hazard ratios play in adjusting the complication rates predicted by UKPDS OM2 equations. For all PSA simulations, we would recommend the presentation of scatter plots of incremental costs versus incremental quality-adjusted life years (QALYs) to inform the reader on uncertainty around the reported outcomes.

Justification of Assumptions

In the report, only four of the base case assumptions are justified (see Table 4.1 for details) and we would suggest none of these would be counted as critical base case assumptions. This falls short of what would be expected, for example, in any manufacturer's submission for health technology assessment in other countries and, most likely, what would be needed to successfully publish in a peer-reviewed journal.[5] Key justifications are needed around the choice of model risk equations (UKPDS OM2 risk equations for the US setting); at present only implementation challenges are cited as the reason for choosing UKPDS OM2 equations for the model. The authors could also explore the likely impact of this choice by employing other published risk equations in sensitivity analyses. Similarly, assumptions around risk factor progressions, triggers of treatment intensification, the additive approach to estimating QALYs (ignoring published regression formulae based on the same data), body mass index- and treatment device-related utilities, and the use of hazard ratios to adjust the risk of complications in the base case are not justified in the report. Finally, the choice of cohort should be justified given that the 387 patients selected from NHANES (Table 4.2) do not appear to be representative of the type 2 diabetes population in the US in certain respects.[6]

Improving transparency

To ensure the credibility of the cost-effectiveness analysis in ICER's ongoing review of tirzepatide in type 2 diabetes, we would encourage the reviewers to follow the recommendations for transparency laid out by the Mount Hood group in 2018. This would produce an expanded report but having a transparent, reproducible modeling analysis would

greatly enhance the credibility of the cost-effectiveness evaluation and acceptance of ICER's findings by almost all key stakeholders.

ICER should go further and share the cost-effectiveness model in Microsoft Excel beyond the small group of stakeholders currently afforded access for review. A version of the model with all commercial-in-confidence data removed that could be reviewed by a larger group of interested parties would do much to improve its validation. Further, ICER should share a version of the model without password protection to all stakeholders. So far as can be ascertained from the report, there is little substantive intellectual content in the model that should be proprietary to ICER. There should, therefore, be no barrier to sharing the model with a wider review group; a step which would improve transparency and validation as well as building confidence in the quality of the model implementation.

We would also suggest that an appendix be prepared that describes the validation analysis (with input settings and results) for inclusion in the overall report. Given the choice of risk equations for the model and the approach of applying unadjusted hazard ratios to model outcomes, validation analyses against CVOTs as well as in type 2 diabetes populations comparable to the US population are needed to support the existing model.

The role of independent health economic analysis to inform decision-making in the US is clearly an important one. Given this status and the public scrutiny of the work, themes such as transparency and credibility become even more pertinent and ICER should strive to conduct and report their cost-effectiveness modeling analyses to the highest possible standards. We wish the ICER team well with their ongoing review and hope this feedback is helpful.

Authors

William J. Valentine, Director of Health Economics, Ossian Health Economics and Communications, Basel, Switzerland

Richard F. Pollock, Director, Covalence Research Ltd, London, UK

References

1 Palmer AJ, Lei S, Tew M, et al. Computer Modeling of Diabetes and Its Transparency: A Report on the Eighth Mount Hood Challenge. Value Health 2018; 21: 724-31

2 Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. Med Decis Making 2012; 32: 733–43

3 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: 1093–103

4 American Diabetes Association Consensus Panel. Guidelines for computer modeling of diabetes and its complications. Diabetes Care 2004; 27: 2262–5

5 National Institute for Health and Care Excellence. Single technology appraisal: User guide for company evidence submission template. Process and methods [PMG24], Section 3 Cost-effectiveness. Available at: https://www.nice.org.uk/process/pmg24/chapter/cost-effectiveness. Accessed on December 6, 2021

6 Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Available at: https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html. Accessed on December 6, 2021

We are interested to read the ICER evidence report for tirzepatide for type 2 diabetes. Compared with semaglutide, tirzepatide showed consistently superior clinical benefits for all dose groups (5mg, 10 mg, and 15 mg) compared with semaglutide in terms of HbA1c, body weight, waist circumference, blood pressure, HDL and triglyceride. The differences in improving LDL and total cholesterol still favor tirzepatide, although not statistically significant. Finally, tirzepatide has achieved greater improvement in quality of life and health utility.

We re-assessed the cost-effectiveness analysis of GLP-1 agents in a published systematic literature review. [1] Among a total of 48 CEA studies using the diabetes models based on the UKPDS risk engine, we found that better long-term effectiveness results were driven by better improvements in biomarkers (HbA1c, LDL, and BP) in 47 CEA studies. Because the evidence report also used the UKPDS, it is plausible that long-term effectiveness analysis of tirzepatide versus semaglutide would favor tirzepatide. However, the tirzepatide was less effective in QALY (Table 4.5) in the base case scenario. In addition, we are puzzled by the methods of applying hazard ratios (Table E.2. page E3) for tirzepatide, semaglutide, and empagliflozin in the draft evidence report. We are not clear about how the hazard ratios were applied into the UPPDS OM2, and how the detailed processes of long-term effectiveness were derived.

Although a CV outcome trial with tirzepatide has not been completed it is in progress, even though the FDA no longer mandates such trials. Analysis of previous CVOTs has demonstrated that improvements in biomarkers were very good predictors of CVOT results. This has been determined by mediation analysis of the LEADER trial (Buse et al) and utilization of a more sophisticated modern risk engine in other trials. [2] Thus, it is very likely that a CVOT will have a beneficial outcome and such a set of results can be fitted into the model for determination of cost-effectiveness.

Lizheng Shi, Ph.D., MsPharm, MA

Regents Professor, Interim Chair

Department of Health Policy and Management

School of Public Health and Tropical Medicine

Vivian Fonseca MD

Professor of Medicine and Pharmacology

Assistant Dean for Clinical Research

Tullis Tulane Alumni Chair in Diabetes

Chief, Section of Endocrinology

Tulane University Health Sciences Center

References:

1. Hong D, Si L, Jiang M, et al. Cost Effectiveness of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors, Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists, and Dipeptidyl Peptidase-4 (DPP-4) Inhibitors: A Systematic Review. *PharmacoEconomics.* 2019;37(6):777-818.
2. Shao H, Shi L, Fonseca VA. Using the BRAVO Risk Engine to Predict Cardiovascular Outcomes in Clinical Trials With Sodium–Glucose Transporter 2 Inhibitors. *Diabetes Care.* 2020;43(7):1530-1536.

PIPC Partnership to Improve Patient Care

December 8, 2021

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

Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates this opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report on treatments for type 2 diabetes. Diabetes is very prevalent in the United Sates impacting more than 34 million adults, and the vast majority of those individuals have type 2 diabetes.[1] Appropriate management of type 2 diabetes can greatly improve patients' quality of life and lessen their reliance on the health care system. For this reason, treatments that meet patients' needs and encourage adherence are critically important in diabetes management. PIPC requests ICER consider the following comments.

ICER's assessment is, once again, premature.

With this report, ICER continues its concerning habit of undertaking assessments at far too early a date to have accurate inputs for its assessment. In this case, ICER has undertaken this exercise before final results on primary outcomes, such as the relative risk of major cardiovascular and renal events, are available from phase three trials. We are troubled with ICER's release of consistently more premature reports. Payers are clear that they use ICER's assessments in their decision-making processes, and PIPC has real concern that this assessment will lead to negative impacts for patients when it is based on incomplete data.

Since ICER has chosen to conduct this assessment before a price has been set and before completion and publication of key phase three trial results, there are key data points missing, and the model relies heavily on inputs on hazard ratios of major cardiac events: major adverse cardiovascular events (MACE), congestive heart failure (CHF), and nephropathy. In the report it states that due to lack of evidence the hazard ratios for all three key events are set to 1.00– i.e., tirzepatide is assumed to have no effect on these outcomes. There is a lack of consistency in this approach, as available data does show reductions in HbA1c, lipid levels, blood pressure, and body weight. These factors are known to be strongly associated with the relative risk of MACE and CHF. Numerous previous models in cardiovascular disease have used changes in lipid levels or blood pressure levels to derive proxy

[1] https://www.cdc.gov/diabetes/basics/type2.html

estimate of reductions in relative risk of major cardiac events.[2,3,4] To assume that a drug that has strongly significant impact on HbA1c, lipid levels, blood pressure, and body weight has zero effect on the risk of a heart attack or a stroke does not hold up to scientific rigor.

There was no differentiation between therapies with respect to adherence rates in the model

ICER chose not to investigate difference in adherence rates for different therapies. This is concerning as one of the key potential value drivers for a chronic and progressive disease, like diabetes, is the role of relative adherence to treatment. Recent studies have suggested the hospitalization and mortality rates can be twice as high in non-adherent patients than in adherent patients.[5]

ICER assumes that all discontinuation across evaluated therapies is identical in its modeling, but ICER itself noted in both its background and patient review sections that the delivery devise for tirzepatide is known to be preferable to the alternative therapies. Delivery method can play a major role in adherence in a real-world setting, and ICER would make strides in categorizing the actual value of the treatments in question if it were in include adherence in its model.

The ICER model omits outcomes that matter to patients.

ICER does not incorporate the benefits of weight loss and achievement of glycemic control, two factors patients highly value, in its report.

A large majority of Type 2 Diabetes patients both globally and specifically in the United States are overweight or obese. Obesity is known to complicate their disease and worsen outcomes in those patients.[6] A major potential benefit of tirzepatide is its impact on obesity and the complications that stem from obesity.

In addition to a reduction in obesity, a substantial number of patients achieved near-normal glycemic control (defined as a HbA1c <5.7%) in the trial evaluating tirzepatide (SURPASS-2). Type 2 diabetes patients consistently cite glycemic control as one of the more important outcomes for managing their diabetes. Research also shows that glycemic control may also slow progression of disease, particularly if achieved early in the disease course.[7,8] Prevention of progression and potentially of development of the micro- and macro-vascular complications of type 2 diabetes could both improve the productivity of

[2] Jena AB, Blumenthal DM, Stevens W, Chou JW, Ton TG, Goldman DP. Value of improved lipid control in patients at high risk for adverse cardiac events. Am J Manag Care. 2016 Jun 1;22(6):e199-207.
[3] Pandya A, Sy S, Cho S, Weinstein MC, Gaziano TA. Cost-effectiveness of 10-year risk thresholds for initiation of statin therapy for primary prevention of cardiovascular disease. Jama. 2015 Jul 14;314(2):142-50.
[4] Grabowski DC, Lakdawalla DN, Goldman DP, Eber M, Liu LZ, Abdelgawad T, Kuznik A, Chernew ME, Philipson T. The large social value resulting from use of statins warrants steps to improve adherence and broaden treatment. Health affairs. 2012 Oct 1;31(10):2276-85.
[5] Pednekar P, Heller DA, Peterson AM. Association of medication adherence with hospital utilization and costs among elderly with diabetes enrolled in a state pharmaceutical assistance program. Journal of Managed Care & Specialty Pharm. 2020 Sep;26(9):1099-108.
[6] Sullivan P, Ghushchyan V, Ben-Joseph R. The impact of obesity on diabetes, hyperlipidemia and hypertension in the United States. QOL Research. 2008 Oct;17(8):1063-71.
[7] Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet.* 2010;376(9739):419-430.
[8] Spellman CW. Achieving glycemic control: cornerstone in the treatment of patients with multiple metabolic risk factors. Journal of Osteopathic Medicine. 2009 May 1;109(s51):8-13.

patients and lessen caregiving burden. We encourage ICER to include these factors that matter deeply to patients in its model.

ICER's model oversimplifies the disease and fails to capture full benefit to patients.

ICER's model assumes the only quality of life effects generated by a new therapy are movement between broad health states. As we have discussed in past comments, the reality for patients is the incremental improvements matter deeply, and improvements in one area can lead to other benefits, like increased productivity or reduced anxiety that make a significant positive different in patients' lives.

In the case of this model, there is a growing body of evidence that successful treatment of cardiovascular risk factors have 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, one 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.[9] Similar results have been seen in drugs used to treat high blood pressure.[10] We can anticipate similar results with reduction in cardiovascular risk in these treatments for diabetes.

The costs for cardiovascular and renal hospitalization events in the model are based on a younger population than the population of need. This is likely to underestimate true cost savings from effective treatment.

Thee cost estimates used in the model specific to major cardiac events and disease sequelae are taken from a study that was limited to patients under the age of 65.[11] The description of the ICER model very clearly states that each patient simulation is run for a lifetime, so the majority of the time for which ICER' is modeling, the patients are over the age of 65. There is considerable evidence in the literature that costs associated with hospitalization for both cardiovascular and renal events for patients over 65 years of age are significantly higher than for those patients younger than 65 years of age.[12,13] Since costs are shown to increase with age, it is likely the costs ICER uses in the model are underestimates, which means any cost savings from reducing risks of events due to successful treatment will be underestimated in the model. We encourage ICER to update the inputs for the cost data, so the model more accurately captures the cost savings.

ICER continues to rely on the discriminatory QALY.

---

[9] 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.
[10] 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.
[11] Yang W, Cintina I, Hoerger T, et al. Estimating costs of diabetes complications in people< 65 years in the US using panel data. *Journal of Diabetes and its Complications.* 2020;34(12):107735.
[12] Curtis LH, Hammill BG, Bethel MA, Anstrom KJ, Gottdiener JS, Schulman KA. Costs of the metabolic syndrome in elderly individuals: findings from the Cardiovascular Health Study. Diabetes care. 2007 Oct 1;30(10):2553-8.
[13] Chee JH, Filion KB, Haider S, Pilote L, Eisenberg MJ. Impact of age on hospital course and cost of coronary artery bypass grafting. The American journal of cardiology. 2004 Mar 15;93(6):768-71.

PIPC would like to reiterate the point it has made to ICER in past comment letters that the use of the Quality-Adjusted Life Year (QALY) is inappropriate in assessing treatments for chronic illnesses. The QALY is known to discriminate against those with disabilities and chronic illnesses,[14] like type 2 diabetes. We encourage ICER to look to more innovative methods to assess value that do not immediately put treatments for those with disabilities and chronic illnesses at a disadvantage.

Conclusion

ICER's model omits outcomes that matter to patients and does not incorporate critical factors, like adherence. We urge ICER to address these shortcomings prior to release of its evidence report.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

[14]https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf