Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value
Response to Public Comments on Draft Evidence Report

November 1, 2019

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Manufacturers		
Merck		
1.	**I: Life Years and QALY calculations** As shown in table 4.10, the life years gained range from 3.13 to 3.50 years and QALYs range from 1.76 to 1.95. These seem very low and overall unreasonable from the lifetime perspective. Given that average baseline age of patients is 62.7 years in the cohort, it does not seem plausible that patients would only gain another 3 years. This further doesn't benchmark against other published studies including those referenced in the draft evidence report (Laiteerapong 2018, Neslusan 2018, Shah 2018). While the methods section (4.2) report mentions that the numbers were compared to other publications, it is not clear what publications had similar numbers. **Recommendation:** - This is a major issue and questions the technical validity of the model. If the reported LYs and QALYs are validated, please provide information on what was used for the validation.	We have updated the implementation of the mortality risk equations in the revised version of the model, which was shared with the manufacturers during the public comment period. The revised life year and QALY estimates are in the updated report.
2.	**II: Rates of comorbid conditions** The proportion of patients with certain comorbidities seem very high and much higher compared to published literature. For example: The incidence of end-stage renal disease (ESRD) estimated from the model is very high (approx. 50%). In essence, this means that every second patient would be hemodialysis dependent which is clearly not the case in the real world. Given that the baseline ESRD rate was not reported and only renal complications rates were mentioned, it is unclear why the results suggest such high ESRD rates. The representative Neslusan 2018 cost-effectiveness analysis of canagliflozin vs. dapagliflozin found a cumulative ESRD rate of 6.75% (no baseline value reported). **Recommendation** – Similar to the first concern identified, this is another major issue that warrants confirmation of the technical validity of the applied model.	The rates of ESRD in the initial draft were higher than expected and are updated in the revised model.

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3.	**III: Price Assumption for Sitagliptin** As mentioned in earlier communications, the analysis should account for the price of sitagliptin after patent expiration. The price of sitagliptin is expected to decline significantly with the entry of generic competition by end of 2022. The use of the branded price for the result in a significant over-estimation of potential treatment cost for patients on the sitagliptin over both short-term (3-5 year) and lifetime model time horizons. **Recommendation:** We recommend of incorporation of the expected price decrease of sitagliptin at time of patent expiry in the analysis. In fact, when we calculated cost-effectiveness of oral semaglutide vs. sitagliptin using anticipated LoE price change using the new model that UW shared on Sept 30, as expected the results further dramatically change in terms of costs per QALYs gained.	ICER's cost-effectiveness analyses do not generally include estimates of price changes across comparator treatments linked to patent and exclusivity time horizons. Including assumptions about price changes is not currently the standard in academic or health technology assessment agency cost-effectiveness analyses. In part this is because it is very difficult to predict the pricing landscape years into the future (e.g., whether prices may increase in the years preceding loss of exclusivity, whether prices will drop substantially when patents and exclusivity expire, and whether prices of relevant comparator drugs may change as well).
4.	**IV: Patient Cohort Selection** The analysis uses the entire NHANES population for cohort development without use of appropriate selection criteria. The NHANES population does not represent individuals from which clinical efficacy data (PIONEER studies) were drawn. For example, the treatment effects for oral semaglutide were based on higher baseline HbA1c but applied to NHANES population with much lower HbA1c; this is not appropriate or realistic. For example, the proportion of patients with HbA1c below 7% was 51.4% and those with eGFR less than 45 were 11.8%. These patients would either not require an intensification in therapy or may not be eligible to receive SGLT-2i based on renal function. Furthermore, due to lack of availability of amputation, blindness, foot ulcer, and hypoglycemia data in NHANES, all patients are assumed to enter the model with no prior history of these events. Also, it is not clear why GE Centricity data was not used throughout the analysis rather than using different sources of data for different model inputs. **Recommendation:** The analysis using NHANES population should use appropriate criteria based on information of population included in the PIONEER trials for cohort selection process. Also useful to use one source of data is possible (Perhaps, GE Centricity database could have been used without the need to use NHANES).	We have restricted the modeled population to only those subjects from NHANES with an HbA1c of 7 or above in the revised model.

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5.	**V: Combining Data for Injectable and Oral Semaglutide** • In the analysis, the model inputs included hazard ratios for MACE and renal HR which included data from both oral as well as injectable semaglutide. This was justified by noting that a phase 2 dose finding trial showed similarities of effect between various oral and injectable formulations. This approach could overestimate the effects of oral semaglutide. • Based on our review, injectable semaglutide had possibly better HbA1c effect compared to oral formulation in (-1.% with lower dose and -1.6% with the higher dose of injectable vs. -0.9%, -1.2% and -1.4% for oral semaglutide) [Pratley 2018 and Aroda 2019] • There could be differences in other outcomes as well – for example, in table 3.9, injectable semaglutide had numerically lower hazard ratio for the 3-point MACE effect compared to oral semaglutide. Recommendation: Consider the use of only oral semaglutide data or run a sensitivity analysis excluding the data for injectable semaglutide to evaluate how results change with this exclusion.	This comment mischaracterizes what was said about the Davies 2017 study; it was mentioned in a description of why we were not relying on the head-to-head data on oral and injectable semaglutide. We feel we adequately described the uncertainties and the decision to combine MACE results. We note that while overall MACE was slightly higher for oral than injectable, the HRs for CV death and all-cause death were much lower. We think our approach was a reasonable balance of issues with the data, but it remains possible that oral semaglutide is more or less effective on MACE overall, or individual components of MACE, than injectable semaglutide.
6.	**VI: Adherence and Effect of Treatment** As mentioned in our earlier correspondence and as also pointed out on page 50 of the report in the section on "Controversies and Uncertainties", adherence is an important factor that determines effectiveness in the real world for different drug classes. In this context, a US study comparing real world efficacy of injectable GLP-1 receptor agonists to DPP4 inhibitors, the investigators reported a similar reduction at the end of 12 months (-0.52% for GLP-1 receptor agonists and -0.51% for DPP4 inhibitors) [Rosenstock 2019]. There have also been differential discontinuation rates of different therapies, given the different safety and tolerability profiles, in the PIONEER program; In PIONEER 3, the adverse event related discontinuation rate in the semaglutide arm was 11.6%. However, the analysis did not account for these differences. **Recommendation:** We propose a sensitivity analysis to help compare results of the model while adhering to the clinical trial efficacy data and of a model reflecting the clinical trial discontinuation data and/or documented real-world effectiveness for the different drug classes when available.	Trial-based discontinuation rates are included in the model estimates. However, we have no long-term adherence data for oral semaglutide and thus have assumed equal adherence in subsequent model cycles. We did also model scenarios with waning differences in treatment effect (MACE and renal outcomes) which may serve as a proxy for adherence over time.

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Intarcia Therapeutics		
1.	**Negligible Improvement Over the Past 15 Years** Over the past 15 years, more than 40 products have been approved by the FDA for the treatment of Type 2 diabetes. Nonetheless, over this same time period, there has been negligible improvement in overall rates of glycemic control based on a recently published analysis of NHANES cross-sectional data from 2005-2016. Of great concern is the proportion of patients with Hemoglobin A1c (HbA1c) values above 9, which remains above 30% of all Type 2 diabetes patients in 2016 just as it did in 2005. The authors conclude that the diabetes care cascade in the United States has not significantly improved between 2005 and 2016 and that gaps in diabetes care that were present in 2005 persist.1	We agree that adherence is an important aspect of diabetes treatment and that achieving clinical benefits from a therapy typically requires adhering to its use at rates similar to what was seen in the clinical trials.
2.	In a peer-reviewed analysis designed to assess the factors influencing glycemic control differences in the real-world relative to randomized, controlled clinical trials entitled Type 2 Diabetes in the Real World: The Elusive Nature of Glycemic Control, Drs. Edelman and Polonsky conclude that the majority of this difference is due to suboptimal adherence.	See above.
3.	**Other Relevant and Important Questions - GLP-1 receptor agonist outcomes** The ICER review poses the question of "whether having an oral GLP-1 receptor agonist will produce better outcomes due to many patients remaining on oral treatment who would otherwise require escalation of therapy using a once-weekly GLP-1 receptor agonist." Although an important consideration, in the context of the challenges that all Type 2 diabetes patients face when managing their chronic metabolic control issues with advancing therapeutic options, this may not be the most relevant question. Perhaps a more appropriate question is whether oral semaglutide will produce adherence rates that meaningfully exceed rates for either once-weekly injectable GLP-1 receptor agonists such as dulaglutide (the current market leading GLP-1 RA) or SGLT-2 inhibitors (the current preferred branded oral class of anti-diabetic medicines).	We think there are issues here not just around adherence, but around willingness to accept an additional therapy. Some patients are very hesitant to take a medication that requires injections.
4.	No matter what the choices are for initial or combination treatments, adherence rates of type 2 diabetes therapies are far from optimal. Below are 6-month adherence rates, as measured by the Proportion of Days Covered (PDC) >80%, for SGLT-2 inhibitors as a group and the market leading once-weekly GLP-1 receptor agonist. The methodology used for these analyses can be found in the references to this commentary. • SGLT-2 inhibitors 61.4%3 • Dulaglutide 54.2%4	See above.
5.	In real-world clinical settings, as patients are faced with all of the complexities of managing a chronic condition such as type 2 diabetes, 4 out of 10 patients who started therapy with a SGLT-2 inhibitor and almost half of patients who began therapy with a once-weekly injectable GLP-1 RA were not adherent over a six-	See above.

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	month period of time. The clinical implications of non-adherence include higher total medical costs and inferior glycemic control.	
6.	**Other Relevant and Important Questions - suboptimal medication adherence with oral SGLT-2 inhibitors** Based on the realities of suboptimal medication adherence with oral SGLT-2 inhibitors (requiring a straight-forward once daily oral regimen) and the market-leading GLP-1 RA (utilizing an optimized once-weekly injection where the patient does not see or handle a needle and simply uncaps the delivery device, places the device on the site of administration, unlocks the safety lock and presses the autoinjector button enabling the device to automatically insert and retract the needle after delivering the necessary dose)6, it will be important to anticipate and track adherence rates with oral semaglutide.	We agree. Real world evidence will be needed to better understand adherence to oral semaglutide, and suboptimal adherence will reduce potential benefits.
7.	Factors that could impact oral semaglutide adherence rates will likely include the following: • Three-step titration regimen: 3 mg for 4 weeks, followed by 7 mg for 4 weeks, followed by 14 mg, as needed for additional glycemic control. • Complexity of administration for a once-daily oral medication: To comply with dosing instructions for oral semaglutide, the patient needs to be in a fasted state for at least 6 hours; can consume no more than 4 ounces of water; must stay fasted for an additional 30 minutes without additional fluids, food or other medications. If this strict administration regimen is not followed, the bioavailability of oral semaglutide drops significantly, thereby limiting its effectiveness.7 • Significant GI adverse event rates: 20% nausea rate for oral semaglutide vs. 2% for empagliflozin, in the PIONEER-2 Head-To-Head trial8, which was likely to be a strong influence on the discontinuation rate of 11% for oral semaglutide.	See above. Also, we have added more information about the dosing burden with oral semaglutide to several sections of the report.

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8.	**Conclusion** At face value, one could reason that oral semaglutide might offer reduced therapeutic complexity relative to injectable GLP-1 RA products that would significantly improve patient outcomes based on its oral route of administration. However, given the real-world adherence challenges for both oral SGLT-2 inhibitors as well as the market leading once-weekly injectable GLP-1 RA dulaglutide, which one could argue would be no worse than the real-world adherence rates for oral semaglutide given the complex daily oral administration instructions and the expected gastrointestinal symptoms and tolerability challenges, it is premature to conclude that oral semaglutide will improve patient outcomes. These factors all contribute to uncertainties about the magnitude or durability of the long-term benefits of oral semaglutide. Once oral semaglutide is available to patients and has sufficient treatment experience, it will be important to conduct real-world analysis with oral semaglutide, including relevant comparisons to oral SGLT 2 inhibitors and injectable once-weekly GLP-1 RAs, in order to assess its clinical and economic value.	See above.
Novo Nordisk		
1.	**Patient-Centric Approach** Timely and effective treatment of T2D is needed to reduce the risk of developing long term, complications, yet even with numerous treatment options available, many patients do not achieve their individual HbA1c targets. GLP-1RAs provide effective glycemic control along with weight reduction and low risk of hypoglycemia.1,2 Rybelsus® offers an innovative solution that can help patients meet T2D treatment goals through an oral mode of administration where previous GLP-1 RA formulations were only available by injection.	We agree.
2.	**Patient-Centric Approach cont.** The American Diabetes Association (ADA) has stated that patient-centered care should be a focus and a priority when selecting a treatment regimen for a patient.3 The latest ADA-EASD Consensus Report significantly updated recommendations for pharmacologic treatment of T2D to specifically consider important comorbidities such as ASCVD, chronic kidney disease and heart failure, along with key patient factors, such as hypoglycemia risk, body weight, costs and patient preference. Therefore, drug classes should be considered carefully when applying this patient-centric approach considering both efficacy and key patient factors when choosing an appropriate pharmacological treatment.	We agree.

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Boehringer Ingelheim		
1.	**Real-World Evidence** While clinical trials remain the gold standard for determining treatment efficacy, real world studies provide additional information that is important for stakeholders. Treatment effectiveness in the real world can differ substantially from treatment efficacy, as measured in clinical trials. There are a number of reasons for this 'efficacy-effectiveness gap', including disparate patient populations, and sizeable differences in adherence outside of the highly controlled clinical trial setting.13 This difference is even more problematic for chronic diseases where the duration of treatment in the real world may vastly surpass the treatment period allotted to a clinical trial; even in an open label extension trial.14 Evidence of long-term effectiveness and sustainability are of great importance to patients and payers. BI suggests that ICER note the importance of relevant RWE in decision making criteria for treatment, as leveraged by healthcare providers and stakeholders.	As discussed above, we agree that RWE will be important to understanding real world use and benefits of medications for DM, particularly where there are concerns about adherence. However, clinicians, patients, and all stakeholders will need to make decisions about treatment long before data become available that would allow comparisons between oral semaglutide and other options for therapy.
2.	**Contextual Considerations** There are a number of treatment characteristics of high importance to patients and providers, such as tolerability, adherence, and productivity impacts. BI would suggest including in the section on contextual considerations, treatment burden and mode of administration. Oral semaglutide has to be taken at least 30 minutes before first food, beverage, or other medications with no more than 4 ounces of plain water.17 Additionally, oral semaglutide must be titrated after 30 days from 3 mg to 7 mg, and can optimally be titrated up again, after an additional 30 days.17 Oral semaglutide also requires titration over 2 months to determine the optimal dose. In comparison, treatment administration for empagliflozin has significantly less restrictions: to be taken once daily in the morning with or without food.18 Treatment burden is an important consideration, as the relationship of treatment burden to adherence and persistence has been well documented for both T2DM and other disease areas.19-22 In addition to mode of administration and number of doses, treatment complexity was found to be a key factor in treatment adherence in a survey of T2DM patients.23	We have added more information about dosing burden to several sections of the report.
3.	Given the importance of treatment burden and complexity to adherence and real world effectiveness, BI believes these are important treatment characteristics to highlight as additional contextual considerations for the treatments under evaluation. Furthermore, in the contextual considerations, BI encourages ICER to include treatment characteristics that may be as important as clinical safety and efficacy to patients, caregivers, and providers. Treatment characteristics to consider include robustness of clinical evidence, uncertainty introduced by clinical trial design, and subgroups of interest for whom efficacy evidence may be available.	See above. Also, we believe we have addressed issues of safety, efficacy, and uncertainties in the report.

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4.	**Model Transparency** BI commends ICER for providing a version of the model for review (for a nominal transaction fee), along with the model information included in the appendix of the report. However, the model is not entirely transparent, making it difficult to review the accuracy of results, and to provide recommendations for model adjustments. As an example, it is difficult to interpret the cost per MACE and cost per heart failure results as the inputs to the underlying calculations are not clear. Specifically, it is difficult to determine what cost was used in the calculation, whether it was total cost or only cost associated with the outcome. Further, in reviewing the calculations of 3-point MACE in the model shared, BI was only able to confirm the inclusion of first MI, subsequent MI, first stroke, and subsequent stroke in the calculation, not CV death, as described in the report. Additionally, it would be important for ICER to clarify how CV death was calculated, as it is not an outcome that was included in the original OM2 model. **BI recommends** including the calculations underlying the model either in the report or with the model when delivered. Increasing the transparency of the economic assessment, will only serve to improve the quality of both models and outputs.	CV death was assumed for deaths that occurred in the year of MI or stroke events (i.e. deaths triggered by the 'event' mortality equations). In the draft version of the model, all MI and stroke events were counted in the cost per MACE avoided calculation. The updated model has included a breakout of CV deaths for clarity.
5.	**Overall Report Approach** Lastly, BI urges ICER to provide further explanation regarding model inputs and calculations, as well as detailed interpretations for all figures and tables contained in the report. Without sufficient explanation and context, the data contained in the figures and tables could be easily misinterpreted or mischaracterized. For example, the legend in Figure E1 is cut-off, and the probabilistic sensitivity analyses do not have written interpretations. Additionally, as part of this effort, BI encourages ICER to perform a thorough quality check of all data and results in the report. As an example of an error that should be corrected, the cost per MACE averted for empagliflozin is listed as $940,000 in the top paragraph on page 67, but as $1,170,000 in Table 4.11 on page 67, which also differ from the values in Appendix Table E3. Since BI was unable to view the detailed calculation steps, BI was unable to confirm which number ought to be the correct value or why there might be a discrepancy between text and table. BI suggests ICER provide additional detail on the inputs and calculations as well as interpretations of the presented figures and tables.	Thank you. We have performed a thorough review of the updated report and we appreciate your thoughtful evaluation of the model and report

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Patients/Patient Groups		
Institute for Patient Access		
1.	**II: The Report Does Not Adequately Account for the Benefits of a Once-Daily Oral Formulation** Current evidence demonstrates that, as a pill rather than an injection, oral semaglutide improves patients' adherence and willingness to take the medicine that is most appropriate for them. Oral semaglutide should, therefore, improve overall health outcomes and decrease overall disease management costs. Injectable drugs are often an obstacle to patient adherence. In describing the introduction of oral semaglutide, the American Journal of Managed Care noted that the entire purpose of the drug is to … address an unmet need in patients with T2D [Type 2 diabetes] and CV [cardiovascular] risk who are overweight, as the GLP-1 receptor agonist class has been shown to help patients achieve significant weight loss. However, not all patients are willing to use an injectable drug, even one only needed once a week. An ACC panel discussion reviewed case studies on when to prescribe GLP-1 receptor agonists or SGLT2 inhibitors, and cardiologists said there are cases in which GLP-1 receptor agonists are indicated, but patients will not take an injectable drug. In one scenario described during the ACC session, an obese female patient was prescribed an SGLT2 inhibitor instead, but the physician commented that while this would control her blood sugar, it would not provide the same weight loss benefits. The draft evidence report fails to adequately incorporate these benefits, thereby underestimating the cost effectiveness of this drug.	Thank you, we think the report addresses these issues. Additionally, interest in an oral GLP-1 receptor agonist was a primary motivator for this ICER review.
2.	**III: The Report Does Not Adequately Account for Co-Morbidities** A number of serious and complex co-morbidities are associated with Type 2 diabetes. The existence of these co-morbidities significantly limits the reliability of the results derived from the cost-effectiveness model. Cardiovascular disease, for example, is a common comorbidity of Type 2 diabetes. Cardiovascular disease imposed over $555 billion in costs in 2015, and is projected to impose $1.1 trillion in costs by 2035. Oral semaglutide is associated with a lowered rate of adverse cardiovascular outcomes for patients with Type 2 diabetes who also had high cardiovascular risks, and it improves patient adherence and patient willingness to use a GLP-1 receptor. Therefore, an additional benefit from oral semaglutide is that it will reduce the costs associated with cardiovascular disease. Similar benefits are derived from other co-morbidities associated with Type 2 diabetes.	Thank you, cardiovascular disease outcomes are included in the model and the important outcomes of myocardial infarction, stroke, and CV death are modeled as a composite in the model aligned with the cardiovascular outcomes trials of these medications.

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3.	While these benefits are significant, it can take years for patients or the health care system to fully realize them. In other words, it is difficult to "reliably predict" the full benefits from oral semaglutide to include the benefits gained by reducing the co-morbidities associated with Type 2 diabetes. The draft evidence report admits that these concerns are a significant limitation to the cost-effectiveness model.	The model's base case utilizes a lifetime time horizon and applies the benefits observed in the clinical trials for the duration of the patient's life. This assumption grants the medication an optimistic scenario in terms of effectiveness and adherence.
4.	The overarching limitation of this model is the complexity of T2DM, its large number of co-morbidities, and its patient-specific clinical management. This complexity demands a patient-level microsimulation. Yet, it is extremely challenging to expect regression equations to reliably predict any one patient's actual outcomes, therefore we undertook a large number of sensitivity and scenario analyses in order to avoid depending on a single deterministic output. Sensitivity analyses, however, do not adequately address this limitation. In reality, the public health effects of oral semaglutide cannot yet be fully understood, and accurate lifetime cost-effectiveness estimates are simply unknowable at present.	Decision makers must make a well reasoned decision today and our effort is to produce an estimate of value for this product with the available data.
5.	**IV: The Report Underestimates the Costs Associated with Diabetes** Diabetes was the seventh leading cause of death in the United States as of 2015. The draft evidence report notes that the estimated total direct and indirect costs of diabetes were $245 billion; on a per-patient basis, there were $7,900 in annual health expenditures directly attributable to diabetes. These cost estimates are as of 2012, however. The costs are undoubtedly higher today. To get a sense of how much these costs could have grown, as of 2007, the estimated costs of diabetes were $174 billion. Thus, the American Diabetes Association is estimating that the direct and indirect costs of diabetes grew 41 percent between 2007 and 2012. While there are no estimates for how much these costs have increased over the past seven years, applying the past five-year growth rate over a seven-year timeframe (a conservative assumption) would imply that the direct and indirect costs of diabetes could be more than $345 billion today. The implications of this growth are not immaterial. A 41 percent increase in the economic costs of diabetes meaningfully changes the cost effectiveness of oral semaglutide. Without accounting for these higher costs, the report underestimates the economic burden that Type 2 diabetes imposes on society.	Thank you, we have updated that sentence to more accurately reflect the underlying time frame/data.

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6.	**V: The Report Fails to Fully Account for Patient Heterogeneity** Current treatments are not effective for all patients. Given the high cost of diabetes, there is a significant value to a medicine that can effectively treat patients who have not achieved adequate control with current therapies for Type 2 diabetes. As the draft evidence report notes, oral semaglutide has properties that can make it more appropriate for many patients. Nevertheless, the report does not account for the value that is created when patients who did not have an effective option now do.	The ICER value framework does account for this as a potential other benefit. However, stakeholders will need to consider how this applies to a therapy that exists already in injectable form.
7.	**VI: The Analysis Contains an Excessive Amount of Uncertainty** While uncertainty is inherent with all models, the base case results of the long-term cost effectiveness model are plagued with an excessive amount of uncertainty. When discussing the base case results, the draft evidence report states: we urge caution when interpreting these findings as they are highly uncertain. The uncertainties are reflected both in statistical variance in the model input parameters and risk equations, as shown in the probabilistic sensitivity analyses, and in the additional uncertainties from the NMA caused by concerns about whether effect modification could result from differences in the underlying CVOTs.	Health care payers must make decisions about funding now and cannot hold out for perfect information. We appreciate the concern that uncertainty and heterogeneity exist, and thus our report produces a range of cost-effectiveness estimates and thresholds with confidence ranges to aid decision makers.
8.	The best interests of patients cannot be served when a medicine's cost effectiveness is based on "highly uncertain" findings. Due to this uncertainty, it is not possible to know whether the estimated cost-effectiveness thresholds are overly restrictive, thereby denying patients access to a medicine that would provide value to them. Given the number of patients living with Type 2 diabetes in the United States, such errors will be excessively costly to the health care system. If the uncertainties that plague the base case model cannot be reduced, ICER should delay its analysis until such time that the results can be modeled with an acceptable level of uncertainty.	See above.
9.	**Conclusion** Comparing the efficacy of a treatment when robust post-marketing data does not yet exist is always problematic. It offers an understanding of the drug's benefits that is, by definition, constrained, increasing the uncertainty of any cost-effectiveness evaluation. The sheer number of times the draft evidence report notes "significant uncertainties" raises serious red flags regarding the accuracy of the cost-effectiveness results. As a result, IfPA is concerned that the report provides an inaccurate picture of the benefits that oral semaglutide could offer patients living with Type 2 diabetes.	We do not understand how highlighting uncertainties paints an inaccurate picture.
Patients Rising		
1.	Institute for Patient Access & Affordability is a new program division of Patients Rising with the mission to provide patient-powered pathways to help both public and private payers as they make critical coverage decisions for patients with rare and chronic diseases.	We congratulate Patients Rising on having yet another new named organization.

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2.	**People-Centered Perspectives** The draft report does a good job of describing the complexity of type-2 diabetes, and presents a reasonable although limited overview of the range of possible treatment options. For example, it would be good to note that weight loss for people with T2DM – which may be achieved with "nutrition therapy and physical activity ("lifestyle changes")" – can help reduce the significance of the disease and lessen a person's need for medicines. As good clinicians know, support for such life style changes requires a variety of resources and skills within the care team, such as cognitive behavioral therapy. It has also been proposed that gastric bypass surgery (or similar interventions) may be reasonable treatment options for obese people with diabetes since it may lead to remission or a cure for their diabetes.	Thank you. We agree, but more detailed discussions of these issues is outside the scope of this particular review, though very important to management of diabetes in general.
3.	We point out these treatment options for people with diabetes and urge ICER to consider and evaluate the full spectrum of treatment options in their analyses – including all the associated cost, benefits, risks, and people-centered factors. In the report, we believe ICER could use more patient friendly language, such as specifying that "hospitalizations for major cardiovascular disease (CVD)" means heart attacks and strokes. We note this because the hospitalizations are actually for sequela from the underlying CVD, such as a heart attack or stroke. That is, if someone has stable CVD they would likely not be hospitalized simply because they have CVD. Using those terms for CV events requiring hospitalization is akin to the military using the term "collateral damage" to refer to civilian deaths.	The term "major cardiovascular disease" as a reason for hospitalization was used in the underlying CDC report and likely includes non-MI ACS and procedures for CAD, carotid disease, and PAD in addition to MI and stroke.
4.	We appreciate ICER noting that costs of medicines are a concern for patients, and citing the CDC's survey about the impact of those costs for people with diabetes and how it effects their adherence to medications. »Related to that point, it would appropriate for the draft report to note that the July 17, 2019 notice from the IRS that enables high deductible health insurance plans staring in 2020 to cover treatments for diabetes ("Insulin and other glucose lowering agents") before a person has met their deductible amount. In the past, we have commented on ICER's limited use of focus groups – including its inclusion of information about a focus "group" that only included three people. In the same vein, we note that the current draft report cites information from a single patient. Since an anecdote is not data, we continue to urge ICER to work with patient groups on real data collection through responsible methodologies such as well constructed surveys and focus groups.	We suspect that coverage issues for drugs for diabetes, including insulin, will likely come up at the policy round table at the meeting of the NE CEPAC.

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5.	**Timing of Report** Because on September 20th the FDA approved oral semaglutide (brand name Rybelsus), and that the price will reportedly be $772 per 30 tablets across all doses, the report's text, tables and analyses at a minimum should be updated with that information. However, we believe it would be more appropriate to revise and reissue the draft report with updated information. Further supporting our rationale for ICER to put forth a revised draft report rather than a final version is that ICER has modeled a variety of scenarios beyond the base case and plans on including a modified societal perspective in a future version of the report. We read this to mean that ICER is withholding other modeling and analysis. We are particularly troubled that a societal perspective is considered an after-thought to be completed later, or has been done and is being withheld. If ICER simply did not have the time to complete that analysis, that would be another reason why a revised draft report rather than a final report should be issued. ICER needs to explain those statements in greater detail and justify its decisions for not including such modeling – whether completed or not.	ICER has, as per its usual procedures, update this version of the report with the price for Rybelsus that is now available. The modeling in this report involved microsimulations, and so some scenario analyses were not completed by the time of the draft report. However, the model structure and inputs were available and reviewed by manufacturers. We agree that a modified societal perspective is not an afterthought, however the primary purpose of the draft report is to get adequate input to appropriately revise the report. Results of the modified societal perspective analyses are presented in this report.
6.	Because CV events (i.e., Major Adverse Cardiovascular Events or MACEs) is the "Key Measure of Benefit" chosen by ICER for the draft report (with HgA1c and renal function considered as "Intermediate Outcomes" of "Clinical Benefit"), wouldn't it be more useful and responsible for ICER to withhold a final report and instead issue an updated draft report after the FDA acts (or not) concerning the indication for CVD, which is expected in early 2020?	Whether or not the FDA approves semaglutide as a treatment for CVD will not affect the benefits of oral semaglutide for CVD in patients with type 2 DM and inadequate glycemic control.
7.	We particularly think this is warranted since ICER has stated in its proposal for updating its framework assessment process that it will only review and update its reports a year after the date of its final reports – which means that ICER might not update the final report for oral semaglutide until a year after the FDA has acted on the CVD indication. Of course, if ICER were to state that its 12-month timeline for potentially updating reports is only a guidance and that it will update this report after the FDA acts on the CVD indication, that would be a reasonable approach too. (We also note that the Preamble to the draft report ICER leaves itself that option by stating – without a specific timeframe – that it "may revisit its analyses in a formal update to this report in the future.")	The proposed changes to the ICER VAF process include a formal review after one year to see if new evidence has emerged that would require an update to the report. This does not prevent earlier updates to reports.

#	Comment	Response/Integration
8.	**Individualized Treatment Approaches for Diabetes** In the section on Clinical Guidelines, we are curious why ICER did not mention the 2019 guidance and algorithm from the American Association of Clinical Endocrinologists and the American College of Endocrinology. We recognize that the AACE/ACE publication may not be as deep and granular an exploration of treatment options for type-2 diabetes as some of the other guidelines cited, but it does present a prioritized treatment approach and algorithm that is consistent with the recommendations from the other sources cited. Since the primary audience for ICER's work is in the United States, would it not make sense to cite the recommendations from the two leading groups of clinicians for people with diabetes in the U.S.?	ICER had included these guidelines in early versions of the report, but received input from clinical reviewers that led to our removing these guidelines from the draft report.
9.	The draft report notes that "oral semaglutide is administered on an empty stomach, which may affect adherence and acceptability" but does not pair that notion with the similar concept that patients might prefer swallowing a pill once a day rather than a subcutaneous injection once a week – particularly in a population that is likely already taking other oral medications. We note that this concept is raised later in the report: "Oral semaglutide is likely to allow many patients to remain on oral treatment who would otherwise require escalation of therapy using either an injectable GLP-1 receptor agonist or insulin." We also note that an additional advantage of the oral form of semaglutide is that unlike the injection formulation, it does not have to refrigerated prior to initial use, which could be a factor for use for people without access to adequate refrigeration. Such adherence factors should be discussed together rather than separated.	We have added the benefit of avoiding the need for refrigeration to the report.
10.	**Data Uncertainty** There are a variety of ways ICER embraces uncertainty in the draft report, and Institute for Patient Access & Affordability believes ICER should highlight statements where it declares such uncertainties in bold type and declare them up front in the preamble to the report much like the FDA does with Black Box Warnings. And of course, such important caveats should also be prominent in the Conclusions section.	Thank you. While we appreciate the formatting suggestions for the report, we feel we have adequately highlighted uncertainty.
11.	**Data Uncertainty cont.** The draft report cites data about increased risk for retinopathy with oral semaglutide, but the FDA approved label states "Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied." This should be cited and noted in the report, particularly since ICER seems so enamored with projecting long-term outcomes without data. »What is ICER's justification for developing and using an unvalidated model, e.g., "To our knowledge, ours is the first and currently only microsimulation model to undertake such a novel approach to predict these long-term events in T2DM."	Thank you. We have added language from the label in our discussion around retinopathy.

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12.	**Other Analytical and Methodological Concerns** In the Base Case Analysis, Table 4.1 indicates that 33.3% of the population are current smokers. This is a much higher percentage than the overall U.S. adult population (14%) – particularly those over age 64 (8.2%). Does ICER have data to indicate that the target population for the draft report's analysis (i.e., "adults with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s)") actually have such a high rate of smoking? That is, is the data source for this base case population appropriately representative of the target population in the U.S.? This is a critical point since smoking is an independent risk factor for vascular disease.	The NHANES survey asks patients if they are a current smoker and we included responses that were either every day or some days as a current smoker in our patient demographics. This survey includes approximately 5000 participants and is considered nationally representative.
13.	»In the Utilities section of the draft report it is stated that the "annual disutility for daily injection of insulin (for patients who discontinue treatment) and liraglutide based on Boye et al., who used standard gamble interviews of T2DM patients in Scotland to estimate the utility values for injection-related attributes." Does ICER have any evidence that the utility values derived from interviewing patients in Scotland represent the same utility perspectives as in the United States?	We acknowledge that there could be differences in patient preferences between countries. However, we did not identify any other sources for the disutility associated with injections in people with Diabetes that were specific to the U.S.
14.	»For the Budget Impact Analysis, it seems that ICER is assuming that oral semaglutide would completely replace other medicines in the other classes. »Please explain how that is any way a realistic assumption – even for patients who are not adequately controlled on their current regimen? »How can ICER assume that other interventions – including non-pharmacological such as lifestyle changes or surgery – would not used by some of those patients, or that they would just continue to have their diabetes suboptimally managed and with inadequate glycemic control?	Our potential budget impact analysis does not assume that oral semaglutide will completely replace other medicines, or that some patients would not use other interventions. Rather, our analysis tries to estimate the total number of patients that might be considered eligible for treatment with oral semaglutide, and then to estimate the potential net budget impact as varying proportions of the eligible population are treated. This analysis makes no assumption of how many patients will actually be treated with oral semaglutide.
15.	● »What is the purpose of ICER analyzing and reporting on health plan coverage since it does not seem to factor into its analysis for the rest of the report? Since health plans and insurance companies know their own coverage policies and can benchmark themselves against their peers and competitors, what is the "value" of including that information in the draft report?	ICER reports are read by many different stakeholders and we have found that including coverage policies is helpful. It also helps provide input to the policy roundtable discussions.
16.	● »Similarly, since it is well known to ICER that health plans do not have coverage policies for unapproved compounds (except under their experimental treatment policies and protocols), what is the point of "looking" for such coverage policies – or in the case of oral semaglutide – using the injection form of the same compound as a surrogate even though there is no evidence that coverage policies may translate to the yet to be approved medicine?	See above.

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17.	● »Why did ICER look for economic models for something that hasn't been approved and for which there wasn't a price (until after September 20, 2019), or any sales of utilization data? If ICER is concerned about using its resources to provide useful information and analyses, searching for things that are known to not exist seems like an extreme waste of time and resources. Please explain the rationale for conducting such pointless activities.	Prior economic models of diabetes are useful to find and review even if a particular drug has not yet been reviewed.
18.	● On page 37 (last sentence of first paragraph under "Adherence and Use of Rescue Medicine") there seems to be a typo since the description of Table 3.7 and the table's data seem to contradict each other, i.e., the table indicates a higher rate of rescue medicine use for people taking placebo compared to oral semaglutide in the PIONEER 1 and 8 studies (15.2% v. 1.1-2.3% and 31% v. 15.5-16.5%).	Thank you. We have fixed the error.
19.	● Because the analysis of the subgroup with moderate renal impairment had a mean age of 70 years old it would seem appropriate to analyze this group within the context of Medicare as a payer rather than continue to view ICER's analyses as applying to the entire U.S. health care system, population, and all payers and insurance plans.	ICER reports generally do not separately analyze therapies based on public or private payers.
Partnership to Improve Patient Care		
1.	**ICER Continues to Omit Quality of Life Data Deemed Valuable by Patients, Instead Relying on Faulty Data That Claims Health States Worse Than Death** In this report, as in previous reports, ICER assumes the only impact a new therapy has on quality of life are movement between specific, clinical health states. In reality, there is a growing body of evidence that successful treatment of cardiovascular disease risk factors in patients, including those suffering from diabetes, have had strong effects on psychological wellbeing and quality of life beyond gains associated purely with their event risk effects or movements across health states.	We utilized preference-weighted health-related quality of life estimates from the literature that are based on regression equations. The input estimates listed in the draft report are not health states with utility values worse than death, although we do not argue that such states are impossible. Instead the coefficients for the events must be combined in the full regression in order to estimate the utility for a given patient with a given set of characteristics. Furthermore, we utilized multiple sources of utility estimates because there was not a single source that could provide all of the necessary input values for the model.
2.	For example, a recent study in long-term statin users showed lower depression, anxiety, and hostility after adjustment for the propensity for statin use and potential confounders. The beneficial psychological effects of the statins appeared to be independent of the drugs' cholesterol-lowering effects. Similar results have been seen in drugs used to treat high blood pressure.	We would welcome such data specifically from a Diabetes population

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3.	We are especially concerned about ICER's use of utility data. It is unacceptable that ICER continues to use negative utility values, which imply there are health states worse than death. ICER has used negative utilities in previous reports and has been heavily criticized for it. The academic literature has also shown negative utilities to not really exist. We cannot stress enough the ethical ramifications - and irrational consequences - of using such methods to attribute a value to treatments that may then be used by payers to determine whether to cover a new treatment.	The utility values that were calculated were not negative utility values. Rather, the parameters represent coefficients from a regression equation, which must be combined in order to estimate an individual patient's utility value.
4.	We also take serious issue with the source of the utility data. The utilities used for baseline Type 2 Diabetes, and various complications of Type 2 Diabetes are the most significant drivers of variance in the model. The source of these weights is cross-walked from unrelated studies, rather than waiting for actual data from ongoing trials, bringing into question the longer-term validity of the base case results. ICER even goes on to state in its report that; " … Utility values for events modeled from the risk equations were drawn from two sources due to a lack of a single comprehensive source of health-related quality of life inputs. It is also important to point out that the two sources used different preference-weighted measures (EQ-5D and HUI3), and these two instruments are known to produce slightly different utility estimates". (Page 73) It is difficult to understand how ICER can justify reporting findings based on this data and approach given what is stated above.	We recognize that there are limitations to the available data and balance that with the needs of decision-makers in the process of health technology assessments. We utilized the most appropriate available input values for the events included in the model.

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5.	**ICER Ignores the Heterogeneity of Type 2 Diabetes Patients** A glaring limitation of ICER's analysis is its reporting of a single ratio of cost effectiveness of oral semaglutide against each comparator. Theoretically, the shift to microsimulation models should give outputs on an infinite number of potential patient types, but instead of taking advantage of this, ICER has retained a base case that gives just one set of cost-effectiveness ratios. Type 2 Diabetes is particularly difficult and sensitive to treat, given the complexity of co-morbidities. This means that prescribing and prognosis are particularly heterogeneous and specific to individual patients. ICER admits this itself when describing the model: "The overarching limitation of this model is the complexity of T2DM, its large number of co-morbidities, and its patient-specific clinical management." (Page 72) ICER also notes that the primary aim of the report will be to evaluate the new drug in four very specific subgroups: 1. Patients at high risk for CV events 2. Patients with moderate-to-severe renal impairment 3. Patients requiring a second antihyperglycemic agent (i.e., second-line therapy) 4. Patients requiring a third antihyperglycemic agent (i.e., third-line therapy) Despite this nod to the fact that patients are heterogeneous and react differently to different treatments, there are no more references to these essential subgroup classifications in the section on cost-effectiveness. This exemplifies ICER's tendency to oversimplify and its unwillingness to accept that it is impossible to determine whether a treatment is "cost-effective" for the general population when patients are heterogenous with different comorbidities and treatment needs. Healthcare is becoming more and more complex, and more and more specific to individuals with particular sets of diseases, complications, and co-morbidities. A continued reliance on a population perspective in reporting value statements is likely to become more and more misguided and less and less beneficial to decision makers.	ICER's cost-effectiveness analyses are not meant to inform patient-level decisions, but are intended to inform decisions at the population or payer level. Whenever possible from available data or data provided by manufacturers, ICER includes an evaluation of the heterogeneity of treatment effect for key clinical outcomes. In this case, we were unable to identify clinical subpopulations for which data were available to determine relative effectiveness. We do present within the evidence report distributional statistics for key outcomes, beyond means and medians, whenever the data are available.
6.	**ICER Again Uses Artificially Narrow Definition of Major Adverse Cardiovascular Event** As in ICER's assessment of treatments for cardiovascular disease, ICER chooses to use an incredibly narrow definition of Major Adverse Cardiovascular Event (MACE). The definition of MACE in the base case is a shorthand version including only MI, stroke, and CVD death. More common and more comprehensive definitions of MACE include revascularizations and other events such as severe angina and heart failure. Exactly how MACE is defined and what events are included is known to have a significant impact on outcomes. It is concerning that, with this knowledge, ICER selected a less comprehensive measure of MACE.	Please see the discussion in ICER's recent report on Additive Cardiovascular Therapies for information on why 3-point ("hard") MACE is often chosen by researchers and others as the best outcome for comparisons of therapies. However, outcomes available in the clinical trials of these agents were used in the model.

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7.	**The Source of Risk Equations for Patient Underestimates Value of Therapies** The risk equations ICER has chosen to use may artificially underestimate the value of therapies. The model used is based on data from a United Kingdom-based sample. Metabolic syndrome conditions and diabetes itself are more prevalent in the population of the United States, so using a United Kingdom data set may underestimate risk of cardiovascular events in the population of need, hence underestimating absolute benefits from successful treatment.	The absolute event estimates from any set of risk equations may not exactly represent the events experienced by a given population. However, the value estimates of interest in our report are comparative in nature. We utilized the same risk equations for each treatment, modified for MACE and renal outcomes using the NMA for oral semaglutide. Therefore, we contend that the incremental comparisons between the interventions in the report provide useful estimates for decision-makers.
8.	It is also worth pointing out that the risk algorithms generated from the United Kingdom Prospective Diabetes Study (UKPDS) are less reliable generally, and for an American population specifically, than those generated more recently by the RECODe study using data from the Action to Control Cardiovascular Risk in Diabetes study (ACCORD; 2001–09). Nevertheless, both sets of risk equations suffer from the fact they are generated on a very narrow selection of participants, as they rely on data from clinical trials rather than being taken from a real world population that is likely to be more representative of the actual population that could benefit from the treatment under investigation. A number of studies have highlighted the limitations of trial data only in generating risk equations for models that will ultimately make decisions about actual populations of need, and all suggest that both risk and event rates are underestimated as a result.	See above.
9.	**ICER's Budget Impact Model Continues to be Concerning as it is Equivalent to Budget Capping in Health Care.** We continue to be concerned with ICER's problematic tactic of budget capping in healthcare. Following ICER's disturbing pattern, this report assumes that only a little over 4% of eligible patients could be treated with oral semaglutide in a given year without crossing ICER's arbitrary budget threshold. As we described at length in our recent comments on cardiovascular disease, budget capping both presents a significant ethical problem and is also illogical. This concept tells us we can only give a new, effective drug to a certain number of people who could benefit from it. Since the goal of the healthcare system is ultimately better health, this premise does not make sense.	As we noted in our response to your comments on ICER's recent cardiovascular report, ICER's potential budget impact threshold is explicitly not a budget cap. It is instead intended as one part of a process to determine when to raise an "affordability and access alert," in specific cases where the potential budget impact is likely to be large. Its purpose is not to say that "we can only give a new, effective drug to a certain number of people" but to allow payers and others to plan for the potential budget impact so that appropriate access to beneficial treatments can be maintained.

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10.	The model itself is also not sound. ICER's budget impact model assumes a take-up rate of 100% over five years for these new drugs, which assumes that every single person that could theoretically benefit from these interventions will ultimately receive it. This is illogical and have been proven incorrect time and time again, yet ICER persists in making this assumption. A prime example of this is ICER's budget impact model for PCSK9i drugs in 2015. That report also relied on the unrealistic assumption of full take-up over five years. Four years later the take-up rate of PCSK9 inhibitors is estimate at less than 1%.	Our potential budget impact analysis does not assume any specific take-up rate. Rather, our analysis tries to estimate the total number of patients that might be considered eligible for treatment with oral semaglutide, and then to estimate the potential net budget impact as varying proportions of the eligible population are treated. This analysis makes no assumption of how many patients will actually be treated with oral semaglutide.
11.	**Conclusion** ICER continues to use a flawed methodology, ignoring the reality of heterogeneous patient populations and quality of life outcomes that matter to patients in favor of data that easily crosswalks into the discriminatory QALY metric. We urge ICER to consider alternative methodologies that will foster improved health care decisions for individual patients.	We suggest urging manufacturers and researchers to carefully measure quality of life in their clinical trials. The QALY does indeed discriminate between therapies that improve quality of life and those that don't.
Other		
Ronald Carico Jr, Clinical Pharmacist, Marshall Health **Karrie Murphy,** Assistant Professor University of Charleston School of Pharmacy		
1.	**Comparisons with Empagliflozin and Liraglutide** We deeply appreciate ICER's continued dedication to patient-oriented outcomes, such as cardiovascular events and length of life. We feel that the comparisons with empagliflozin and liraglutide are fair, and give oral semaglutide a chance to distinguish itself from other agents with proven cardiovascular benefits. We also value the use of comparative-effectiveness and long-term studies whenever they are available. Analyses that use patient-oriented outcomes and comparative effectiveness research provide vital "real world" perspectives.	Thank you.
2.	**Limited Patient Access** Our first concern about the applicability of the model to our patients centers on adherence. As discussed in the DER's limitations, data on the impact of partial adherence to many of the treatments are limited. We often serve rural Appalachian patient populations who may have limited access to primary care providers or endocrinology specialists. Our patients therefore face many geographic and financial barriers to continuous medication access. We encourage ICER and other interested entities to continue to investigate the relevant costs and benefits, and to incorporate any resulting findings to real-world, patient-oriented models.	As discussed above, we agree that RWE will be important to understanding real world use and benefits of medications for DM, particularly where there are concerns about adherence.

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3.	**External Validity** We have other concerns related to external validity. While published data on patients with diabetes in our region are limited, our patients may differ from the simulated patients used in ICER's model in key ways. The NHANES-derived patients used in ICER's base case are often older (mean age of approximately 63 years) and may have a lower A1c (mean value 7.4%) than many of our patients. By contrast, BRFSS-derived analyses have found that residents of economically-distressed Appalachian counties are more likely to be diagnosed with diabetes at a younger age than residents of other parts of the United States2.	We have updated the base case analysis to be limited to patients with a HbA1c of 7 or higher and included the full NHANES T2DM patient population as a scenario analysis.
4.	This finding is concordant with data that we extracted from the 2017 BRFSS results showing that more than half of patients who self-report a history of diabetes diagnosis in West Virginia are under the age of 45 (Table 1 below). As economically vulnerable populations, we believe our rural patients may be of special interest to ICER, and we will want to use ICER's models to advise our healthcare systems on treatments that provide a good balance of quality and cost. Our patients may be followed by the healthcare system for decades; we believe they will have a great deal of time to accumulate benefits, costs, and risks of treatment. As the data permit, we would be interested in sensitivity analyses (or possibly forthcoming scenario analyses) that combine younger patient population with a higher baseline A1c.	Thank you, we have updated the model base case to be patients with a higher baseline HbA1c, and included the full population as a scenario in the report.