Semaglutide and Tirzepatide for Obesity: Response to Public Comments on Draft Evidence Report

OCTOBER 29, 2025

Table of Contents

#	Comment	ICER Response
Manufacturers		
Boston Scientific		
1.	In the background section, ICER acknowledges multiple modalities for treating obesity, including lifestyle modifications, medications, and bariatric surgery. We urge ICER to also recognize endoscopic bariatric and metabolic therapies (EBMT) as an additional option for weight loss. Notably, in its 2026 Patient-Centered Outcomes Research Institute (PCORI) funding announcement, PCORI identified "Addressing Obesity" as a Special Areas of Emphasis (SAEs). As stated in the announcement, *"PCORI is interested in supporting high-quality, patient-centered research to study the comparative clinical effectiveness of intensive lifestyle interventions, anti-obesity medications, endoscopic procedures and bariatric surgery, as well as combination approaches, as appropriate."* PCORI explicitly recognized endoscopic procedures as a distinct category, underscoring their role alongside other established weight loss options. Many global specialty societies including the American Society for Gastrointestinal Endoscopy (ASGE), European Society for Gastrointestinal Endoscopy (ESGE) and International Federation for the Surgery of Obesity (IFSO), the leading international society for bariatric and metabolic surgeons, have issued guidance on EBMTs for weight loss in patients with obesity. In conclusion, BSC requests ICER to include endoscopic bariatric and metabolic therapies (EBMT) in the description of alternative weight loss procedures. Recognizing EBMT aligns with current practice and supports patient-centered care. We appreciate the opportunity to provide this comment and thank you for your consideration.	***Thank you for your comments. Our population of interest is adults with obesity who are interested in treatment with semaglutide or tirzepatide. Although we agree that endoscopic bariatric and metabolic therapies (EBMT) are options for weight loss, we believe that the population interested in medication is frequently not interested in pursuing EBMT and vice versa. Therefore, we did not include EBMT or any other surgical procedure as comparators in our report.***
Eli Lilly		
1.	ICER's decision to entirely forgo a network meta-analysis (NMA), which would have integrated direct and indirect evidence from clinical trials of the obesity management medications (OMMs) under review, presents a serious methodological concern. This concern is compounded by ICER's subsequent decisions to: (1) conduct a meta-analysis (MA) for only one intervention of interest (i.e., injectable semaglutide); and (2) devote very little attention in the DER to the head-to-head (H2H) evidence comparing tirzepatide to injectable semaglutide from SURMOUNT-5. Together, these decisions may undermine the balance and validity of this assessment's clinical evaluations, have downstream impacts on its economic analyses, and pose challenges for the appraisal committee during deliberations and voting on comparative effectiveness. To begin addressing the abovementioned concerns, Lilly recommends that ICER uniformly apply the standard set forth in this assessment's research protocol by conducting an MA to generate pooled estimates of tirzepatide's treatment effect versus lifestyle modification (LSM) using data from SURMOUNT-1 and -3. Results from that MA should, as with injectable semaglutide, be	***We appreciate the suggestion that we should conduct a meta-analysis of SURMOUNT-1 and SURMOUNT-3 for tirzepatide and conduct a network meta-analysis for the interventions in this review.*** ***We have concerns about the comparability of populations between SURMOUNT-1 and SURMOUNT-3 due to the trial design of a 12-week lead-in period of intensive lifestyle modifications leading to at least a 5% weight loss. There may be underlying differences in participants who are able to lose 5% body weight with intensive lifestyle modification compared with those who could not. We also did not have access to unadjusted data from either trial, and the meta-analysis conducted on the injectable semaglutide trials used unadjusted data. Therefore, we chose not to pursue meta-analysis for tirzepatide.***

	used to inform the following inputs in ICER's cost-effectiveness model (CEM): (1) mean percentage change in body weight (%ΔBW); (2) all-cause discontinuation (ACD); and (3) severe gastrointestinal (GI) adverse events (AEs).	
2.	Further, we strongly recommend that ICER revisit its analysis of SURMOUNT-5 to ensure that the trial's findings are adequately reflected in the interim evidence report (IER). In its prior assessments of treatments for type 2 diabetes (T2D) and OM, ICER devoted significant attention to discussing evidence from scope-germane H2H trials (i.e., in-depth review of H2H evidence from SURPASS-2 comparing tirzepatide to injectable semaglutide in the 2022 T2D assessment, in-depth review of H2H evidence from STEP-8 comparing injectable semaglutide to liraglutide in the 2022 OM assessment). In the DER for this assessment, however, sufficient attention has not been paid to the totality of H2H evidence from SURMOUNT-5 comparing tirzepatide to injectable semaglutide. Apart from cursory examinations of reported weight-related outcomes and AEs, SURMOUNT-5 is absent from ICER's quantitative and qualitative evaluation of tirzepatide's clinical benefits. There is zero discussion of data from that trial showing tirzepatide's effect on cardiometabolic parameters or its potential impact on prevention of cardiovascular (CV) events, both of which are central to this assessment, in the DER. Lilly urges ICER to evaluate clinical benefits and harms in the IER by separately addressing: (1) each intervention versus placebo (PBO); and (2) tirzepatide versus semaglutide.	***The weight loss results from SURMOUNT-5 were very similar to the results from the individual trials. We discuss the differences in the magnitude of weight between agents in our summary section, acknowledging the superiority of tirzepatide compared with injectable and oral semaglutide.*** ***Cardiometabolic markers are risk factors for cardiovascular disease. Since we have data on actual cardiovascular outcomes and we have seen in GLP-1 trials that the surrogate outcomes have not correctly predicted CV outcomes, we chose to focus on the cardiovascular outcomes trials, rather than surrogate markers, to understand the impact of semaglutide and tirzepatide on reduction in cardiovascular risk.*** ***In the Summary and Comment section, our draft evidence report discusses the benefits and harms of each intervention compared with placebo. We also discuss the head-to-head comparisons, taking the data of harms and benefits in totality. We continue to have uncertainty about the magnitude of cardiovascular benefit of tirzepatide vs semaglutide, and this uncertainty is reflected in our summary and evidence rating.***
3.	Lilly recognizes that conduct of an NMA comparing the three interventions of interest and their impact on key outcomes would present challenges at this stage in the assessment. Nevertheless, we recommend that ICER explicitly recognize the limitations associated with the absence of NMA results and provide a clear and transparent rationale as to why, despite apparent feasibility, one was not pursued.	***Because the outcomes are so similar across trials and SURMOUNT-5 is a head-to-head trial, we did not feel that a network meta-analysis would have added substantial information to our analysis and conclusions. Furthermore, we did not have unadjusted weight loss data from the SURMOUNT trials (and we did from the STEP trials), making a network meta-analysis infeasible for this outcome.***
4.	Transitive assignment of clinical benefits from trials of injectable semaglutide to oral semaglutide is not supported without robust scientific rationale and/or direct comparative evidence supporting such assignment. Without explicit support and justification of its choices and assumptions, ICER's assignment of such benefit is methodologically unsound. Oral semaglutide has lower and more variable bioavailability, requires higher and more frequent dosing, and results in less predictable systemic exposure compared to injectable semaglutide, all of which can significantly influence clinical outcomes. Thus, ICER's transitive assignment of clinical benefits from injectable semaglutide to oral semaglutide in this review would be supported only with: (1) a mechanistic justification based on validated pharmacokinetic and pharmacodynamic data; and (2) direct comparative evidence demonstrating dose- and formulation-specific equivalence for the specific outcome(s) and specific population(s) under review. In its DER, ICER provides neither form	***The same molecule is producing weight loss in trials of injectable semaglutide and oral semaglutide. As such, we believe that extrapolating from data on injectable semaglutide, adjusted for the weight loss seen with oral semaglutide, is a reasonable choice.*** ***We note that since 2022 it has become clear that extrapolating from risk equations does not correctly predict the CV benefits of semaglutide.***

	of support to justify its decisions to: (1) model an increase in the mean %ΔBW from week 64 to week 104 for patients taking oral semaglutide based on the primary endpoint from a two-year trial of injectable semaglutide (i.e., STEP-5); or (2) use a hazard ratio (HR) derived from a prespecified secondary analysis from the cardiovascular outcomes trial (CVOT) of injectable semaglutide (i.e., SELECT) to model the direct impact of oral semaglutide on the risk of developing T2D. Lilly sees no supported rationale for ICER's choice to model additional weight loss beyond 64 weeks for oral semaglutide. Each semaglutide formulation has been studied independently in OM, and they are not considered interchangeable. While longer-term data (>1 year) on %ΔBW from baseline is available for injectable semaglutide, results from trials examining only that formulation (e.g., STEP-5, SELECT) should not be directly extrapolated to oral semaglutide. Absent justification and/or additional evidence, Lilly strongly recommends that ICER assume in its base case that the absolute difference in mean %ΔBW for oral semaglutide is the same at the year one and year two timepoints in its economic model. Further, in its 2022 OM report and the revised scoping document for this assessment, ICER notes that, when direct evidence is unavailable for an intervention, best practice is to estimate treatment effects indirectly using validated risk equations. Thus, Lilly recommends that ICER use exponential regression from Edelman et al. to estimate the indirect impact of oral semaglutide on T2D in its base case, consistent with the approach used in its prior OM assessment.	
5.	Additional direct and indirect evidence supporting tirzepatide's potential cardioprotective benefits and impact on reducing the risk of major adverse cardiovascular events (MACE) has recently been made available. This evidence could potentially influence results and should be incorporated into ICER's IER.	***We have reviewed the data released from SURPASS-CVOT and SURMOUNT-5 and have incorporated relevant data into our report and in the report supplement.*** ***Our inclusion of SURPASS-CVOT is limited due to the fact that there is no peer-reviewed publication from this trial. We prefer not to make final judgments about results until peer-reviewed publications are available. Additionally, SURPASS-CVOT compares tirzepatide to dulaglutide, and without more detailed data, we are unable to estimate tirzepatide's effect on MACE compared with placebo.*** ***As we discussed above, the cardiovascular data from the post-hoc analysis of SURMOUNT-5 is based on surrogate markers and we prefer to use direct data on cardiovascular outcomes from the existing cardiovascular outcomes trials.***
6.	ICER acknowledges in the foreword of the DER that new and emerging evidence may be released in close proximity to its publication and, as such, data that could potentially influence results may not yet have been incorporated or reflected in the preliminary findings. New evidence from SURPASS-CVOT and	***We reviewed the data that Lilly released from an indirect comparison of tirzepatide with placebo from the REWIND and SURPASS-CVOT trials. Unfortunately without knowing more details of the methodology used for matching and without access to either the individual-level patient data used to conduct this indirect comparison or a peer-***

	SURMOUNT-5 has recently been released and should be fully incorporated into ICER's IER. Detailed results from SURPASS-CVOT were presented on September 18, 2025, and they are now available for ICER's reference. As such, Lilly's pre-specified indirect comparison of matched patient-level data from the REWIND and SURPASS-CVOT should be used to inform ICER's base-case input for tirzepatide's direct CV effect in its OM CEM (i.e., HR of 0.72). Should ICER wish to retain a modeling scenario that leverages the SELECT HR as a "placeholder" value (i.e., HR of 0.80) for tirzepatide, this should be included only as a scenario analysis (SA), which may take a similar form to the SA from the DER that explored alternative direct diabetic impacts for oral and injectable semaglutide. A post-hoc analysis from SURMOUNT-5, which found that tirzepatide was associated with a significantly greater reduction in predicted 10-year cardiovascular disease (CVD) risk compared to semaglutide in adults with obesity and without T2D, was recently published. Details from that publication should be reflected in the applicable clinical benefit narratives in ICER's forthcoming IER.	***reviewed publication presenting these data, we do not feel we have sufficient confidence in the results to incorporate the hazard ratio of 0.72 into our model.*** ***With regard to the post-hoc analysis of SURMOUNT-5 looking at tirzepatide's effect on predicted 10-year CVD risk – again, we are most interested in actual cardiovascular outcomes rather than cardiovascular risk or surrogate outcomes. We have summarized secondary clinical outcomes from SURMOUNT-5 in the Supplement.***
7.	ICER's use of fixed annual thresholds and non-empirical uptake assumptions in its approach to budget impact modeling remains a significant concern. By applying a fixed annual budget impact threshold (i.e., $880 million in 2025) and relying on non-empirical uptake assumptions (i.e., 100% of the eligible population at the end of 5 years), ICER is limiting the utility and practical relevance of its analyses. Continued reliance on these methods risks biasing decision-making and could negatively affect patient access. Lilly strongly recommends that ICER reconsider its approach for this and future assessments. At a minimum, we would strongly encourage methodological modifications for reviews involving large eligible populations.	***ICER's analyses of potential budget impact are intended to provide an alert if the anticipated cost to the overall health care system has the potential to exceed specific growth targets due to high incremental costs and/or population size. While the calculations are based on 100% uptake over five years, ICER does not assume that this uptake will occur in the real world; expert opinion about desired use contributes to the decision about whether to issue an alert. That decision will be made for the Final Report after the Public Meeting.***
8.	ICER's decision to focus its clinical evaluation on "unadjusted" and "adjusted" mean %ΔBW from baseline, as opposed to the two reported estimands from the OASIS, STEP and SURMOUNT clinical trials, raises important methodological concerns. The choice to present and leverage observed means (i.e., *unadjusted* values) is highly unusual and may distort stakeholders' perceptions of average treatment effect for the primary endpoint from all of the key OM trials included in this assessment. ICER appears to be relying on digitized graphs and/or manufacturer-submitted data in its examination of the mean %ΔBW from baseline across key OM trials of injectable semaglutide and oral semaglutide. For injectable semaglutide, ICER presents observed means from each trial's full analysis set (FAS) population during the in-trial observation period at the 68 week visit (STEP-1, -3, -8, -10) and 104 week visit (STEP-5). For oral semaglutide, ICER appears to have followed the same approach to present mean %ΔBW at the 64 week visit (OASIS-4). For tirzepatide, ICER has noted that the observed means from the included SURMOUNT trials' FAS populations are not reported graphically and/or publicly available. As such, no *unadjusted* values of mean %ΔBW are presented in the DER for tirzepatide at the 72 week visit (SURMOUNT-1, -3, -5).	***We appreciate the opportunity to clarify our choice of outcomes reported in the Draft Evidence Report.*** ***We did not find any evidence that percentage change in body weight varies by baseline BMI so we felt that using unadjusted data was more appropriate, given the risk of small number variation with respect to the trial populations. Furthermore, treatment regimen estimands are not reflective of the intention-to-treat population and therefore may present biased estimates of effect. Thus, we felt that the unadjusted estimate of change in body was the most unbiased estimate of effect for weight loss.*** ***Each manufacturer was given the opportunity to submit data in response to ICER's data request, including data to be kept academic-in-confidence if necessary. We prioritized using data points submitted by manufacturers and relied on digitized data only when we were not provided the appropriate data by the manufacturer or the manufacturer directed us to digitize the graphs***

	Across all three interventions' key OM trial publications, treatment policy and treatment regimen estimands are used to quantify the average treatment effect in all randomized participants, regardless of adherence or intercurrent events, by imputing missing data using prespecified statistical models. In contrast, the observed means that are graphically reported in the above-referenced STEP and OASIS trials' publications reflect only those participants who had a %ΔBW measurement at a specific visit. As such, these means, while adherent to the intention-to-treat (ITT) principle, may overestimate or underestimate the average treatment effect when compared to the reported estimands that account for available data across each trial's full duration for the mean %ΔBW endpoint. In the case of semaglutide, it appears as though the observed means presented in the DER overestimate the average treatment effect when compared to the reported treatment policy estimands: on an absolute difference (AD) basis for mean %ΔBW, ICER's MA of STEP-1, -3, and -8 presents an *unadjusted* AD value of -13.1% and an *adjusted* AD value of -12.0% as estimates of injectable semaglutide's treatment effect at 68 weeks, while the *unadjusted* and *adjusted* AD values presented for oral semaglutide at 64 weeks from OASIS-4 are -11.9% and -11.4%, respectively. Lilly strongly recommends that ICER: (1) highlight the two estimands that each manufacturer leveraged in its key publications and regulatory filings for this assessment's evidence narratives and tables (i.e., the treatment policy estimand and trial product estimand for both semaglutide formulations, the treatment regimen estimand and efficacy estimand for tirzepatide); and (2) use the reported treatment policy and treatment regimen estimands in its MA for injectable semaglutide and, if pursued, its MA for tirzepatide. Use of *unadjusted* values creates unnecessary complexity and incongruencies, introducing a variable that may impact the comparability, transparency and relevance of ICER's assessment as observed means are not represented in other value assessments, systematic reviews and/or clinical guidelines.	***because they were not able to supply the requested data to ICER.***
9.	ICER's evidence ratings should reflect the totality of intervention-specific evidence across the outcomes of interest in this assessment's defined scope. Assignment of a "Superior" (A) rating when comparing oral semaglutide to LSM and a "Promising but Inconclusive" (P/I) rating when comparing tirzepatide to injectable semaglutide and oral semaglutide is inappropriate and runs counter to established precedent and ICER's own guidance on application of its Evidence Rating Matrix (ERM). ICER's evidence ratings are conditioned on two factors: (1) the magnitude of the difference between an intervention and its comparator in net health benefit (i.e., the balance between clinical benefits and risks and/or AEs); and (2) the level of certainty, based on the strength of evidence, of net health benefit. These factors are assessed within the framework of an assessment's "PICOTS" (Population(s), Intervention(s), Comparator(s), Time Horizon(s), Setting(s)). In assigning P/I ratings when comparing tirzepatide to injectable and oral semaglutide, ICER appears to have focused narrowly on	***On the issue of oral semaglutide, as discussed above, the same molecule is being administered in injectable and oral forms. We have data on oral semaglutide in patients with DM and we have data looking at relative weight loss between oral and injectable semaglutide. We feel that assuming a CV benefit at the weight loss dose is appropriate, however even if the CV effect were neutral, oral semaglutide would still appropriately receive an "A" rating compared with lifestyle management based on its weight loss benefits. Only if it had harms, particularly CV harms, would this rating be inappropriate; we feel this is extremely unlikely.*** ***With regard to the relative ratings of tirzepatide and semaglutide, it is necessary to recognize that the CV risk reductions seen with injectable semaglutide are large and extremely important in a population that includes patients with established CV disease as in this report. Relatively small differences in CV benefits would have major***

	"CV effects" (i.e., impact on the rate of CV events, including nonfatal stroke, nonfatal myocardial infarction, non-fatal stroke and CV death) and, more specifically, the lack of H2H evidence from a CVOT comparing tirzepatide to injectable and oral semaglutide. The population of focus for this review was "adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition, who are actively seeking medical management for weight loss; adults with established diabetes are excluded." The PICOTS-defined outcomes of interest extend far beyond direct CV effect and, based on ICER's own guidance and precedent from prior reviews (e.g., ICER assigned a C+ rating to tirzepatide versus injectable semaglutide in its 2022 T2D review; the lack of H2H evidence on direct CV effects was acknowledged, but the rating ultimately reflected the full PICOTS). Lilly strongly recommends that ICER revisit its P/I ratings in the IER. The evidence base for tirzepatide is robust and adequately powered, with indirect evidence from publicly available meta-analyses and direct evidence from SURMOUNT-5 showing statistically significant and clinically meaningful superiority to semaglutide in reducing body weight and waist circumference; a recently published post hoc analysis also found that tirzepatide was associated with a greater predicted 10-year CVD risk reduction compared with semaglutide. In consideration of the full PICOTS and tirzepatide's body of evidence in OM, ICER's ERM would suggest a minimum "Incremental or Better" rating (B+) for tirzepatide versus both semaglutide formulations based on point estimate of a small-to-substantial net health benefit while recognizing uncertainty on direct CV effects. To reflect residual uncertainty on CV effects, ICER could consider two distinct ratings: (1) an evidence rating comparing tirzepatide to both semaglutide formulations in the population of focus for this assessment, with consideration of the full PICOTS; and (2) an evidence rating comparing tirzepatide to both semaglutide formulations in a subpopulation of adults with obesity or overweight with established, or at increased risk of developing, CVD. In that subpopulation, tirzepatide would likely command a minimum rating of C++ against semaglutide based on: (1) the factors outlined in our above comments regarding new evidence supporting tirzepatide's potential cardioprotective benefits and CV outcomes and; (2) the fact that there is no evidence to suggest a "small (but nonzero) likelihood of a negative net health benefit" for tirzepatide versus semaglutide, which is required for a P/I rating. As discussed in Lilly's comments on unsupported equivalence assumptions, it appears as though ICER is deriving some degree of certainty regarding oral semaglutide's clinical benefit from injectable semaglutide's evidence base. Lilly recognizes that a single trial can be enough for a "A" rating, but only when that trial is exceptionally reliable, directly relevant, precise, and supported by other lines of evidence. More commonly, an intervention with only a single scope-germane trial would be deserving of a more conservating rating. Given that ICER explicitly separates magnitude from certainty, ICER's ERM would suggest a B+ rating is most appropriate given a point estimate of moderate-to-large net health benefit, but only moderate, not high, certainty due to the degree of evidence evaluated in the DER (i.e., OASIS-4 only). ICER should justify its rating choice more sufficiently in the IER.	***clinical implications for which patients should receive which therapy for obesity. The indirectness from comparing drugs studied in different trials against different comparators necessarily leaves uncertainty about whether one therapy might have greater CV benefits than another. Tirzepatide produces greater weight loss than semaglutide and if it has superior (or even comparable) CV outcomes it will be the superior drug. The manufacturer of tirzepatide might consider running a head-to-head trial to answer a question where there is uncertainty – which therapy has better CV risk reduction – rather than the trial they chose to run that "answered" a question about weight reduction where the answer was already known.***

10.	ICER should reconsider its choice of model inputs to estimate the AD in %ΔBW by year one and year two. The current approach is inconsistent and introduces bias in this review. As conferred in Lilly's comments regarding ICER's evidence synthesis methods, we strongly recommend that ICER conduct MAs for both injectable semaglutide and tirzepatide; these should be leveraged to derive several key clinical inputs for ICER's CEM (i.e., AD in %ΔBW, ACD, severe GI AEs). We also suggested in our comments regarding weight loss outcomes that ICER use reported treatment policy and treatment regimen estimands, as opposed to *unadjusted* means, in any MAs. Finally, in Lilly's comments regarding unsupported equivalence assumptions we urged ICER not to assign benefit, unless supported and justified in the IER, to oral semaglutide based exclusively on evidence from trials of injectable semaglutide. With those factors in mind, Lilly believes that a level playing field in ICER's economic analyses is largely dependent on whether an MA is conducted for tirzepatide with SURMOUNT-1 and -3. If ICER chooses not to pursue an MA for tirzepatide, the minimum acceptable path forward is for ICER to: (1) reflect the correct value from the graph that they chose to digitize to estimate the AD %ΔBW by year one (i.e., at 72 weeks); and (2) digitize that same graph to either the 98- or 111-week timepoints to approximate the AD %ΔBW for tirzepatide by year two. If ICER chooses to conduct the recommended MA and use its outputs in the CEM, it would necessitate that: (1) the reported treatment policy and treatment regimen estimands be used for all interventions, due to the fact that observed means from the SURMOUNT-1 and -3 FAS populations during the in-trial observation period at the 72-week visit are not available; and (2) ICER estimate the AD %ΔBW for tirzepatide by year two, with one potential option being extrapolation of available datapoints from the three-year phase of SURMOUNT-1 at weeks 98 or 111 (see Table 1 in the Appendix for additional details regarding these options).	***Please see the responses above.*** ***We felt that it was not appropriate to conduct a meta-analysis of SURMOUNT-1 and 3 due to differences in trial design, specifically the requirement for 5% loss of body weight before randomization to tirzepatide or placebo.*** ***~~Additionally, we have edited the report to include the percent change in body weight at years 1 and 2 provided to us by the manufacturer after the publication of the draft evidence report. The new data provided by the manufacturer did not change our conclusion of clinical effectiveness or the model results.~~*** ***<u>Addendum 11/3/2025:</u>*** ***It has come to our attention that the response above about percent change in body weight at years 1 and 2 is incorrect. The estimates for change in body weight for tirzepatide in the current Evidence Report reflect the result of ICER's digitization of data. We have since been provided updated data from the manufacturer for these time points and will be incorporating the new data into the Final Evidence Report.***
11.	ICER's decision to focus its CEA on LSM-only comparisons does not meet the real-world needs of stakeholders, many of whom are assessing choice and making value-based judgments between OMMs, not between OMMs and LSM. The aim of ICER's evidence reports is to inform population-based medical policy and pricing decisions; ignoring OMM-to-OMM cost-effectiveness (CE) comparisons represents a missed opportunity. Lilly recommends that ICER revisit its decision not to include incremental CE ratios comparing: (1) tirzepatide to injectable semaglutide; (2) tirzepatide to oral semaglutide; and (3) injectable semaglutide to oral semaglutide. We would encourage ICER to carry through the approach from its 2022 OM assessment whereby both OMM-to-LSM and OMM-to-OMM incremental CE ratios were included. Should ICER choose to exclude these from its base-case analysis, they should be included in the IER supplement.	***As noted, CV effects are central to any comparison of semaglutide and tirzepatide. Both drugs are cost-effective compared to LSM. Judging the cost-effectiveness of the therapies against each other with any precision would require knowledge of relative CV effects and we do not know this. While point estimates would provide a result, this result would be uncertain across a range of possible CV outcomes.***

12.	ICER's decision to exclude "Drug X" economic analyses from this assessment reflects a positive development. These types of analyses sow confusion, decrease transparency, and are of little utility to stakeholders. Lilly applauds ICER's decision not to conduct any "Drug X" scenario analyses in its current OM assessment. As conveyed in filed comments pertaining to this assessment and to ICER's 2022 OM assessment, we believe that modeling economic outcomes for inline or pipeline OMMs using inputs from ongoing or recently completed trials without allowing for end-to-end engagement from manufacturers of those products is highly problematic. Lilly encourages ICER to carry through this decision into future assessments.	***We recognize that Lilly was unhappy with ICER's 2022 review that concluded that a drug with the weight loss effects of tirzepatide and the CV benefits of semaglutide would likely be cost-effective. We felt this provided important information to stakeholders at the time and would likely be welcomed by the manufacturer of tirzepatide. On this latter point, we were incorrect.***
Novo Nordisk		
1.	Initially, ICER used data from both SELECT and SURPASS-CVOT clinical trials to comparatively assess major adverse cardiovascular event (MACE) prevention for injectable semaglutide and tirzepatide, respectively. In contrast, ICER subsequently used the SELECT trial data only in the cost-effectiveness analysis to evaluate the economic benefit associated with MACE prevention for both injectable semaglutide and tirzepatide. NNI would like to emphasize, that the SELECT trial was conducted in patients with overweight/obesity and established atherosclerotic cardiovascular disease (ASCVD), where a 20% risk reduction for secondary MACE prevention was specifically observed with injectable semaglutide and standard of care compared with placebo and standard of care. NNI strongly disagrees with the SELECT risk estimates being arbitrarily applied to tirzepatide for the cost-effectiveness portion of this report, particularly in the absence of evidence that indicates a cardioprotective benefit for tirzepatide among those living with overweight/obesity and established ASCVD, without T2DM. NNI would like to further emphasize that employing data from the SURPASS-CVOT trial for tirzepatide may not be suitable for comparative effectiveness in this situation either, given that this trial was conducted among individuals diagnosed with T2DM and did not include a direct comparison with a placebo.	***We agree that the recently released SURPASS-CVOT trial results do not necessarily reflect the cardiovascular risk reduction in the population of interest for this review, as it was conducted in a population with Type 2 diabetes. We have acknowledged this uncertainty in our review and in our evidence rating.*** ***However, given that tirzepatide was shown to reduce major adverse cardiovascular events in the Type 2 diabetes population, we feel that it is reasonable to extrapolate some level of cardiovascular benefit to the obesity without diabetes population given tirzepatide's efficacy in decreasing body weight and improving cardiovascular risk factors. Although the SURPASS-CVOT trial was conducted with an active comparator, the manufacturer released an indirect comparison using data from the REWIND trial showing a 28% reduction in cardiovascular events compared with a putative placebo (HR 0.72). Given that we are currently unable to evaluate the validity of the indirect comparison estimate and the differences in population from our model population, we did not feel that it was appropriate to use the 0.72 hazard ratio in the model. In the absence of direct data, we chose the less favorable (to tirzepatide) assumption that the cardiovascular benefit is equivalent to that seen in the SELECT study.*** ***As we noted above, relative CV effects are extremely important in comparing tirzepatide and semaglutide. If a manufacturer feels that their drug provides greater CV benefit, it would be extremely helpful to clinicians and patients if the manufacturer performed a randomized head-to-head trial to answer this question definitively.***

2.	Additionally, for oral semaglutide, ICER used data from the SOUL trial to model MACE prevention, where a 14% risk reduction was observed. NNI would like further clarification on ICER's justification for this, as the SOUL trial was conducted in patients with high-risk T2DM and a lower dose of oral semaglutide was used compared to the dose assessed in the Draft Evidence Report (3 mg starting dose up to 14 mg maintenance dose).	***While the SOUL trial population and dosage differ from our model, no available data perfectly align with our model specifications. We therefore evaluated multiple estimation approaches, and selected the most favorable option (lowest hazard ratio) to minimize potential bias against oral semaglutide due to data limitations. The approaches considered were: (a) estimates from the SOUL trial alone, (b) a meta-analysis of the SOUL and PIONEER 6 trials, (c) SELECT trial estimates adjusted for weight loss differences between injectable and oral semaglutide, and (d) Framingham risk calculations. The first two approaches yielded identical base-case estimates for direct CVD impact (HR=0.86), while the latter two produced less favorable results. If the manufacturer of oral semaglutide would prefer we use one of the less favorable HRs for CV benefits, we will make this change for the Final Report.***
3.	Since ICER published the Draft Evidence Report, data has been presented from the STEER real-world evidence study that compared the potential benefit of semaglutide and tirzepatide for MACE risk reduction in patients with established ASCVD. Compared with tirzepatide, injectable semaglutide demonstrated hazard ratios (HRs) of 0.71 (95% CI, 0.50 to 0.99) for prevention of revised 3-point MACE and 0.78 (95% CI, 0.62 to 0.99) for prevention of revised 5-point MACE. This difference was even more pronounced when limiting the analyses to patients who remained on treatment, with HRs of 0.43 (95% CI, 0.24 to 0.78) and 0.57 (95% CI, 0.39 to 0.83) for revised 3- and 5-point MACE, respectively. Although not specific to a weight management population, further evidence that the cardioprotective effects of semaglutide are perhaps molecule-specific does come from data recently presented from the real-world REACH study that compared semaglutide (Ozempic®) with dulaglutide, another glucagon-like peptide-1 receptor agonist (GLP-1 RA), in Medicare recipients with T2DM and CV disease. A 23% reduction in the risk of heart attack, stroke and death was observed with semaglutide versus dulaglutide. However, in the SURPASS-CVOT trial, tirzepatide (Mounjaro®) was associated with a non-inferior, non-statistically significant 8% risk reduction of heart attack, stroke, or CV death when similarly compared with dulaglutide in individuals with T2DM and established CV disease. **Recommendation:** We urge ICER to carefully consider the existing as well as recently emerging evidence suggesting that the cardioprotective benefits of semaglutide are, to the best of our knowledge, molecule-specific and not solely attributable to weight loss. We also request that ICER reconsider using data from the	***We have included the STEER study in our review of real-world evidence observational studies in our revised report.*** ***However, real-world evidence observational studies, by nature, are prone to selection bias and confounding. As acknowledged in the presentation at the European Society of Cardiology Congress, administrative claims data is prone to coding inaccuracies and there is a potential for unmeasured confounders. Furthermore, the data provided do not indicate what doses of semaglutide and tirzepatide were included in the study, and mean follow-up time was just over 8 months, which is a short-time frame for the development of cardiovascular events. Additionally, the Kaplan-Meier curves start to diverge from each other almost immediately for the 5-point MACE and by 3 months for 3-point MACE, which given randomized trial results, seems less likely. Finally, a recent real-world evidence study using observational data from the TriNetX database comparing tirzepatide to other GLP-1 RA, including semaglutide, found that treatment with tirzepatide was associated with 40% reduction in the composite outcome of acute myocardial infarction, ischemic stroke, and all-cause mortality (HR: 0.60, 95% CI: 0.43-0.84, P < 0.001) (Dani et al, JACC: Advances 2025;4(5)). Thus, we continue to be cautious about using RWE studies to make conclusions about a drug's effect.***

	SOUL trial to assess the efficacy of oral semaglutide (25 mg) in the patient population being assessed.	
4.	In the cost-effectiveness analysis, the weight loss associated with each treatment is determined based on the outcomes observed in trials administering the highest dose of that particular treatment. This approach is predicated on the understanding that clinical practice generally aims for the maximum effective dose, unless constrained by tolerability considerations, or the dose that achieves meaningful weight loss if it is lower than the maximum. NNI would like to stress that both semaglutide and tirzepatide offer multiple dosing options, as outlined in their product labels and reflected in clinical practice. There is published real-world evidence indicating that the real-world usage of the maximum 15 mg dose of tirzepatide is substantially lower than the other maintenance doses. NNI recently published the SHAPE real-world study, and observed that in adults with overweight or obesity and no T2DM, only 25.9% reached the 15 mg dose of tirzepatide at 1 year follow-up. In contrast, 83.5% reached the 2.4 mg dose of semaglutide at 1 year follow-up. This is corroborated by two recent retrospective studies of individuals with obesity or overweight and ≥1 obesity-related complication without T2DM. Both reported that the most common dose of tirzepatide used was 5 mg. In one study, 33.0% received the 5 mg dose even at the sixth prescription fill whereas only 4.6% actually received the 15 mg dose. In the second study, 37.1% received the 5 mg dose at the fifth prescription fill and only 1.8% received the 15 mg dose.	***We appreciate the perspective on real-world dose utilization. However, we still believe that the weight loss observed with the highest dose is an appropriate approach for several reasons.*** ***First, we believe that this approach better reflects clinical treatment goals where providers titrate to the highest tolerated dose to achieve maximum benefit. Modeling maximum doses ensures we reflect each treatment's full therapeutic potential and provides an unbiased comparison.*** ***Second, we have methodological concerns about using these real-world data to inform our base case analysis. Specifically, although fewer patients reached the maximum dose of tirzepatide compared to those reaching 2.4 mg semaglutide at one year, tirzepatide still demonstrated superior weight loss outcomes in this study, suggesting that tirzepatide's therapeutic advantages persist even at lower dosing. And, of course, patients may be stopping dose increases because they reach rate of weight loss goals at a lower weight – it is difficult to know exactly how to integrate such an effect into a model.*** ***Additionally, this study was descriptive and was not adjusted to address any selection bias or confounding. Therefore, the study findings may be confounded by several factors including patient characteristics, provider comfort, insurance coverage, supply issues, time on market, etc.***
5.	NNI would also like to highlight that since ICER published the Draft Evidence Report, clinical data for the 7.2 mg dose of semaglutide has been published, a higher dose than the 2.4 mg injectable dose considered in ICER's cost-effectiveness analysis. The STEP UP trial demonstrated that mean change in body weight with semaglutide 7.2 mg plus lifestyle intervention was -18.7% compared with -3.9% with lifestyle intervention alone, a difference of -14.8% (95% CI, -16.2% to -13.4%). **Recommendation:** NNI believes that ICER should incorporate all indicated maintenance doses of tirzepatide in its analysis to prevent the potential for misinterpretation regarding its overall efficacy and cost-effectiveness in real-world settings. Additionally, NNI recommends that ICER explore the implications of utilizing efficacy data from the 7.2 mg dose of semaglutide in a scenario analysis, given that this data is publicly accessible and that ICER has assessed the maximum dosage of tirzepatide.	***This report is focused on drugs and doses that we know to be approved by FDA or under consideration for approval by FDA.*** ***ICER's Interactive Modeler will be able to take inputs on weight loss, CV benefits, and other outcomes as they are developed for new dosing regimens of existing drugs and new drugs.***
6.	In addition to injectable semaglutide and tirzepatide, ICER also included oral semaglutide in its assessment of clinical and cost-effectiveness. At the time of this ICER review, NNI have yet to make any formal decisions regarding oral semaglutide, including its place in therapy, access and coverage, as well as pricing strategy. In the Draft Evidence Report, the annual net price of oral semaglutide was	***ICER routinely reviews drugs that have not yet received FDA approval and tries to time its reviews to be available around the time of expected FDA approval. Reviewing oral semaglutide for weight loss is a typical decision by ICER.***

	assumed to be equivalent to injectable semaglutide and data that was presented at Obesity Week in late 2024 was used to model the efficacy of oral semaglutide. Since ICER published the Draft Evidence Report, clinical data has been published in peer reviewed journals not only for oral semaglutide, but notably for another pipeline oral GLP-1 RA, orforglipron. It is important to consider that oral semaglutide and orforglipron convey the same status in that they are both pipeline GLP-1 RA monotherapy products administered orally, with published clinical data, yet the decision was made by ICER to omit orforglipron from this assessment. The recent OASIS 4 trial data demonstrated that oral semaglutide 25 mg alongside lifestyle intervention was associated with a mean change in body weight of -13.6%, relative to -2.2% for placebo plus lifestyle intervention, a difference of -11.4% (95% CI, -13.9% to -9.0%).[17] In ATTAIN-1, the highest dose of orforglipron (36 mg) alongside healthy diet and physical activity was associated with a mean change in body weight of -11.2%, relative to -2.1% with placebo plus healthy diet and physical activity, a difference of -9.1% (95% CI, -10.1% to -8.1%). **Recommendation:** As oral semaglutide is a pipeline product that has yet to receive Food and Drug Administration (FDA) approval, NNI continues to recommend that ICER should refrain from including oral semaglutide in its review. However, NNI firmly believes that since oral semaglutide was included, other GLP-1 RA products, namely orforglipron, the next oral GLP-1 RA closest to launch following oral semaglutide, should now be evaluated as well.	***ICER held off on re-reviewing therapies for weight loss until CV data on tirzepatide (in DM) were expected to become available because this is such an important issue in assessing these therapies. Furthermore, the review focused on molecules where we felt CV benefits could be estimated. As such, we do not feel we can appropriately assess orforglipron at this time.*** ***As noted, using ICER's Interactive Modeler, stakeholders can put in assumed CV effects of a new drug and assess estimated cost-effectiveness if they so choose. We would caution that for new molecules and new mechanisms of action, any such results are likely to have substantial uncertainty.***
7.	In the cost-effectiveness analysis, ICER included liver cirrhosis as one of the obesity-related outcomes that were modeled. However, earlier stages of liver fibrosis were not considered. Semaglutide recently received an indication based on the ESSENCE clinical trial for treatment of noncirrhotic MASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) in adults,[11] which can ultimately lead to cirrhosis. Indeed, several studies have demonstrated that MASH incurs a high cost burden in the US; therefore, a treatment that promotes steatohepatitis resolution and reduces fibrosis progression has the potential to drive economic value by reducing healthcare costs and improving health outcomes. **Recommendation:** NNI highly encourages ICER to reconsider MASH in their evaluation, as its exclusion will likely lead to an underestimation of the clinical and economic benefits that semaglutide affords.	***While earlier stages of liver fibrosis may be an indication for treatment, and ICER's modeling certainly includes patients in these earlier stages, F2 and F3 fibrosis are risk factors for progression to clinically apparent disease and generally not clinically apparent themselves. ICER has reviewed therapies for MASH on a number of occasions and we recognize that there is some controversy about whether MASH may have some associated fatigue, but a trial of a GLP-1 would need to demonstrate benefits on fatigue independent of weight loss for this to be relevant to our modeling.***
8.	In the budget impact analysis, ICER assumed all patients who met the indications for weight management in the FDA labels would take semaglutide (injectable and oral) or tirzepatide over 5 years. This includes all individuals in the US with obesity or overweight (plus one weight-related comorbidity), without T2DM. NNI considers this to be an overestimation of the true number of people in the real world who will take these treatments in the next 5 years. Several considerations are likely to impact how patients will access or pay for these drugs and include (but not limited to): (1) indications for use other than weight management (e.g., MACE risk reduction, MASH etc.);[11] (2) potential supply constraints that may limit utilization over time; (3) barriers to access for those who are	***ICER's analyses of potential budget impact are intended to provide an alert if the anticipated cost to the overall health care system has the potential to exceed specific growth targets due to high incremental costs and/or population size. While the calculations are based on 100% uptake over five years, ICER does not assume that this uptake will occur in the real world; expert opinion about desired use contributes to the decision about whether to issue an affordability and access alert. ICER's access and affordability alert represents a potential trigger for policy mechanisms to improve***

	commercially insured, which at present, reflects about 55% of the eligible population. NNI reiterates that the weight management drugs assessed by ICER were highly cost-effective, representing excellent value for money. However, ICER's budget impact analysis found that these drugs are unaffordable due to an analysis that significantly favors treatments that are targeting smaller populations and is biased against people living with prevalent conditions. NNI notes that to meet ICER's budget impact threshold of $880 million, weight management drugs would only be affordable if they cost less than $10 annually ($880 million / 92 million lives). Going forward, NNI recommends that ICER should consider more equitable methods of assessing affordability based on the prevalence and severity of this condition. Highly cost-effective therapies, like semaglutide, risk being excluded from coverage despite the high unmet need among people living with obesity. This is solely due to the large burden that obesity imposes in the US, while treatments that are not cost-effective but affordable, for example, may end up being covered, simply because they target a smaller population size. This runs contrary to ICER's purpose of seeking to provide evidence-based assessments on the economic value of medications. In short, NNI believes that ICER's budget impact analysis could lead to restricted access for patients with high prevalence conditions such as obesity and that it appears to justify denying valuable treatment options solely due to patients having a common disease. Indeed, a bias against common diseases could set a precedent that stifles development of innovative medicines for highly prevalent chronic conditions.	***affordability, such as changes to pricing, payment, or patient eligibility. That decision will be made for the Final Report after the Public Meeting.***

#	Comment	ICER Response
Patient Organizations		
Global Liver Institute		
1.	GLI appreciates that ICER included liver-related outcomes in its model but believes these outcomes were too narrowly defined. ICER's assessment incorporates cirrhosis as a patient-important outcome but only includes MASH/NASH as a surrogate endpoint. It is well known in the literature that MASH/NASH impacts clinical outcomes of patients with obesity. Addressing MASH/NASH by promoting steatohepatitis resolution and reducing fibrosis progression in patients before it advances to cirrhosis will both lead to better outcomes for patients and less cost to the system. FDA has approved semaglutide for MASH, and the American Association for the Study of Liver Disease (AASLD) guidelines recommend semaglutide for treatment of MASH, also recognizing its cardiovascular benefits for patients with obesity/overweight. Patients with non-cirrhotic NASH with subsequent progression to a more severe disease state are estimated to have 1.6 times higher follow-up spending than non-progressors, indicating that treatment preventing progression has a significant impact on financial burden for patients. In order to better capture the benefits of treatments for obesity, GLI would encourage ICER to account for the benefits of treating MASH in its model.	***While earlier stages of liver fibrosis may be an indication for treatment, and ICER's modeling certainly includes patients in these earlier stages, F2 and F3 fibrosis are risk factors for progression to clinically apparent disease and generally not clinically apparent themselves. ICER has reviewed therapies for MASH on a number of occasions and we recognize that there is some controversy about whether MASH may have some associated fatigue, but a trial of a GLP-1 would need to demonstrate benefits on fatigue independent of weight loss for this to be relevant to our modeling.***
2.	Patients will respond differently to the same treatments. They have different characteristics, biology, and treatment goals that will mean a treatment that is optimal for one patient will not be optimal for a different patient. In reviewing the ICER draft report, we are very concerned that it does not clarify how the two treatments assessed may differ in providing value to patients. Too often, health economics models assume that each patient is the average and that treatments are one-size-fits-all. In our experience with patients using medications indicated for obesity and related conditions, they will report that one treatment provides them with a desired outcome with fewer side effects compared to others. We are very concerned that ICER's final report may be used by payers to force patients into a treatment protocol that does not optimize their outcomes.	***While we acknowledge that individual patients may respond differently to the same treatment, this model is designed to inform population-level pricing and coverage decisions, not individual treatment choices.***
3.	ICER correctly finds treatments for obesity to be beneficial to patients and cost-effective. That being said, ICER uses its artificial budget threshold to assume that only 1% of eligible patients could be treated. ICER's use of a budget threshold that inherently devalues treatments for large populations is problematic. The United States is not like foreign countries operating in a single payer market that embraces health care rationing. It is inappropriate for ICER to artificially impose a budget threshold that supports an unnecessary — and un-American — health care rationing scheme that payers may use to limit patient access to needed treatments.	***ICER's analyses of potential budget impact are intended to provide an alert if the anticipated cost to the overall health care system has the potential to exceed specific growth targets due to high incremental costs and/or population size.***

	ICER's use of finite fiscal thresholds in assessing budget impact biases its assessments against any intervention for a common condition, regardless of the severity of the condition or the cost-effectiveness of the intervention. It also ignores the compelling studies and real-world experiences indicating that access to obesity medications reduce other health system costs. It would be more efficient to tackle population health problems by empowering solutions that work for large populations — not to penalize health care with expansive potential patient populations that would benefit. The precedent for this direction would be contrary to American efforts to prevent and reduce chronic disease. Therefore, we have significant concerns that ICER's final report will be used by payers to justify reduced access to care through restrictive coverage decisions.	
4.	Multiple studies have shown that cost-effectiveness models relying on the quality-adjusted life year (QALY) discriminate against patients with chronic conditions and people with disabilities. There is widespread recognition that the use of the QALY is discriminatory. The QALY has historically been opposed by the American public and policy makers. The National Council on Disability (NCD), an independent federal agency, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments.	***Thank you for your comments. Here are some materials explaining ICER's use of cost-effectiveness measures including the QALY and the evLY:*** • ***A patient-focused explanation of these measures.*** • ***A peer-reviewed academic explanation of these measures.*** ***ICER's reports are consistent with federal guidelines that detail how to use these measures while protecting those with disabilities.***
MAPRx		
1.	While we commend the focus of this ICER report, we must concurrently express our disappointment that the Medicare Part D program remains an outlier among payers. Medicare Part D's current statutory coverage exclusion of AOMs prevents a significant, vulnerable population—older Americans and those with disabilities—from accessing necessary, Food and Drug Administration-approved, and clinically effective therapies. This exclusion stands in contrast to the coverage policies of other major federal health programs and many state Medicaid plans, which increasingly recognize the critical role AOMs play in improving health outcomes, reducing disease progression, and promoting health equity. Our white paper, "Clinical Evidence Driving Patient Access in Medicare Part D" summarized the health threat posed by the prevalence of obesity and the need for Medicare to update its coverage policy. We sincerely hope that ICER's final evidence report will robustly highlight the compelling clinical data and economic value of these treatments. The findings from this assessment are paramount, as they can serve as crucial evidence to motivate policymakers, including the Centers for Medicare & Medicaid Services (CMS) and Congress, to rectify the long-overdue exclusion of AOMs from Medicare Part D. It is our belief that by thoroughly evaluating the full spectrum of patient and population value, including the long-term impact on comorbidities and associated healthcare cost, ICER can provide the necessary clarity to ensure more equitable	***Thank you for your input.***

	coverage for all, particularly for Medicare Part D beneficiaries who are currently denied access to this essential care.	
Obesity Action Coalition		
1.	Despite these benefits, access to the medications remains the greatest challenge. Many patients are excluded from treatment due to lack of insurance coverage, restrictive exclusion policies or prohibitive out-of-pocket costs. These barriers to obesity care perpetuate health inequities, particularly for women, people of color, and lower-income communities who are disproportionately affected by obesity. I urge ICER to underscore the importance of fair coverage and affordability in its final report. Recognizing obesity as a chronic disease and ensuring equitable access to these therapies will not only improve individual lives but also reduce long-term health system costs by preventing downstream medical complications.	***Thank you for your input.***
2.	I agree with ICER's finding of treatments for obesity to be both beneficial to patients and cost-effective. However, there are limitations with the affordability assessment method that concluded only 1% of eligible patients could be treated. This framework is not ideal for therapies taken by large patient populations. The approach ignores evidence that broader access to obesity medications reduces downstream health system costs. I fear that it could penalize patients from getting access to the innovations, where this precedent could be used by payers to justify exclusionary coverage policies. More context and clarity is needed.	***ICERs results around affordability are not intended to limit access but to warn the healthcare system when budgetary strains are likely to occur with a new therapy. We can see these strains with GLP-1 therapies as we warned about in a prior review. When a highly beneficial therapy (see the "A" ratings for semaglutide and tirzepatide) is causing budget problems, it is important for all stakeholders to consider ways to maximize access within a system that always has constrained resources.***
3.	I applaud ICER for including patient perspectives as a central part of this assessment process. Including lived experiences of people with obesity helps ensure that evaluations reflect not only clinical and economic outcomes, but also the real-world impact on daily life, dignity, and equity. I encourage ICER to continue prioritizing patient voices and provide context for the affordability assessment as it finalizes this report and formulates recommendations that will shape access to these safe and effective innovations.	***Thank you for your input.***

#	Comment	ICER Response
Other		
Capital District Physicians' Health Plan, Inc. (CDPHP)		
1.	I am submitting a comment regarding the estimated net prices for injectable semaglutide and injectable tirzepatide for the DRAFT Evidence Report "Semaglutide and Tirzepatide for Obesity: Effectiveness and Value" published September 9, 2025. In the executive summary it is noted that estimated net prices from SSR Health were used in the cost-effectiveness analysis. Specifically, $6,830 for injectable semaglutide and $7,973 for injectable tirzepatide. As a pharmacist who is employed in a regional, not for profit, payer organization, I can attest that these net prices are not available to us. I have read other information and blogs from others which would suggest that this is a similar theme across payers. If a payer is getting rebates for these drugs, the net prices are still substantially higher than those apparently used in the cost-effectiveness analyses. If a payer is not getting rebates, the prices used are up to two-fold higher than those figures. Without understanding how SSR Health obtains commercial rebate data to provide estimated net pricing, one concern is that 340B prices, health system GPO prices, manufacturer discounts to wholesalers, and/or Medicaid Drug Rebates could be included which would markedly dilute the overall net prices and such prices are not available to commercial payers. Importantly, the diabetic versions of semaglutide and tirzepatide have lower WACs and are more heavily rebated that the obesity management versions. Is it possible that the net prices of the diabetes agents were conflated with the obesity versions? Injectable semaglutide and tirzepatide are both administered weekly and both are dispensed as a pack of four pens equaling a 28 day supply. For a full year supply, that would require 13 packs of four pens. It is a common oversight to multiply a per prescription drug price by 12 when it should be 13 to correctly calculate the annual expense when the drug is a 28 day supply. It is important that the costs used in the analyses reflect real world circumstances and the net prices (particularly for semaglutide) warrant adjustment in the final evidence report.	***Thank you for your comment regarding our net price estimates. We appreciate your perspective as a practicing pharmacist and understand that net prices can vary substantially across payers due to a range of factors. The SSR Health estimates used in our analysis represent national average net prices across the entire US market—including not only commercial payers, but also other channels such as Medicare Part D, Medicaid, 340B-eligible entities, and self-pay segments. These values therefore reflect a population-weighted average across all payer types. While we recognize that some payers may experience higher or lower net prices than our estimates, our approach is intended to capture costs at the US market level, rather than from any single payer's perspective.*** ***For this analysis, we applied obesity-specific net prices (Wegovy/Zepbound) instead of adjusting costs from the diabetes formulations of semaglutide or tirzepatide. We derived annual net prices directly from SSR Health, rather than estimating them by multiplying package prices by the number of packs used per year.*** ***We would also like to note that payer-specific assumptions, including drug price inputs, can be explored in the ICER Analytics platform which allows users to customize cost-effectiveness results based on their own estimates.***
Dhruv S. Kazi, MD, MSc, MS		
1.	I understand that your rationale for using a baseline BMI of 37 is that this is who is currently using the drug. This would be a break from the usual	***Thanks for the comment. We don't typically encounter***

	approach to CEAs – I couldn't have modeled PCSK9is by restricting the base case to a substantially higher risk population than those eligible for the drug. Have you used this approach in other models? A quick analysis of NHANES suggests a lower BMI in the treatment-eligible population (In the 2017-2020 and 2021-2023 combined cycles, there are 106.8 million people who meet eligibility criteria for weight management and do NOT have DMI; the mean BMI for these people is 33.34 kg/m2). Cost-effectiveness among current users is a different question, but given rapidly increasing use, not a super interesting one. I still think the starting BMI should be 33; 37 should be a secondary analysis.	***situations where a drug is already being used by tens of millions of Americans at the time of a review. Therefore, we typically define the modeled population based on the clinical trial population or, preferably, the eligible population. In this case, however, we have observational data showing who among the eligible population are really taking these medications and that seems like a fair basis for the modeled population. While, in the future, that population may change, the ways it may change and the therapies that may be used are currently unpredictable. For these reasons, we feel that modeling the entire eligible population would not provide a useful estimate for decision makers at this time.***
2.	But if you assume the question of interest is among current users, then the effectiveness estimate must also be among current users. In my opinion, the best real-world estimate of weight-loss comes from the Truveta analysis (there may be others): https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2821080. In that model, weight loss is approx. 8.3% for semaglutide and 15.3% for tirzepatide at 12 mo. So the weighted change would be ~11-12%. Using baseline BMI from the real-world and %BMI change from the trial (17%) feels like stacking the cards in favor of GLP1s. My base case would be treatment-eligible (BMI 33) and real-world reduction in weight.	***Although this study included current users, we believe its use in the model is problematic. First, as a real-world observational study, it is inherently subject to uncertainty and bias arising from unmeasured confounding, missing data, measurement error, etc. In general, random error in RWE tends to bias results toward the null. Therefore, when available, we consider estimates derived from randomized clinical trials to be more reliable and appropriate for use in the model. Moreover, the mean BMI of current users from our observational data was very similar to that in the RCTs, and thus we think the estimates from the trials are the best estimate of effectiveness in the modeled population.*** ***In addition, we do not agree that an estimate of approximately 11–12% of weight change from the real-world study aligns with the***

		model's target population. This estimate was derived from a mixed population that included individuals both with and without T2DM, who comprised about 50% of study participants. Weight loss was greater among participants without T2DM—the population represented in our model. Furthermore, the study population consisted of individuals receiving tirzepatide or semaglutide products labeled for T2DM (Mounjaro and Ozempic), rather than formulations indicated for obesity. Consequently, dosing patterns may differ from those used for obesity treatment, further limiting the applicability of these results to our modeled population.
3.	The QoL assumptions again very strong (I believe you are assuming -0.01 for every unit increase in BMI, even after the effects of CVD, CKD, DM, OSA without or with excessive daytime sleepiness are taken out and modeled multiplicatively). The model is basically saying that going from a BMI of 30 to a BMI of 37 is a lot worse than having a stroke (after accounting for the side effects of weight gain).	***The direct impact of BMI on QoL (-0.007) was derived from a study that adjusted for multiple comorbidities, including CVD, T2DM, musculoskeletal, respiratory disorders, and others. So, we believe the effects of CVD and T2DM were already accounted for. We selected this study because it had the largest sample size and the most comprehensive set of adjustments; however, we acknowledge that the estimate is on a higher side than those used previously and reported in other studies (0.003~0.006). Also, we agree that there may also be some double counting of the effect of OSA. To address this, we thought it would be reasonable to back-calculate and remove the OSA-related penalty (~0.001) from the direct BMI effect following your suggestion and test a wide range in a sensitivity analysis.***
4.	(Regarding diabetes) Found the QoL assumption large given that you are accounting for CVD and CKD separately (and multiplicatively) – there feels to be some double-counting here, but I may be wrong.	***The disutility associated with T2DM was derived from a study that was adjusted for comorbid cardiovascular and kidney diseases. Therefore, we do not***

		anticipate major double-counting of disutility.
5.	(Regarding diabetes) incident diabetes tends to level off at 65	***Although the incidence of T2DM may vary by age, we believe that our assumed incidence rate produces a reasonable prevalence of T2DM in the modeled population when compared with external data sources. According to CDC data, the prevalence of T2DM in the general US population is 29% among those aged 65 or over.{CDC, 2024, 3125} Because the prevalence of T2DM is higher among those with overweight or obesity compared to those with normal weight (approximately 2~4 times based on CDC data), we expect higher prevalence of T2DM in our modeled population.{CDC, 2024, 3126} In our model, the resulting T2DM prevalence among those aged 65 or over without the interventions was approximately 45%, which we consider reasonable and consistent with external evidence.***
6.	Re – OSA: The model assumes a nearly 40% prevalence at baseline. At age 65 years in the model, prevalence is 37% in the control arm and 21% in the treatment arm (16pp difference, which is enormous). A third are assumed to have excessive day time sleepiness, which the model assumes carries a qol penalty equivalent to living with a stroke. While I agree OSA is important, these assumptions feel unreasonable. At the very least reduce the qol penalty here to 0.02 or 0.03. My sense is that you are double-counting the qoL penalty of OSA and BMI, which would be expected for a condition that is this prevalent. Unless you have very strong data otherwise, I would back-calculate the OSA penalty out of the BMI penalty (and apply to both the baseline and during follow-up).	***We re-reviewed our prevalence estimates and found them to be reasonable based on both study findings (a recent meta-analysis reporting a prevalence of moderate-to-severe OSA of 26% among individuals with BMI of 25~30 and 41.4% among those with BMI ≥ 30) and our clinical understanding. Thank you again for flagging the potential double counting — we adjusted by removing the OSA-related penalty from the BMI effect.***
7.	While this is a small driver of costs, my intuition is that some of your annual costs of CVD are too high. For instance, it's hard to imagine that "other CVD (besides MI, stroke, HF?)" incurs 10K per year on average across a 46 yo population. This is important because half the incident CVD events are in this other category I believe.	***We revisited the estimates and determined that using a lower cost for other CVD (~$8,000) would be more appropriate to better reflect the age of our patient population.***
8.	I also didn't look at your assumptions regarding discontinuation (any sustained benefits from prior GLP-1RA treatment? I would assume none). In prior work, the model was sensitive to the duration and magnitude of any benefits that were sustained after discontinuation (as you would expect for a treatment with a lot of discontinuation). It leads to unreasonable conclusions about therapy duration (treating for 1 year and stopping can have the lowest ICERs).	***We assumed that treatment discontinuation patterns mirrored those observed in the ITT populations of the clinical trials. Patients who remained on therapy during the trial***

		period (two years from treatment initiation) were assumed to continue treatment for the duration of the model, reflecting the chronic nature of obesity management. Accordingly, all treatment efficacy estimates (e.g., weight loss and effects on CVD and T2DM) were derived from the ITT population to implicitly account for the dilution of treatment effects due to discontinuation observed in trials, rather than explicitly modeling differential benefits before and after discontinuation.
9.	There seems to be a disconnect between how sick this population appears at baseline and their observed mortality.	***While people with obesity likely have higher mortality than those without, the magnitude is unclear. Consistent with previous obesity models, we used general population mortality at baseline and applied comorbidity-specific mortality separately. This approach may underestimate mortality due to other obesity-related outcomes not included in the model, but may overestimate it because general population rates already include obesity-related deaths. When we compared our model's estimated life years to other obesity models, our results were comparable (discounted life years: 20 years in our model vs. 18-30 years in other models). Given the comparable results and our inclusion of major obesity-related comorbidities (though not all), we believe the mortality estimates are reasonable.***
Health Strategy		
1.	We were disappointed to see that liraglutide was excluded from this analysis. The extraordinary cost of these new anti-obesity medications at a population level – laid bare by the budgetary impact projected in section 7 – makes it critically important to understand not only the cost-effectiveness of each agent relative to commonly used thresholds, but also each agent's cost-effectiveness relative to other agents in its class. For a drug class where expense is such a tremendous burden for payers and patients, the exclusion of the one agent in this class that is available as a generic is notable, representing what we view as a missed opportunity.	***Thank you for your comment. In our discussions with clinical experts during the review, they indicated that liraglutide was not their preferred agent for first-line obesity medication due to its lower weight loss potential and more inconvenient daily dosing***

	The FDA has approved generic versions of liraglutide both for diabetes (generic Victoza) and obesity (generic Saxenda). While liraglutide drives less weight loss than semaglutide or tirzepatide, its efficacy has been proven in many trials (including the LEAD series and LEADER trial for diabetes and cardiovascular risk reduction and the SCALE series for obesity), earning liraglutide FDA labeling for weight management in adults and adolescents as well as for glycemic control and cardiovascular risk reduction in diabetes. Recognizing its importance in the treatment landscape, ICER appropriately included liraglutide in its 2022 evidence report. That report systematically surveyed the literature on liraglutide, semaglutide, and other drugs to establish their cost-effectiveness. However, the price of these agents has decreased precipitously since that analysis was performed. In that 2022 report, the net cost of liraglutide was estimated at $11,000-12,000 annually and semaglutide was estimated at $13,000-14,000. While ICER acknowledges in its 2025 report that the annual net price of semaglutide has reduced to $6,000-7,000 – which dramatically changed the estimate of its cost-effectiveness compared to the 2022 report – the exclusion of liraglutide means that its increased cost-effectiveness by virtue of price reductions is not captured. This is an important omission because liraglutide has not only experienced list price deflation as the other agents in this class have in recent years, but it has also lost its exclusivity and is now available as a generic, which has significant ramifications for the price paid by payers, patients, and the public for this drug. In its April 2025 report on obesity medications, ICER noted that the annual net price of liraglutide (Saxenda) was $9191, compared to semaglutide (Wegovy) at $7401 and tirzepatide (Zepbound) at $8700. If these figures held true today, it might be reasonable to focus the analysis on the latter two agents and exclude the former. However, since that report, Saxenda is now available as a generic, which impacts its net price in multiple ways. First, the list price of generic Saxenda is lower than its branded counterpart, and due to loss of exclusivity, it is possible that competition may further drive down prices for liraglutide. Second, for generic drugs, the true amount paid by a plan sponsor (a health plan or an employer group) is significantly lower than its list price, because generic drug prices are reconciled at much lower effective rates (as a percentage of average wholesale price) than branded drugs in contracts between plan sponsors, pharmacy benefit managers, and pharmacy networks. Together, these two forces drive significant discounts, making liraglutide a far more affordable option for patients and our health care system overall. We have observed this deflationary process occur in the diabetic indication for these agents, where generic Victoza costs self-insured employers and their members (employees and dependents) a small fraction of Ozempic or Mounjaro. Given this experience, we expect that the cost-effectiveness of liraglutide in today's environment will be far greater than was estimated in the 2022 report. In fact, it may even meet or exceed cost-effectiveness thresholds, and do so by a greater margin than semaglutide or tirzepatide. Take for example the QALY-based threshold analyses in Table 4.11 of the 2022 report (page 54). There, ICER estimated that the annualized net price to achieve a benchmark of $100,000 per QALY gained was $7500 for semaglutide and $3800 for liraglutide. While semaglutide's current annual net cost (accounting for rebates) according to ICER's estimates is quite close to its threshold value, generic liraglutide's net annual cost today (accounting for its reconciliation as a generic in pharmaceutical purchasing contracts) is far below its threshold and may even be getting lower (as competition grows). While efficacy does vary between these agents, so does the cost. Liraglutide drives statistically significant and clinically meaningful reductions in weight (as well as HbA1c and cardiovascular outcomes); that these benefits are less in	***compared with semaglutide and tirzepatide, and that liraglutide was only prescribed when it was required by the payer (e.g., VA) before moving on to semaglutide or tirzepatide. Therefore, we did not think that it would be a relevant comparator to semaglutide and tirzepatide. Additionally, we evaluated liraglutide in our 2022 review of obesity medicines and those who are interested in the cost-effectiveness of generic liraglutide can use ICER's interactive modeler to estimate its cost-effectiveness.***

magnitude than the corresponding markers for semaglutide or tirzepatide would only comprise grounds for its exclusion from a cost-effectiveness analysis if the net prices of these agents were comparable. They are not. When viewed from a value-oriented perspective, it is essential to understand whether the incremental weight loss associated with semaglutide or tirzepatide relative to liraglutide is "worth" the additional money spent on those newer, more expensive agents. Whether the differences in efficacy are justified by their differences in cost is an empirical question that can only be answered through rigorous analysis of the type that ICER is known for.

Some might argue that liraglutide need not be considered in an analysis like this because, as the April 2025 ICER report stated, clinical interest is greater in semaglutide and tirzepatide than in liraglutide because liraglutide produces less weight loss and requires daily injections (page 8). In contrast, we believe liraglutide remains an important option in today's pharmacologic toolkit to treat obesity for several reasons:

- **Affordability**: By virtue of now being available as a generic, liraglutide is far more affordable than its peers and has a similar mechanism of action to semaglutide, while earning similar FDA indications for weight management, diabetes, and cardiovascular risk reduction. Not only is this important for payers seeking to manage budgets under increased financial pressure, but greater drug affordability also reduces premium growth and out-of-pocket expenses for patients and contributes to improved adherence.
- **Evidence**: Liraglutide has been robustly evaluated in randomized trials dating back 10+ years, earning it the earliest approval for a GLP-1 agonist and making it the longest-studied agent in its class. Moreover, it is still actively studied in cutting edge trials today. Consider, for instance, the SCALE Kids trial, which appeared in the February 2025 issue of the New England Journal of Medicine and generated significant editorial discussion in the May 2025 issue. This drug is still highly relevant to the scientific and medical communities.
- **Clinical Benefits:** While the clinical efficacy liraglutide is sometimes discounted because it leads to fewer pounds of weight loss than semaglutide or tirzepatide, this view assumes that the benefits of GLP-1 agonists are mediated primarily by weight loss. However, weight loss explains only a fraction of the clinical benefits of this class of drugs. It is widely accepted, for instance, that the cardiovascular benefits of GLP-1 agonists are mediated by mechanisms independent of weight loss. This view is supported by several data points, including that the cardiovascular benefits emerge early after treatment initiation, often preceding substantial weight loss, and objective evidence that GLP-1 agonists improve markers of inflammation, a key contributor to cardiovascular events. The American Heart Association notes that the cardiovascular benefits of GLP-1 agonists are not solely attributable to improvements in glycemia or weight but also involve pleiotropic effects on vascular biology and inflammation. Overlooking liraglutide because it leads to less weight loss than other GLP-1 agents ignores the fact that the benefits of these drugs go well beyond the pounds lost.
- **Side Effects**: Some argue that liraglutide has more side effects than semaglutide or tirzepatide, but the literature is somewhat mixed on

this point. For example, the SUSTAIN 10 trial comparing semaglutide and liraglutide concluded both agents had similar overall safety profiles, with a higher incidence of GI adverse events (nausea, vomiting, diarrhea) with semaglutide versus liraglutide, leading to a higher discontinuation rate with semaglutide. The STEP 8 trial, however, showed the opposite trend. In both trials, the majority of these side effects were mild or moderate and occurred primarily during dose escalation. Meta-analyses have also pointed to a higher absolute rate of GI symptoms and total adverse events with semaglutide compared to liraglutide, while other data suggest that the tolerability profile is similar across the class.

- **Utilization:** While current use of liraglutide is less than semaglutide or tirzepatide, many people still use it. Even a 5% market share in the massive and growing global market for anti-obesity drugs comprises millions of patients and hundreds of millions of expenditures. While publicly available peer-reviewed data is lacking, one platform (ClinCalc, which uses the Medical Expenditure Panel Survey from the Agency for Healthcare Research and Quality) reported that liraglutide was prescribed almost 2.2 million times in 2023.

Liraglutide is an FDA-approved agent for some of the most common medical conditions nationwide with proven efficacy and safety and is more affordable than its peers in a class of medications that is causing severe affordability challenges for health plans, employers, and patients. Understanding its relative cost-effectiveness is imperative not only for purchasers but also for society.

Self-insured employers, whose health care costs are rising much faster than inflation, are facing hard choices in their pharmacy benefits for employees. Growing pharmaceutical spending has crowded out investment in the core business for some, while contributing to layoffs for others. Working families are also experiencing mounting financial pressure from growing drug costs, which are increasing premiums, deductibles, and in some cases leading to benefit losses. Similar trends are occurring in Medicare and Medicaid. If we are to successfully improve population health without bankrupting our nation's governments, businesses, and citizens, we must leverage the full cache of what science has to offer our patients. Liraglutide is part of that cache. The inconvenience of daily versus weekly injections is not inconsiderable but surely convenience is only one factor of many to consider when dealing with financial pressures at a scale that they contribute to job losses and affect economic growth.

Moreover, due to their need to be responsible financial stewards of limited resources, many public and private payers (including several large employers) do not cover *any* GLP-1 agonists for weight loss, which limits access for broad segments of the eligible population. A better understanding of the cost-effectiveness of liraglutide – and its presentation alongside its peers – may help demonstrate that this more affordable alternative to semaglutide or tirzepatide is an option they can responsibly cover, offering at least one GLP-1 agonist to patients who otherwise would have zero options (besides paying out-of-pocket through direct-to-consumer channels, a luxury that few can easily afford).