Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis with Fibrosis
Response to Public Comments on Draft Evidence Report

July 21, 2020

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Clinicians/Researchers		
Mazen Nourredin, MD		
1.	**Pioglitazone:** As you mentioned, fibrosis in NASH is the prognostic factor that correlates with morbidity and mortality, especially in subjects with F2 fibrosis. You compared Obeticholic Acid (OCA) to pioglitazone, using a meta-analysis that commented on the effect of pioglitazone in reversing fibrosis. In Page 13 you stated, "*However, sufficient data were identified to perform a meta-analysis of studies comparing pioglitazone to placebo on the fibrosis improvement outcome. This analysis was performed using a random effects model using R*." I believe that evidence that pioglitazone treatment improves fibrosis in NASH is weak, including that of the meta-analysis you cited (Mantovani et al. Diabetes & Metabolism 2020). Those authors stated that, "*With regard to a possible improvement of liver fibrosis, glitazones were not superior to placebo or other active molecules, except for one RCT using pioglitazone 45 mg/day for 18 months in patients with biopsy-proven NASH and T2DM/ prediabetes.*" Please note that the study they refer to is that by Cusi et al. (Ann Intern Med, 2016), in which the result for fibrosis improvement was not statistically significant. Most importantly, patients enrolled in the pioglitazone trials you mentioned were mainly those with F2 fibrosis; few patients had F3, although patients with F3 are those in the most urgent need for treatment, as your sub-analysis has shown.	It may not have been clear that we performed our own meta-analysis and this suggested, with very little heterogeneity, that pioglitazone does improve fibrosis, even though the small individual trials were unable to demonstrate this.
2.	The side effects of dyslipidemia: I agree with your concerns that OCA can unfavorably alter serum lipid panels, especially LDL. Indeed, that was a major concern of many experts in the field when the FXR agonist drugs emerged as a treatment for NASH. It is now believed that the dyslipidemia resulting from these drugs, and from ACC inhibitors, should be managed/mitigated with statins. Indeed, many of our patients are already receiving statins, as NAFLD/NASH is itself associated with dyslipidemia. Your analysis would have been more inclusive if you had considered the use of statins in managing NAFLD/NASH and in mitigating the dyslipidemia associated with OCA.	For the CV analysis, we assume that statins are the standard of care for all NASH patients. As such, we looked at the increases in LDL-C with OCA that are seen in patients who are already receiving statins.
Manufacturers		
Intercept		
1.	ICER should not include patients with cirrhosis in its value assessment of OCA. Based on the positive results from the Phase 3 REGENERATE study interim analysis, Intercept is seeking approval of OCA for the treatment of NASH patients with fibrosis who have not yet progressed to cirrhosis. OCA therapy must be discontinued if a patient shows signs or symptoms of cirrhosis, consistent with our New Drug Application (NDA) for approval of OCA for liver fibrosis due to NASH. If OCA is approved, informing healthcare providers, patients and other stakeholders about the appropriate patient population for OCA will be a central part of our educational efforts. Accordingly, ICER should not include OCA use in patients with compensated or decompensated cirrhosis in its model and instead should only include costs consistent with the indication for which we are seeking approval. The FDA specifically provides separate guidance for drug development in NASH patients with compensated cirrhosis because the clinical considerations and management strategies are different for these patients. We are conducting a second Phase 3 study, the REVERSE study, to determine the safety and efficacy of OCA in patients with compensated cirrhosis due to NASH. Until results from REVERSE are available,	Thank you for clarifying the intended label for OCA. We have updated our base case model to discontinue treatment at F4 and have moved the original base case that allowed 50% of patients reaching F4 to continue treatment and potentially improve to a scenario.

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	it is premature and inappropriate to consider OCA treatment for NASH patients with cirrhosis, and ICER should remove this population from its analysis.	
2.	**ICER is including theoretical cardiovascular events in its assessment, despite a lack of evidence that OCA treatment is associated with an increase in cardiovascular events.** Intercept believes it is appropriate to include costs of lipid lowering medications in the cost-effectiveness assessment for OCA. However, it is not appropriate for ICER to extrapolate estimates of cardiovascular events that have not been demonstrated in adequate and well-controlled clinical trials. ICER's analysis takes the LDL-C changes observed with OCA at 12 weeks in CONTROL2, a Phase 2 study of 84 patients (of which only 22 patients received OCA 25 mg) and uses that to project a rate of future hypothetical cardiovascular events. The LDL-C data from CONTROL is at odds with the evidence from the 18-month interim analysis of the much larger and longer Phase 3 REGENERATE study3 of 931 patients, which is more reflective of LDL-C management in clinical practice. The ICER draft evidence report suggests that the increase in LDL-C observed with OCA at the 12-week timepoint in a Phase 2 trial will persist for the remainder of a patient's life and that healthcare providers will take no action to manage the LDL-C increase. In real-world clinical practice, healthcare professionals can manage increases in LDL-C seen with OCA according to standard practice guidelines. In the REGENERATE study, increases in LDL-C were observed at Month 1 in patients treated with OCA and slowly diminished over time and trended back down through Month 18, but remained higher than baseline; in the OCA 25 mg group, the mean change in LDL-C was approximately 3 mg/dL above baseline at Month 18. Among OCA-treated patients who initiated statins, the initial LDL-C increases reversed to below baseline levels as of month 6 and were sustained through month 18. Thus, statins appeared to be effective in reducing the LDL-C increase observed with OCA. The incidence rates of prospectively and independently adjudicated core and expanded major adverse cardiovascular events (MACE) were generally similar across treatment groups in the Month 18 analysis of the REGENERATE study. Because these analyses are limited by the small number of CV adverse events and limited follow-up duration, it is not possible to definitively assess potential for CV risk.	Thank you, but we believe that we adequately explained our concerns about lipid effects in the section titled "OCA Effects on Lipids" and reiterated some of the uncertainties around this in the section "Controversies and Uncertainties". In brief: the studies to date are not adequate to exclude an effect on CV outcomes; raising LDL in a high risk population is worrisome; that LDL can be lowered with statins is why the calculations we used were based on patient assumed to be on statins; we believe the vast majority of patients with NASH should be on statins anyway given their high CV risk; as such, we feel that the increase in LDL seen with OCA in patients on background statin therapy is appropriate to consider when assessing CV risk.
3.	**ICER's analysis of noninvasive tests (NITs) for assessing fibrosis in patients with NASH fails to account for the limitations of biopsy and does not reflect how NITs will be used in clinical practice to identify potential candidates for OCA treatment.** We agree with ICER that sequential use of NITs results in a 92% specificity and 91% sensitivity in identifying patients with advanced fibrosis due to NASH. This compares favorably to the 89% specificity and 85% sensitivity of liver biopsies in patients with advanced fibrosis read by expert histopathologists.4 Because expert capacity is limited, liver biopsies are likely to be performed and read by nonexperts in real world clinical practice, resulting in greater variability and inaccuracy. However, ICER's analysis assumes that liver biopsy provides 100% specificity, an assumption that contradicts decades of research in the field.	If liver biopsy is not assumed to be accurate, it would be hard to know what the accuracy is of NITs. Liver biopsy has been the gold standard in making such judgments.

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4.	Along with sensitivity and specificity, the prevalence of the population to be assessed is a key determinant of the utility of the screening/diagnostic test. This utility involves the calculation of what is known as the positive predictive value, or the probability that subjects with a positive screening test truly have the disease. ICER relied on "expert opinion" and a meta-analytic assessment that estimated a general population of patients with nonalcoholic fatty liver disease (NAFLD) to estimate the population that would be tested with NITs. Applying NITs to this broad population results in an unusually high number of patients incorrectly diagnosed with advanced fibrosis. In actual clinical practice, we expect that potential candidates for OCA would not be identified from a pool of general NAFLD patients.	We disagree. Once there is an effective therapy for NASH fibrosis, we believe patients with NAFLD will routinely be screened for fibrosis.
5.	Instead, we expect that specialists would be identifying potential candidates for OCA from a population of patients more likely to have advanced disease who will have been referred from primary care practitioners due to the presence of one or more of the following clinical risk factors: age>50, presence of type 2 diabetes mellitus and/or obesity, abnormal liver biochemistry, irregular findings on imaging (e.g., steatosis) and/or previous high NIT scores. The prevalence of advanced fibrosis is expected to be substantially higher in this population treated by specialists and thus the rate of false positive tests will be much lower.	We believe such screening will be done in the primary care population.
6.	The entire NASH ecosystem of stakeholders including patient groups, professional societies, academic researchers, manufacturers, and regulators, are engaged in broad collective efforts to advance the role of NITs in the management of NASH, given the limitations and risks associated with liver biopsy. We appreciate ICER's attempt to evaluate the utility of NITs in its assessment of OCA, but this section of ICER's draft evidence report requires significant revision and, in its current form, may have a deleterious impact on patient care if used as a rationale to justify exposing more patients to biopsy. ICER reports a 0.2% mortality associated with biopsy, which is essentially 20 deaths per 10,000 biopsies performed, a sobering statistic.	We believe that using evidence to guide such decisions is more important than a collective effort to advance the role of NITs.
7.	**Pioglitazone is not a valid comparator.** In our comments on the draft scope for the review, Intercept and most of the other stakeholders who commented were unanimous and critical of ICER's decision to include pioglitazone as a comparator and we remain concerned about the inclusion of pioglitazone in the draft evidence report. We agree with ICER's statement (pg. 42) in the draft evidence report that "we clearly have inadequate evidence to compare OCA with pioglitazone." Pioglitazone is not widely used as a treatment for NASH; fewer than 2% of patients in the 18-month interim analysis of REGENERATE were treated with pioglitazone at baseline despite no limitation on pioglitazone use in the study protocol. ICER's assessment is accurate in noting that no study has demonstrated a significant fibrosis benefit with pioglitazone. REGENERATE is the only Phase 3 study in which the interim analysis results demonstrate a statistically significant improvement in fibrosis in patients with NASH. Pioglitazone has never been evaluated in a Phase 3 study for the treatment of NASH. The pioglitazone studies included in ICER's assessment vary in quality and relevance, with the largest involving 163 patients[8] treated with pioglitazone or placebo. REGENERATE includes 2,480 NASH patients randomized at over 300 qualified centers worldwide. Given the limited published data on pioglitazone efficacy in NASH, its safety liabilities and its	We agree that we had inadequate evidence to compare outcomes with OCA and pioglitazone and that pioglitazone is not widely used. Our meta-analysis suggests that the overall evidence for pioglitazone efficacy raises a real possibility of benefit and as such makes it difficult to determine whether OCA or pioglitazone has a superior balance of benefits and risks.

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	limited and cautioned use in the AASLD guidelines, pioglitazone does not appear to be a relevant benchmark comparator for OCA. We recommend that ICER remove the voting question about pioglitazone.	
8.	**ICER's budget impact assessment uses a patient population that is six times larger than the population likely to be treated with OCA.** Using an inappropriately large patient population for OCA distorts ICER's budget impact calculations and will compromise the utility and validity of ICER's assessment if not revised in the final evidence report. Throughout the ICER process, in our public statements and external communications, in interviews with journalists and in our interactions with payers, we have been very clear about our strategy of positioning OCA as a treatment for a specific subset of patients with advanced liver fibrosis due to NASH. This is a population with great unmet need, and there is a greater urgency to treat patients with advanced liver fibrosis due to NASH because the risk and associated costs of progressing to cirrhosis, and the myriad of downstream complications as a result of cirrhosis, is so much higher relative to the risk seen in patients with early fibrosis. While estimates of the overall prevalence of NASH vary in the medical literature, Intercept has undertaken extensive research to define the likely OCA population using a combination of published epidemiology data, medical claims data, laboratory report data and multiple qualitative and quantitative market research studies. Based on this work, we estimate that ~500,000 patients with advanced liver fibrosis due to NASH in the United States would be considered for OCA therapy over a period of several years following approval. Note that experience from previous launches shows the population considered for treatment is generally much higher than the population that receives treatment. Our research indicates that 80% of primary care providers view themselves as referrers of these patients vs. 90% of hepatologists and gastroenterologists who see themselves as managers of the patient's care. Intercept's commercial strategy and field force structure do not focus on primary care providers because the company believes specialists should take the lead in managing OCA therapy in these complex patients with advanced disease. To carefully control utilization, Intercept plans to use a limited network of national specialty pharmacies, along with a small number of pharmacies within closed systems of care, to distribute OCA. ICER's prediction that three million patients will be treated with OCA over a period of five years is unrealistic given the intended patient population and prescriber base for the medication. Although Intercept's focus on more advanced patients without cirrhosis is primarily driven by the unmet need in this population and extensive market research demonstrating that healthcare providers have little or no intention to prescribe OCA to patients with early fibrosis, our efforts to narrowly define the patient population for OCA also take into consideration perspectives from health system stakeholders – including ICER – that are concerned about health system costs of new therapies. Ignoring our focus on a narrowly defined patient population for OCA may create a disincentive for other manufacturers to balance their commercial strategies with budget impact considerations. Additionally, inaccurate and exaggerated budget impact assessments may indirectly impact patient access.	ICER's budget impact calculations attempt to find the entire population that could be treated to allow policy makers to make their own estimates of the likely treated percentage of the population. As such, the analysis should not be interpreted as a prediction of who will or will not be treated. That said, we think it is unrealistic to expect that the population to be considered for OCA will not expand beyond those currently cared for by specialists.

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9.	The concern in overestimating budget impact and specifically uptake is not new in ICER assessments. We refer you to Intercept's public comment on ICER's 2020 Value Assessment Framework, the 2016 ICER Assessment of OCA[10] in NASH, and the analysis by the Center for Evaluation and Risk in Health (CEVR) of six ICER budget impact assessments.[11] NASH is a new disease category with OCA potentially being the first treatment for NASH patients with fibrosis. There is considerable uncertainty in estimating anticipated uptake of OCA even within the more narrowly defined population.	ICER does not attempt to predict uptake in its budget impact assessments. It attempts to estimate the eligible population.
10.	Although our comments have focused primarily on assumptions and inputs that we are calling on ICER to revise, there are multiple sections in the draft evidence report that we believe are thoughtful and well-supported by evidence. Most notably, ICER's description of patient struggles with the shock of diagnosis and complications of cirrhosis (ascites requiring paracentesis, the delirium associated with hepatic encephalopathy) mirrors the concerns that Intercept has heard repeatedly from patients and caregivers. We also appreciate ICER's acknowledgement of the uncertainties in the field and gaps in the medical literature that leave us with a rapidly evolving, but still incomplete, understanding of the natural history of the disease and the costs of managing its complications.	Thank you for this comment.
11.	We close our public comment by emphasizing the "contextual considerations" that we believe should ground this assessment of OCA: Liver fibrosis due to NASH is a disease with a devastating medical and emotional burden, particularly in its most advanced stages when patients progress to cirrhosis and its complications. The unmet need for new therapies that stabilize or reverse the fibrosis progression that leads to cirrhosis is enormous; there are no medications approved for the treatment of liver fibrosis due to NASH in the United States and multiple investigational products have failed in late-stage clinical trials, leaving OCA as the best near-term hope for patients and their families. OCA is an innovative medication with a novel mechanism of action that has emerged from decades of research exploring the therapeutic potential of farnesoid x receptor (FXR) agonism. Our clinical development program has catalyzed a surge of NASH research and drug development investment from other manufacturers and helped establish a regulatory pathway for NASH therapies that did not exist previously.	We appreciate you mentioning these and agree.

Merck		
1.	The conclusion of the report states that: "OCA appears to improve outcomes in people with NASH with fibrosis. At a placeholder price of $80,000 per year, OCA is not cost-effective at traditional cost-effectiveness thresholds. Treating patients with F3 fibrosis without a prior history of CV events may be the population with the highest chance of showing value to the health care system at the placeholder price." This conclusion is a bit misleading to the reader, as we do not see the cost effectiveness analysis results for F3 with no CV in the scenario analysis. **Recommendation:** ICER should reword to include the findings from the F2 and F3 scenario and then state why there is the recommendation that treating patients with F3 fibrosis without a prior history of CV events may be the population with the highest chance of showing value to the health care system at the placeholder price. Also, we would recommend that ICER report in detail the cost effectiveness analysis results for patients with F3 fibrosis without a prior history of CV events in the scenario analysis.	Thank you for the suggestion to clarify this sentence. We have re-worded this sentence in the conclusion.
2.	In the model, ICER included LDL-C and how that may predict CV events. However, it is stated on pg. 30 regarding pioglitazone: "BMI increased between 0 and 1.8 kg/m2 from baseline in the pioglitazone arms in the five trials that reported BMI compared to between 0 and 0.7 kg/m2 in the placebo or vitamin E arms (see Table 4.13).37,41-44 Body weight increased between 1.2 and 5.7 kg from baseline in the pioglitazone trials compared to between -0.2 and 0.7 kg in the placebo or vitamin E arms in four trials that reported weight.37,41-43 This is significant considering that the incidence of metabolic syndrome and obesity is high in the NASH population." Weight gain is not in itself a harm as the clinical impact of weight gain depends on both the magnitude and nature of the weight gain (e.g. fluid retention versus increase in muscle mass). While increased adiposity is generally associated with increased insulin resistance and its consequences (hyperglycemia, hyperlipidemia, steatosis), increased adiposity occurring with thiazolidinedione (pioglitazone, rosiglitazone) treatment is associated with improved insulin sensitivity and metabolic benefits. This illustrates the need to assess the health implications of weight gain based on specific clinical consequences, which may depend on the drug mechanism of action. **Recommendation: We would agree that unfavorable effects on lipid profiles should be considered harms. The relationship between magnitude of weight gain in pioglitazone users and its impact on the metabolic improvement has not been assessed quantitatively. As such, it might be premature/inappropriate to consider a <5kg weight gain to be "significant". We would recommend removing the term "significant" without the quantitative evidence to support this.**	Thank you, but we do not think the data suggest that weight gain with thiazoledindiones lacks harmful consequences. We also believe that most clinicians would consider a 5 kg weight gain to be clinically important in a patient with metabolic syndrome.

Patient Advocacy and Research Organizations		
Fatty Liver Foundation		
1.	It would be nice to see in the final report data from a recently published paper confirming that NASH is now the leading indication for liver transplantation among women with HCC - https://doi.org/10.1016/j.cgh.2020.05.064	Thank you, we have added the citation to the Background section.
2.	A minor issue on page 9 where the FDA is cited (and somewhat implied) as the regulatory body of interest for the European medical societies. Should it be the EMA (European Medicines Agency) instead?	Thank you, this has been corrected.
Global Liver Institute		
1.	**Lack of Patient Inclusive Language and Impact on Quality of Life:** Throughout the report there is a lack of patient inclusive or people first language, and acknowledgment of the NASH impact on quality of life. It is critical for ICER to put patients at the center of all of their assessments, and this should be abundantly through their choice of language and recognition of how a disease can impact daily life. Firstly, communication is one of the foundational aspects of patient care that impacts patient satisfaction, morale, and builds rapport between physicians, researchers, and patients. Person-first language is a style of communication in which the person is listed first followed by descriptive terms, which avoids defining a person by his or her disease state, reduces stigma and places the emphasis on the person rather than the disease or disability. Multiple agencies and organizations including Center for Disease Control and Prevention (CDC), American Psychological Association, and American Society of Addiction Medicine encourage person-first language. The American Medical Association (AMA) also recommends the use of person-first language in the AMA Code of Styles. In many instances throughout the draft evidence report the choice of classifying patients as obese or as a diabetic instead of patients with obesity or diabetes, portrays a judgmental tone that is counterproductive to ICER's goals.	Thank you, we will correct this language.
2.	Secondly, patients with NASH experience a range of symptoms that negatively affect their quality of life with the most prevalent being fatigue, but also including major depressive disorder, generalized anxiety disorder, feeling bloated, having discomfort or pain around the liver, sleeping problems and lethargy. Studies have also found greater impairments in quality of life and work productivity in patients with advanced NASH.1 Work absences are also an issue with caregivers, causing lost time, lost wages and sometimes even job loss. It is important for any assessment of NASH treatment to consider holistically the impact on quality of life.	Thank you, we agree that the impact of NASH with fibrosis on quality of life worsens based on fibrosis stage. Our model utilizes health-related quality of life values that attempt to capture those differences between more severe fibrosis stages. The model also includes a societal perspective which includes the indirect costs, specifically productivity loss.

3.	**Model Assumption: NASH Standard of Care:** Standard of or "usual" care is a faulty comparator, as it does not truly exist for NASH. The ultimate aim of treatment for NASH is to reduce progression to cirrhosis or liver cancer and decrease fibrosis progression as well as NASH related mortality. ICER defines usual care as, "usual care includes lifestyle interventions as well as usual care for associated metabolic comorbidities, and may include vitamin E."	For many disorders there is no treatment-specific therapy.
4.	There is a lack of unified approach in early detection and management of NASH. The rate of disease progression is not uniform; some people experience fast fibrosis progression while others follow a much slower course or may even experience regression. Symptoms of NASH, which may include fatigue, lethargy, abdominal pain and sleeping problems, are non-specific so they can often be misinterpreted. Most often patients will present with fatigue alone and are ignored. NASH is typically only detected once it has progressed to cirrhosis or liver cancer, therefore most people live with the disease for years without being aware of the damage accumulating in their liver. Currently there is a lack of guidelines for regular follow up that providers use. In many ways the current NASH standard of care can be compared to previously outdated standards for one of its comorbidities, prediabetes, and diabetes. For decades prediabetes was ignored as well.	We agree about the need for evidence-based guidelines.
5.	With this said, we ask for the clarification of a few critical points when discussing "usual care" in the final report. First, 7-10% weight loss is truly rare and only achieved by a small portion of patients. Second, while Vitamin E has shown some success as a treatment for early stages of NASH, it has limited to no effect on reversing advanced stages of fibrosis and cirrhosis.[i] Finally, the use of Pioglitazone as an adequate comparator does not accurately account for the variability in effectiveness and lack of agreement between experts in the field.	We agree with the comments about the difficulty of weight loss. Vitamin E was included so that we would not exclude patients who received vitamin E from any comparisons. We agree that there is disagreement about the efficacy of pioglitazone and our report highlights why there should be uncertainty.

6.	Due to NASH's strong link to obesity, weight loss, through the combination of diet and exercise, is the most established approach to care.[i] Weight loss also addresses associated comorbidities such as Type 2 diabetes.[7] However, weight loss is difficult to accomplish and sustain.[ii] [iii] A study found that 85% of people with NAFLD could not achieve and maintain a weight loss of 7-10% or more, which is the threshold to induce the highest rates of NASH resolution and fibrosis regression. The patients that did show success achieving the necessary weight loss utilized "intensive lifestyle modification" programs (sometimes called Intensive Behavioral Therapy (IBT), and many times still only were able to attain 7-10% at 6 months (usual peak for weight loss efforts) before regaining the weight back. In response, bariatric surgery becomes one of the only consistent options to reduce weight and improve histology of the liver. [i] [ii] [iii] Bariatric Surgery is an invasive procedure that is typically limited to those with severe obesity with its own set of risks costs and significant barriers to access; thus its potential as a widespread treatment for NASH may be limited as is demonstrated by its overall low overall utilization (less than 1% of people eligible utilize surgery).[iv]	We agree.
7.	We also understand that for a cost effectiveness model to operate as intended there needs to be a base comparator. In this case, we understand why Pioglitazone has been chosen. Pioglitazone is a drug approved for Type 2 diabetes that has also shown positive improvement of NASH in some patients. [i] [ii] However, Pioglitazone may only be worthwhile for leaner populations where weight gain is not a factor. Multiple studies have found that patients with type 2 diabetes experienced some negative side effects of weight gain, issues with water retention, edema, and risk of fracture. For patients with NASH who also have type 2 diabetes and obesity, the use of Pioglitazone could be problematic, and can lead to questions about the risk-benefit ratio.[i] This point is highlighted when we understand that in people with obesity and type 2 diabetes, NAFLD prevalence is approximately 50-70% and NASH prevalence is approximately 56%.[ii] [iii] There are also cardiovascular concerns for this patient population when anywhere from 20-80% of patients with NASH currently have hyperlipidemia.[25] This is especially alarming for patients with preexisting cardiac dysfunction where Pioglitazone has been shown to increase the risk of congestive heart failure. NASH care can look markedly different depending on when a patient is diagnosed, and the unique complications experienced by each patient. Currently the model utilizes methods that do not adequately account for the variability in care for NASH. There is a lack of specialist and clinician agreement on how to treat NASH. Due to this lack of standardized care, treatment plans administered often vary drastically depending on the unique characteristics of each patient. This must all be factored in to and acknowledged in any cost model analysis for NASH.	Thank you for these comments, we agree that there would have been additional complexities with modeling pioglitazone, which is why it is only included in the comparative effectiveness section of the report but not as a comparator in the cost-effectiveness model. The cost-effectiveness model employs a 'standard care' comparator that is modeled based on the placebo arm of the REGENERATE trial. Furthermore, we appreciate the concern regarding individual patient heterogeneity and acknowledge that averages of patients overlook unique patient characteristics while still allowing for pricing and policy decisions.

8.	**Model Assumption: "Gold" Standard Diagnostic:** In this draft evidence report ICER has chosen to reference liver biopsy as the "gold standard" for diagnosing NASH. We have a few serious concerns with this classification. First, liver biopsy is a risky, invasive procedure that can be subject to sampling variability, and is increasingly only used after many other diagnostic and non-invasive tests (NIT) have been exhausted. We understand that the American Association for the Study of Liver Diseases (AASLD) currently refers to liver biopsy as the strongest diagnostic option however, we have come to understand that they plan to revise and modernize this recommendation in the near future. Second, it plays a role in unnecessary high costs associated with the care for NAFLD independent of its metabolic comorbidities. Third, liver biopsy is rarely performed outside of a specialist setting, creating an access barrier and in some cases an extended wait time, contributing to misreporting and underdiagnosing of NASH.	It is common that the gold standard for diagnosis is either too expensive or too invasive to use routinely on all patients.
9.	Liver biopsy can artificially inflate the cost of care for NASH, and unnecessarily lengthen treatments. This is especially important to understand when trial data for OCA (25 mg) suggests that 38% of patients with NASH experience improved fibrosis. On average liver biopsies cost more than $7,000 per patient, and the lengthy conventional diagnosis pathway in total can run up to more than $10,000 per patient.[1] The largest increases in health care utilization and costs in NAFLD are represented by liver biopsies and hospitalizations.	Our analyses suggest that, depending on the price of OCA, liver biopsy may save money by avoiding inappropriate treatment.
10.	Liver biopsy is not the only diagnostic option. Currently, there does exist acceptable and accurate NIT to assess for liver fibrosis.[i] [ii] [iii] NITs lead to fewer patient visits, quicker diagnosis, and are more cost-effective with no surgical risks. We understand that there currently is no consensus around a single NIT to diagnose NASH and replace liver biopsy.[34] [iv] [v] However, we already see many gastroenterologists and hepatologists frequently diverge from published practice guidelines that previously classified liver biopsy as the "gold" standard for NASH diagnosis. It has been found that less than 25% of clinicians routinely require it to make the diagnosis of NASH.[vi] From initial diagnosis to monitoring treatment change and deciding length of treatment, NITs can play a valuable role throughout the entire NASH care pathway. NITs should be prioritized within this ICER cost effectiveness model.	Using liver biopsy to diagnose NASH is quite different from using it to assess stage of fibrosis for patients considering treatment.
11.	**Model Assumption: Length of Treatment:** The current ICER model makes the assumption that patients will be using OCA treatment under optimal prescribing conditions "for life as long as they continue to respond to treatment." This is highly unrealistic. It is typical in drugs taken for chronic conditions for patients to take treatment holidays, often when the treatment is effective, and at times when it is ineffective, as agreed by their physicians.	We based this assumption on input from clinical experts. Treatment holiday would not affect the assumption.
12.	It is also true that drug use, especially of specialized drugs, falls away later in life when pain relief and symptom management become more common. In addition, the model assumes that the price of these treatments will remain the same for the next 20 years, which is very unlikely.[i] What is more likely is that generic substitutes will enter the market, driving down prices. If you factor in this steep drop in price after 10-15 years, along with other potential savings from reducing the	As is consistent with best practices at international HTA agencies and with the great preponderance of academic work in health economics, ICER's cost-effectiveness analyses do not routinely make estimates of price changes across comparator

	incidence of expensive hospital care, end stage liver diseases like liver cancer, and potentially using NITs, the model's cost estimates would drop dramatically.	treatments linked to patent and exclusivity time horizons, given the unpredictability of these changes in the US health care market.
13.	**Solution at Every Stage:** It is important to understand and factor in the reality that NASH must have a different solution and response at each stage of the disease. While weight loss can show success at earlier stages, it is less effective at more advanced stages. As the disease progresses to more advanced stages studies have also found greater impairments in quality of life and work productivity. Currently, at more advanced stages liver transplantation is the only possibility. A liver transplant is one of the single most expensive surgical operations in the United States. It costs on average between $600,000 and $1 million per patient. The procedure requires nearly a year of intensive aftercare, but a lifetime of follow up, a steady supply of organs, high-tech operating rooms and massive quantities of blood for transfusion. Furthermore, liver transplantation is not a cure for NASH, and some individuals may not be eligible for transplantation due to comorbidities related to metabolic syndrome, such as obesity or coexistent CVD. Liver cancer is a factor at all stages of NASH. The costs associated with an outcome of liver cancer must be considered, even when the mechanisms associating NALFD and NASH and the development of liver cancer need further investigation. Estimates vary between studies but suggest that of people with cirrhosis due to NASH, approximately 2–12% develop liver cancer per year. Recent evidence also suggests that people with lean NAFLD are at higher risk of developing severe liver disease compared to patients with NAFLD who also have obesity. There is no "silver bullet" response to NASH. While prevention and weight loss management can be effective earlier, it is difficult, and less effective at later stages. Treatment options for advanced NASH should also not be forced upon earlier, less advanced patients with NASH. Patients at different stages of the disease carry different costs as well. This truth about NASH care must be made clear in the report.	We agree.
14.	**The Cost of Not Treating NASH:** In any cost-effective analysis of a disease, it is important to pose the question of, what if we chose not to treat the disease? With NASH there is both an immense public health and economic burden that must be accounted for.	We agree, and because there is not another FDA approved treatment in the model, this is essentially what our approach is by using the placebo arm from the REGENERATE trial as the comparator.
15.	First, NASH and NAFLD have far-reaching public health effects that are not just limited to the liver. People with NASH have an overall mortality rate of 7.9% within seven years of diagnosis- almost twice that of the general population.[i] NASH and NAFLD have shown significant comorbidities with a variety of other conditions ranging from obesity, Type 2 diabetes, cardiovascular disease, and chronic kidney disease. Cardiovascular disease is the most common cause of death for patients with NASH. Furthermore, NASH has a bidirectional relationship with Type 2 diabetes. If NASH develops first, the patient is likely to develop Type 2 diabetes or conversely, in patients with Type 2 diabetes initially, NASH is a common comorbid occurrence. Diabetes also contributes to greater	Thank you, we agree that the other co-morbidities frequently associated with NASH are important. Our model attempts to isolate the impact of OCA based on currently available information. Further extrapolation would require even more assumptions.

	fibrosis progression of NASH and can accelerate the progression to cirrhosis and liver cancer.	
16.	Second, the rise in prevalence of NASH, its complications, and its comorbidities carry significant economic costs. Costs associated with NASH include inpatient, outpatient, professional services, emergency department and drug costs.[i] As severity of NASH and fibrosis increases, the cost associated with the disease increases as well. Furthermore, comorbidities also contribute to cost not only in healthcare spending but also in indirect costs, such as lost work productivity.[ii] Estimates of other cost models have suggested that the rise of NAFLD will be similar to the rise of obesity prevalence. The estimated total cost of NAFLD in the next 10 years in the United States could be $1.005 trillion dollars	Thank you, we agree that the costs, both direct and indirect, associated with NASH are important. Our model includes increasing costs based on fibrosis stage, which include the medical cost categories you have indicated. The model also includes a societal perspective which includes the indirect costs you have mentioned.
17.	Another model suggested that lifetime costs of all non-advanced patients with NASH in the United States in the year, 2017, was around $222.6 billion. For advanced patients with NASH, which was characterized by those who have reached fibrosis stage 3 or cirrhosis have an estimated total cost of $95.4 billion.[43] Furthermore, comorbidity cost estimates have shown that the total cost of NASH with Type 2 diabetes is $667.9 billion.	Thank you for sharing these citations.
18.	We must be cognizant of the unique issues and costs at each stage of NASH. The standard of care, the impact on quality of life, the truth about liver biopsy, the need for a solution at every stage of the disease, the length of treatment, and the outcome of not treating this life threatening disease, are all crucial factors that must be considered when painting the cost picture for NASH and when considering potential other benefits offered by the intervention.	Thank you, we agree.
Obesity Action Coalition		
1.	Liver health can sometimes be overlooked in people with obesity, where cardiovascular and endocrinological complications take priority. However, the prevalence of nonalcoholic fatty liver disease (NAFLD) is higher in people with obesity compared with the general population, and up to one quarter of people affected by obesity with NAFLD go on to develop NASH. Obesity can also exacerbate genetic predisposition to fatty liver and fibrosis, increasing the risk of developing cirrhosis. Weight-loss and weight management are often the first suggested treatment for NAFLD. However, weight loss is difficult to accomplish and sustain. A study found that 85% of people with NAFLD could not achieve and maintain a weight loss of 7-10% or more, which is the threshold to induce the highest rates of NASH resolution and fibrosis regression. The patients that did show success achieving the necessary weight loss utilized Intensive Behavioral Therapy (IBT), and many times still only were able to attain 7-10% at 6 months (usual peak for weight loss efforts) before regaining the weight back. In these cases, patients should have access to FDA-approved medications for chronic weight management/obesity to help them maintain their weight and manage their obesity. If someone is unable to meet their weight-loss goals and they have a BMI greater than 35, bariatric surgery should be considered. This is particularly true for patients with NASH or fibrosis. Studies show that fatty liver disease improves after surgery a majority of the time, and about half of patients also see a decrease in inflammation. While treating an individual's	Thank you, but we do not think the data suggest that weight gain with thiazolidinediones lacks harmful consequences. We also believe that most clinicians would consider a 5 kg weight gain to be clinically important in a patient with metabolic syndrome.

	obesity can provide beneficial outcomes for those with NAFLD, ICER's modeling should not assume that obesity care and weight loss treatments are covered services under most health insurance plans and that such services are widely available. The unfortunate reality is that coverage for counseling, medications and surgery for obesity is either outright excluded or dramatically limited due to discriminatory benefit design and providers may not provide such services due to such coverage issues. Patients often face arbitrary hurdles to care such as waiting periods, higher copays and separate deductibles that increase their share of the treatment cost or discourage utilization.	
2.	**People First Language:** The OAC has identified many areas where weight bias penetrates today's society, such as media, entertainment, healthcare, employment, education and more. However, one of the most prevalent areas that the OAC is now tackling to eradicate weight bias and stigma is language. The OAC, along with other obesity-focused organizations in the community, are raising awareness of a new initiative titled People-First Language. Quite often, you will see news stories, articles and journal entries refer to an individual with obesity as "obese." By using "obese," we are dehumanizing individuals affected by this disease. For these reasons, the OAC is disappointed regarding the lack of patient inclusive or people first language throughout the report. It is critical for ICER to put patients at the center of all of their assessments, and this should be abundantly clear in their choice of language throughout the report.	Thank you, we will correct this language.
Partnership to Improve Patient Care		
1.	**ICER's model oversimplifies a complex condition.** ICER's model groups the NASH patient populations into just two initial groups based on prior cardiovascular events and stage of fibrosis. Notably, the bulk of patients in fibrosis groups F1, F2 and F3 are combined into a single group. This generalization is problematic as there are significant differences in terms of severity of disease, co-morbidities, and associated risks of transition to worsening health states among patients in F1, F2, and F3 subgroups . One study noted this heterogeneity and suggested that liver-related mortality increased exponentially as patients progress through worsening stages of fibrosis.	Our model makes some simplifying assumptions, but specific fibrosis stage transitions (e.g., F2 to F0, F1, F3, or F4) were included, using a recent meta-analysis of fibrosis progression in NAFLD and NASH patients for probabilities applied to improvement/worsening/no change transitions, as well as different utility and cost values for stages 0-2, stage 3, and more severe stages.
2.	The simplification of a complex disease down to just a small number of health states is concerning as this type of dichotomization or over-categorization of outcomes has been shown to lead to underestimation of treatment effects. Furthermore, this structure also suggests ICER's model does not account nor measure the value of reducing the probability of patients moving from stage F2 to F3, which can offer considerable health gains to patients.	As mentioned above, our model includes specific fibrosis stage transitions (e.g., F2 to F0, F1, F3, or F4), as well as different utility and cost values for stages, by severity.
3.	**ICER's model continues to rely on the discriminatory QALY, which is an inappropriate metric to accurately show health gains for NASH patients.** As PIPC has previously emphasized to ICER, the QALY is a discriminatory metric and has real limitations in measuring true health. The QALY is particularly problematic in measuring the effects of treatments for chronic diseases, which makes it inappropriate for use in evaluating treatments for NASH.	The QALY is a measure of how well a medical treatment improves and lengthens patients' lives, and therefore has served as a fundamental component of cost-effectiveness analyses in the US and around the world for more than 30

		years. In addition, to be responsive to concerns about the QALY, our report incorporates a calculation of equal value life-years gained (evLYG), which evenly measures any gains in length of life, regardless of a treatment's ability to improve patients' quality of life (as described here: https://icerreview.org/material/the-qaly-rewarding-the-carethat-most-improves-patients-lives/).
4.	ICER's model exacerbates the shortcomings of the QALY by discounting the future health gains incorrectly. ICER constructed the model in a way which assumes that all life years 'gained' occur at the end of life. In reality, these gains are a result of a reduced mortality risk – and improved quality of life - in every single year of treatment from the first year of treatment to the final year of life or treatment. This is an important distinction as treatments improve a patient's quality of life consistently over time, allowing them to live more productive and symptom-free lives.	Patients in the model faced a risk of mortality each year, so gains in life years from changes in mortality risk would be captured from treatment initiation over the lifetime horizon of the model. The ability to combine these gains in life years from reduced mortality with "improved quality of life - in every single year of treatment from the first year of treatment to the final year of life or treatment" is the reason we include the QALY in our reports along with estimates of life years gained.
5.	**ICER's report makes incorrect assumptions about liver transplant procedures.** ICER's model assumes when patients need a liver transplant, they get one. But in reality, the waiting list for liver transplants is always longer than the number of available livers in the United States. This means that only a fraction of patients who need a transplant get one. Other studies, such as recent data from the United Network for Organ Sharing (UNOS), suggests this number to be as low as 20% depending on MELD score . Patients with NASH experience additional barriers to receiving liver transplants. One study showed that NASH patients have both the lowest likelihood of receiving a liver transplant while having the highest mortality while on the list, as progression to end stage liver disease is significantly more severe for NASH patients than most patients on the liver transplant waiting list. By not accounting for these factors in the model, ICER is significantly underestimating the value of delaying or averting NASH patients' progression to later stages of disease.	We derived transition probabilities for liver transplants from the 5-year cumulative incidences of liver transplant found in the Thuluvath et al. article on "Waiting List Mortality and Transplant Rates for NASH Cirrhosis When Compared With Cryptogenic, Alcoholic, or AIH Cirrhosis" in Transplantation 2019;103(1):113-121.
6.	**ICER's base case should include societal costs of NASH.** As mentioned previously, NASH is a devastating disease, as symptoms are non-specific and frequently silent. Patients often believe themselves to be healthy until they learn of their diagnosis, at which point the condition has already progressed to severe. The nonmedical costs associated with this diagnosis should be considered in ICER's review. NASH patients often must suddenly withdraw from the workforce due to cardiovascular	We agree that it is important to consider the societal burden of conditions such as NASH. We have consistently reported the societal perspective as a scenario analysis along with base-case results using the health care system perspective,

	events and other complications. This lost productivity has a huge impact on patients' lives and should be reflected accurately in the base case.	as outlined in ICER's Value Assessment Framework.
7.	**ICER incorrectly estimates cardiovascular risk.** ICER's use of prior cardiovascular event as an overarching category for patients is an inappropriate oversimplification of its model. This generalization makes up a considerable proportion of patients suffering from NASH but hides considerable variation in both type of patients and level of risk for both future cardiovascular events and for other prominent comorbidities excluded from the model. The risk of future cardiovascular events for a patient who has suffered a minor event, such as a transitory ischemic attack, is significantly different from the risks associated with a previous myocardial infarction or stroke, and this difference should be accounted for in ICER's model.	This categorization (patients thought of as requiring secondary CV prevention) is used throughout the medical literature.
8.	Another concern is that ICER chose to source data from the Framingham Heart study to estimate cardiovascular risk, as opposed to leveraging real-world data sources. The Framingham risk model has been criticized numerous times as a poor source for real world modeling of outcomes in co-morbid populations as it does not represent the true population of need in the United States. Several national and international clinical and research organizations, including ISPOR, the Royal Society of Medicine , and, most recently, the Second Panel on Cost Effectiveness, have endorsed the use of real-world evidence for baseline risk in the evaluation of new technologies.	We use several different models to categorize risk related to LDL and believe our estimates agree with the medical literature. Of note, the Framingham study generated (and continues to generate) real world evidence.
9.	**ICER's model does not accurately depict the financial impact of this treatment on patients and the healthcare system.** NASH is a disease that not only puts a huge strain on patients, but as mentioned previously, is also very costly to the healthcare system. There are currently no FDA approved treatments for NASH, and the treatments and comorbidities that accompany the disease as it progresses are expensive to treat. The Global Liver Institute and American Gastroenterological Association highlighted this to ICER in their initial comments, stating, "The rise of NASH, its complications and comorbidities carry significant economic costs for health systems and society. The efficacy and side effects of [obeticholic acid] or any other pharmacologic intervention should be evaluated against the cost of disease progression and cost as well as efficacy of current standard of care (weight loss)." With this in mind, it is absolutely necessary that ICER's model should strive to accurately depict the economic value a treatment for NASH would have to the healthcare system.	We agree that it is important to describe the financial impact of treatments, and believe that our model does this as accurately as possible given available evidence on new treatments and current standard care, accounting for the efficacy of each and their impact on disease progression and associated costs.
10.	In order to capture the accurate financial picture, ICER should have used dynamic pricing. The relevance of dynamic pricing is heightened where benefits are accrued over a longer time period, like lifetime models. The NASH model is a lifetime simulation model, where patients live up to another 15-20 years after initiating treatment. This means patients will continue to accrue benefits and the health system will save costs on other interventions they may have needed for this entire duration of time.	In concert with best practices at international HTA agencies and with the great preponderance of academic work in health economics, ICER's cost-effectiveness analyses do not routinely make estimates of price changes across comparator treatments linked to patent and exclusivity time horizons, given the unpredictability of these changes in the US health care market.

11.	Additionally, the uptake of new therapies happens slowly over time. Numerous studies have shown that while using static pricing may make sense for short-term cost-effectiveness modeling, it is not appropriate when developing lifetime models. To assume that the cost of any treatment indicated for NASH will be the same in ten or twenty years from current prices, is highly unlikely. The price pattern for most drugs has seen significant decline after 5-7 years of relative stability, on average resulting in a price close to 10-20% of its launch price after ten years. More accurate cost modeling must be considered in order to paint a true picture of a treatments impact on patients and society.	Rates of uptake would not influence our estimates of cost-effectiveness per patient treated. Attempts to model price changes over time would be speculative in the US market, where changes in prices occur relatively frequently and are difficult to predict. The entry and timing of competitors in the future is uncertain, and while prices for specific branded drugs may decrease as competing drugs come to market, they also may increase over time, sometimes repeatedly.