

Boehringer Ingelheim (BI) Response to Draft Scope Document - July 21, 2021**Primary contact:** Saurabh Ray, PhD (saurabh.ray@boehringer-ingelheim.com)

Thank you for the opportunity to provide comments on the Draft Scope Document. The following are concerns and considerations, from BI, as ICER makes decisions regarding their approach for the evaluation of tirzepatide as a treatment for type 2 diabetes mellitus (T2DM).

BI acknowledges the relevancy of comparing tirzepatide to other injectable GLP-1 receptor agonists, and cautions ICER regarding the assessment of empagliflozin, an SGLT2 inhibitor, as a comparator.

1. Comparison of tirzepatide, an injectable dual GIP and GLP-1 receptor agonist, to other injectable GLP-1 receptor agonists is appropriate. BI would recommend that, in addition to semaglutide and dulaglutide listed in the draft scope as comparators, ICER may consider liraglutide, which is also an injectable GLP-1 receptor agonist with cardiovascular outcomes trial (CVOT) evidence and anticipated to be commercially available as a generic or biosimilar.
2. It is important to consider CV outcomes in addition to weight management and glycemic control for robust assessment of treatments for T2DM. The SGLT2 inhibitor class has demonstrated pleiotropic effects, such as risk reduction in CV death, hospitalization for heart failure (HF), and chronic kidney disease progression, **which do not appear to be driven solely by weight management and glycemic control.** Tirzepatide is a dual GLP-1 and GIP receptor agonist for which little is known about the impact of GIP on CV risk. A cardiovascular outcomes trial (CVOT) with tirzepatide is in progress (SURPASS CVOT); however, the projected completion date is October 17, 2024¹. In the absence of CVOT data, a comprehensive evaluation of tirzepatide as a treatment for T2DM is limited. Long term CVOT data, which are available for the SGLT2 inhibitor class documenting the cardiorenal metabolic benefits, should be captured for a robust evaluation of treatments for T2DM. We strongly caution ICER against making any comparative statements as it relates to the impact on cardiovascular hard endpoints and macrovascular complications in the absence of a completed appropriately designed CVOT with tirzepatide at the present time. wee
3. Head-to-head trials comparing tirzepatide to the proposed comparators, semaglutide² and dulaglutide³, do exist. However, there are no such trials comparing tirzepatide to empagliflozin. Any indirect or multi-step comparison of tirzepatide to empagliflozin would be based on limited and non-directly applicable evidence, thereby neglecting the large body of evidence documenting the independently established benefits of empagliflozin. Furthermore, a comparison could be compromised by the heterogeneity of the patient populations across the trials as well as differences in study design and outcomes measured.

BI would like to highlight some additional considerations for ICER.

1. ICER's draft scope document references obesity as a risk factor for T2DM. Additionally, ICER's approach uses HbA1c as the primary driver of treatment value. BI would like to emphasize that T2DM is a cardiorenal metabolic disease⁴ with implications for a wide range of CV risks and outcomes, including HF and renal outcomes that may be independent of glucose control and weight loss^{5,6}. Given the systemic impact of T2DM on the vascular system, any value assessment of T2DM treatments must emphasize and include CV and renal outcomes^{7,8}.
2. Data for tirzepatide includes data for patients with obesity in addition to patients with T2DM. It is important to differentiate these two distinct patient groups which often achieve different levels of efficacy,

especially in terms of documented different magnitude of on-treatment weight loss in the two populations, and to ensure that only data for patients with T2DM are used for the purposes of the T2DM treatment evaluation.

3. Within the draft scope document, several outcomes were noted in multiple sections. BI would like to highlight that all outcomes should be considered as mutually exclusive, to ensure appropriate attribution of treatment impact. For instance, 1) body weight is listed as a patient important outcome and adverse event; 2) renal outcomes are mentioned as patient-important outcomes, microvascular outcomes, and adverse events and 3) hospitalization is mentioned as a patient-important outcome and in macrovascular outcomes section.
4. The proposed outcome percentage of patients achieving adequate glycemic control or normoglycemia (HbA1c of <5.7%) is not in line with ADA 2021 recommendations on glycemic control targets, stipulating that an A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate⁹.
5. Aside from data on HbA1c levels and weight loss, key outcomes noted for inclusion in the model, such as health-related quality of life or long-term cardiovascular outcomes do not have published data for tirzepatide^{2,3}. Further clarity on how ICER plans to deal with missing outcome data would be helpful.
6. Clinical trial results for tirzepatide endpoints are reported using estimated mean differences (estimands), thus not accounting for differential discontinuation rates or patients not reaching the full dose in the various trial arms^{2,3}. It would be helpful if ICER could clarify how this will be handled in the model.
7. Moving from the UKPDS OM2 model used in ICER's previous evaluation of T2DM treatments to the Building, Relating, Assessing, and Validating Outcomes (BRAVO) risk engine, which is based on a U.S. population and accounts for a broader range of CV and renal outcomes, addresses some of BI's previously voiced concerns around the modeling approach for the 2019 T2DM evaluation. However, in a study evaluating the ability of the BRAVO risk engine to accurately project cardiovascular outcomes for three major clinical trials of SGLT2 inhibitors (EMPA-REG OUTCOME for empagliflozin, CANVAS for canagliflozin and DECLARE-TIMI 58 for dapagliflozin), BRAVO was shown to overestimate both mortality and angina for patients receiving empagliflozin by 20%¹⁰. BI believes that adjustments to the BRAVO risk engine are needed to ensure good model fit and valid projection of clinical events.
8. BRAVO was also unable to capture empagliflozin's preventive effect on chronic heart failure through the biomarkers serving as model inputs¹⁰. Heart failure is a critical outcome for patients with T2DM and a driver of significant value. Inadequately capturing this aspect of treatment benefit would significantly compromise validity of the assessment.

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July 21, 2021

RE: Lilly's Written Response to ICER's Draft Scoping Document

Eli Lilly and Company ("Lilly") appreciates the opportunity to provide feedback on the Institute of Clinical and Economic Review's (ICER's) draft scoping document for the assessment of tirzepatide for type 2 diabetes (T2D). We have outlined several important considerations, with supporting references.

There is high unmet need in T2D that tirzepatide helps to address.

As mentioned in ICER's draft scoping document, despite availability of many therapy options for the management of T2D, a significant proportion of individuals with T2D are not achieving glycemic control (pg. 2). Tirzepatide can address this unmet need by allowing patients to safely achieve lower HbA1c values, with up to 94% of participants in the SURPASS clinical trials on the 15 mg dose achieving the ADA target level HbA1c of <7%, and approximately half of these participants achieving normoglycemia, defined as HbA1c <5.7% (Dahl 2021, Frias 2021, Lilly 2020, 2021a, 2021b, 2021c, Ludvik 2021, Rosenstock 2021).

Uncontrolled diabetes is associated with various complications and comorbidities, including cardiovascular disease (CVD), that increase patient morbidity and mortality (ADA 2021, Cavender 2015). Research has shown the importance of early intensive glucose control in minimizing long-term risk of glycemic complications, such as myocardial infarction and mortality (Holman 2008, Lind 2021, UKPDS 1998). Yet, an HbA1c of <5.7% without an increased risk of hypoglycemia has not been considered safely attainable for many patients with current treatment options. With tirzepatide, this goal was met with a gastrointestinal-related side-effect profile similar to that reported with GLP-1 receptor agonists (RAs). Approximately half of the participants in the SURPASS clinical trials receiving a 15 mg dose of tirzepatide achieved an HbA1c <5.7% (Dahl 2021, Frias 2021, Lilly 2020, 2021a, 2021b, 2021c, Ludvik 2021, Rosenstock 2021). In addition, >90% of patients with T2D are overweight or obese, resulting in difficulty achieving glycemic control, increased risk of complications and mortality, worse quality of life, and increased costs (Bramante 2017, Fridman 2020, Karkare 2019). Tirzepatide has shown promise in treating T2D patients who are overweight or obese on various background therapies, with weight reduction of up to 14% (-12.9 kg) at 52 weeks (Dahl 2021, Frias 2021, Lilly 2020, 2021a, 2021b, 2021c, Ludvik 2021, Rosenstock 2021). In the SURPASS-2 trial, more patients who received tirzepatide than those who received semaglutide met a prespecified exploratory composite endpoint of HbA1c of ≤6.5% with ≥10% weight loss and without clinically significant hypoglycemia or severe hypoglycemia (32-60% vs 22%, respectively) (Frias 2021). Furthermore, many patients who received tirzepatide were noted to have an improved lipid profile as well as improved blood pressure (BP), biomarkers of insulin sensitivity, and liver enzyme levels (Dahl 2021, Frias 2021, Ludvik 2021, Rosenstock 2021). Thus, we believe dual agonism (glucose-dependent insulinotropic polypeptide receptor and GLP-1 receptor) may allow patients to reach near-normal glycemia with potential long-term benefits.

Lilly agrees with the target population chosen by ICER for the assessment of tirzepatide.

The SURPASS clinical trial program assesses the use of tirzepatide in individuals with T2D with different background antihyperglycemic agents and different mean duration of diabetes. Thus, Lilly agrees with the target population as outlined by ICER in the draft scoping document for the assessment of tirzepatide: Adults with T2D with inadequate glycemic control despite current treatment with antihyperglycemic agent(s) (pg. 4). Regarding ICER's subpopulations of interest, the inclusion criteria for the SURPASS-4 trial focuses on patients at high risk for cardiovascular (CV) events, and the SURPASS-2 and SURPASS-3 trials examine tirzepatide in patients requiring a second and third antihyperglycemic agent, respectively. In terms of race/ethnicity and socioeconomic status, Lilly believes that diversity in clinical trials is fundamental to ensuring relevance for broad populations impacted by diabetes, and as a company, Lilly is committed to achieving this across all research programs, including the SURPASS clinical trial program (Lilly 2021d).

Subcutaneous semaglutide 1 mg is the most appropriate comparator for tirzepatide given the availability of evidence from a head-to-head (H2H) randomized controlled trial; comparing tirzepatide to dulaglutide and

empagliflozin is inappropriate due to differences in trial design and technical limitations in forming a valid connected network of evidence, respectively.

Lilly agrees with ICER that injectable GLP-1 RAs are an appropriate comparator for tirzepatide. Given the mechanism of action of tirzepatide and its clinical profile, tirzepatide will likely be used in the place of current injectable GLP-1 RA therapies in clinical practice. In designing the SURPASS clinical trial program, subcutaneous semaglutide 1 mg and dulaglutide were chosen as active comparators for tirzepatide, as they were the leading entrants in the GLP-1 RA market. Direct comparative evidence from a H2H randomized controlled trial is more robust and preferred to an indirect treatment comparison (ITC). Currently, there are no direct H2H phase 3 trial results available for tirzepatide vs dulaglutide, as the SURPASS-CVOT trial comparing these 2 therapies for CV outcomes is still ongoing. The only available H2H trial data at this time using dulaglutide as a comparator is from a phase 2 trial (Frias 2018). Lilly recommends excluding phase 2 trial data for tirzepatide as the dose escalation scheme was different than the scheme used in the phase 3 trials, which considerably improved the gastrointestinal tolerability profile of tirzepatide. Therefore, results from phase 2 studies do not provide the most accurate information on gastrointestinal tolerability of tirzepatide nor does it reflect the expected dose escalation scheme to be submitted to regulatory authorities. In contrast, the SURPASS program included the SURPASS-2 trial that provides H2H evidence for comparing semaglutide to tirzepatide. As tirzepatide can be compared to semaglutide, a weekly injectable GLP-1 RA, through direct evidence, it is not necessary to conduct a comparison against dulaglutide, another weekly injectable GLP-1 RA, through an ITC.

The SURPASS clinical trial program does not include SGLT-2 inhibitors, such as empagliflozin, as an active comparator; thus, there are no H2H data for tirzepatide vs SGLT-2 inhibitors. Conducting an ITC will be necessary to compare tirzepatide to empagliflozin and doing so will require an extended network meta-analysis with bridging studies to link tirzepatide to the SGLT-2 inhibitor network. However, such a comparison will raise technical challenges in forming a valid connected network of evidence. One challenge involves the comparison of important outcomes. The key intermediate outcomes of interest (as indicated later in this document) for T2D, in general, and for tirzepatide specifically are not only HbA1c and weight but also important metabolic indicators such as lipid levels, BP, and waist circumference. Based on a recent systematic literature review that Lilly performed and on reviews of existing network meta-analyses (Kanters 2019), we concluded that tirzepatide can be linked to SGLT-2 inhibitors only via SUSTAIN-8 as a bridging study and only for a small subset of the key intermediate outcomes (e.g., HbA1c, weight) but not for others, such as lipid levels, BP, or waist circumference.

An additional challenge in conducting an ITC with SGLT-2 inhibitors is the timing of the endpoint evaluation. The primary endpoints in all SURPASS trials were assessed at 40 weeks or beyond, whereas the comparable phase 3 trial for empagliflozin evaluated the primary endpoint at Week 24 (NCT01159600). In the SURPASS clinical trials, patients receiving 15 mg of tirzepatide started the study at a dose of 2.5 mg and then increased the dose in a step-wise approach at 4-week intervals to their final maintenance dose of 15 mg after 20 weeks. The dose escalation for tirzepatide will limit direct comparisons that can be made at shorter time points (eg, 24 weeks). As such, endpoint evaluation to capture the full treatment benefits for any comparisons of tirzepatide should be conducted at 40 weeks or longer.

The impact of weight loss in reducing obesity complications (eg, obstructive sleep apnea [OSA], non-alcoholic steatohepatitis [NASH]) should be included in ICER's comparative value analysis.

The outcomes included in the draft scoping document are key and relevant for assessing the impact of treatment in patients with T2D. Given that the overwhelming majority (>90%) of T2D patients are either overweight or obese (Bramante 2017), it is also important to consider the impact of treatment on obesity-related complications. Patients with T2D and obesity are not only at risk for CVD but are also at an increased risk of other comorbidities including major depression, pneumonia, pulmonary embolism, osteoarthritis, OSA, gastroesophageal reflux disease, and NASH, leading to substantial humanistic and economic costs associated with excess body weight (Li 2015, Su 2015). Additionally, waist circumference should be included in the list of patient-important outcomes for this review, as waist circumference is strongly associated with all-cause and CV mortality with or without adjustment of body mass index (BMI) (Ross 2020).

Lack of successful (ie, >10% weight loss) and/or sustained weight management has been identified as a shortcoming of current antihyperglycemic treatments (ADA 2021, Brown 2019). Weight loss is associated with improved glycemic control, quality of life, reductions in CV risk factors and mortality, lower rates of obesity-related complications and reduced healthcare costs in patients with T2D (Fridman 2020, Fruh 2017, Karkare 2019). SURPASS clinical trial results have shown clinically meaningful weight loss with tirzepatide compared to alternative T2D treatments studied in the SURPASS clinical trials.

ICER should use surrogate measures (eg, lipid levels, BP, waist circumference) to predict long-term CV outcomes, as long-term CV data for tirzepatide will not be available during ICER's review.

Long-term CV outcomes from the SURPASS-CVOT trial will not be available at the time of the review. Data on CV outcomes for tirzepatide released to date are based on results from SURPASS-4 (designed to assess CV safety) and a CV safety meta-analysis across the clinical program; these studies were not powered to discern differences in effectiveness on CV outcomes. Because of these data limitations, surrogate measures, such as reductions in HbA1c, weight, lipid levels, BP, and waist circumference, should be used to model CV outcomes associated with tirzepatide. Improvements in HbA1c levels result in a reduction in the risk of both microvascular and macrovascular complications in individuals with T2D, as well as lower costs and improved health-related quality of life (ADA 2021, Kuznetsov 2015, Lage 2020). Systolic hypertension has been demonstrated to be an independent predictor of the risk of a composite outcome of MI, ischemic stroke, or hemorrhagic stroke (Flint 2019). Lipid levels and waist circumference have also been shown to be strong predictors of CVD and various CV outcomes such as CV mortality (Ross 2020, Sone 2016). Treatment with tirzepatide has resulted in a reduction of metabolic risk factors including BP, lipid levels, and waist circumference, suggesting an anticipated CV/metabolic benefit (Dahl 2021, Frias 2021, Ludvik 2021, Rosenstock 2021). The BRAVO model was developed to account for the ultimate impact of small changes on metabolic risk factors and allows for streamlined use of surrogate measures. Treatment effect on these surrogate endpoints can be translated into clinically meaningful outcomes such as stroke and angina incidence using the BRAVO risk engine.

Device preference should be considered as a potential other benefit and used as an important driver of patient outcomes and value.

Patient preference for diabetes treatment is dependent upon several different factors such as route of administration, frequency, and injection device type (Purnell 2014, Matza 2019). The tirzepatide device will be the same as the dulaglutide device, which has demonstrated improved patient preference over the semaglutide device (preferred by 84.2 vs 12.3% of patients, $P < 0.0001$), with more patients perceiving the dulaglutide device to have greater ease of use (86.8% vs 6.8%, $P < 0.0001$) in the PREFER trial (Matza 2019). Another recent study of the dulaglutide and semaglutide devices demonstrated the importance of device preference in health state utility valuations; the identified utility difference between devices is an important consideration when adjusting utilities in economic models comparing the treatments (Boye 2019).

Lilly supports ICER's decision to use the BRAVO risk engine; however, a time horizon of 10 to 15 years should be used for the scenario analysis, as 5 years is not long enough to capture the impact of key outcomes.

The BRAVO risk engine is the appropriate risk engine to use, as it was derived from a relatively recent US population, and its equations can capture the impact of important factors such as HbA1c, systolic BP, and BMI on CV outcomes, costs, and quality-adjusted life-years. Lilly agrees with the use of a lifetime time horizon in the base-case; however, 10 to 15 years should be used for the scenario analyses. Five years likely does not allow enough time for the trajectories of important clinical outcomes (eg, microvascular complications, obesity-related complications) to fully separate.

Lilly appreciates the opportunity to provide written input during the public comment period. We believe that the points made in this letter will support a scientifically sound evaluation for tirzepatide.

Sincerely,



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Novo Nordisk is a global healthcare company that has been making innovative medicines to help people with diabetes lead longer, healthier lives for almost 100 years. As the manufacturer of Ozempic[®] (semaglutide), Novo Nordisk Inc. appreciates the opportunity to provide comment on ICER's June 30, 2021 draft background and scoping document on tirzepatide for type 2 diabetes.

GLP-1RAs provide effective glycemic control along with weight reduction and low risk of hypoglycemia.^{1,2} 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[®] demonstrated superiority in A1C reduction in clinical trials versus placebo and active comparators (sitagliptin, canagliflozin, exenatide extended release, dulaglutide, liraglutide and insulin glargine U100).

Even with numerous treatment options available for type 2 diabetes, many patients do not achieve recommended glycemic targets. The American Diabetes Association (ADA) has stated that patient-centered care is the focus and priority.³ Novo Nordisk's heritage and commitment to putting patients first includes an understanding that chronic diseases such as diabetes disproportionately affect diverse communities, including African Americans, Hispanic Americans, Asian Americans, and Native Americans. We sponsor several programs helping to improve individual and public health in communities of color, and our clinical trials are designed with a goal of ensuring diverse representation. Our continued and evolving efforts to address health disparities and barriers to care reflect our ongoing focus and dedication to patients, providers and communities.

Based on our deep understanding of type 2 diabetes as well as experience with developing multiple treatments for people with type 2 diabetes, we wish to bring up the following considerations to inform development of the revised scoping document.

I. Seeking clarity on HbA1C <5.7% as an outcome

Novo Nordisk applauds ICER in considering a wide range of outcomes, including but not limited to measures of HbA1C, body weight, kidney function, health-related quality of life, major adverse cardiovascular events, and adverse events. The percentage of patients achieving an



HbA1C of <5.7%, though included as a secondary endpoint in the tirzepatide phase 3 SURPASS trials, has not otherwise been studied or evaluated in other clinical trials. Scarce evidence exists linking achievement of HbA1C <5.7% with an improvement in real-world outcomes. Existing evidence from the ACCORD⁵ and ADVANCE⁶ trials suggest an increased risk of adverse events and suggestion of higher mortality rates among patients treated with intensive blood glucose control (targeting HbA1C <6.5%). HbA1C <5.7% represents a more aggressive target than those listed in the American Diabetes Association and the American Association of Clinical Endocrinologists guidelines, and may not be an appropriate treatment goal for all patients with type 2 diabetes.⁷ **With consideration of these issues, Novo Nordisk looks forward to additional clarity from ICER on the role and significance of HbA1C of <5.7% as an outcome in the planned clinical and economic review.**

II. **Seeking clarity on heart failure requiring hospitalization or an urgent heart failure visit as an outcome**

Patients with type 2 diabetes with comorbid heart failure and those at high risk of heart failure represent an important patient group with significant unmet treatment needs. To date, neither tirzepatide nor any GLP-1 receptor agonist has been studied specifically to measure impact on heart failure outcomes.^{8,9} Limited data suggests neither a substantial benefit nor excess harm associated with GLP-1 receptor agonists in regards to hospitalizations for heart failure.⁹ Due to the sparsity of data for tirzepatide and GLP-1 receptor agonists on heart failure outcomes, it may be difficult to conduct a rigorous review of heart failure or any of the specific measures associated with it such as emergency department visits or hospitalizations. **Given the sparse data and lack of indication for GLP-1 receptor agonists in patients with heart failure, Novo Nordisk looks forward to additional clarity from ICER on the applicability and feasibility of including heart failure-related hospitalizations and urgent care visits as an outcome in the planned clinical and economic review.**



We appreciate the opportunity to provide input on the scoping document and look forward to engaging with ICER throughout this review. All future correspondence should be directed to Dr. Michael Radin, Executive Director, Medical Affairs, Novo Nordisk.

Sincerely,

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