Resmetirom and Obeticholic Acid for Non-Alcoholic Steatohepatitis (NASH)
Response to Public Comments on Draft Evidence Report

April 13, 2023

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#	Comment	Response
Manufacturers		
Intercept		
1.	Nonalcoholic steatohepatitis (NASH) is a serious progressive liver disease caused by excessive fat accumulation in the liver that induces chronic inflammation, resulting in progressive fibrosis (scarring) that can lead to cirrhosis, eventual liver failure, cancer and death. Advanced fibrosis is associated with a substantially higher risk of liver-related morbidity and mortality in patients with NASH. The risk of liver-related morbidity and mortality increases as fibrosis progresses, and **patients with advanced fibrosis are at the greatest risk of liver-related mortality** [1-4]. Because of the significant morbidity and mortality risk associated with advanced fibrosis due to NASH, there is an urgent need to treat these patients prior to their progression to cirrhosis.	Thank you for these comments.
2.	There are currently no medications approved for the treatment of NASH, and we strongly believe OCA, if approved, will play an important role in addressing an unmet clinical need. The safety and efficacy of OCA in pre-cirrhotic liver fibrosis due to NASH is supported by a robust body of evidence from the OCA NASH clinical development program, including two positive 18-month interim analyses from the pivotal Phase 3 study REGENERATE and a robust safety assessment of 2,477 patients, with nearly 1,000 on study drug for at least four years.	
3.	OCA has demonstrated a strong and confirmed antifibrotic effect in two interim analyses of REGENERATE. The most recent interim analysis of REGENERATE, presented at NASH-TAG in January 2023 [5] and AASLD in November 2022 [6], showed an improvement of liver fibrosis in 37.3% of patients treated with OCA versus 19.8% of patients treated with placebo with available baseline and month 18 liver biopsies. The OCA 25 mg response rate was double that of placebo for the regulatory primary endpoint of fibrosis improvement by ≥1 stage without worsening of NASH. Further, a higher responder rate was observed in patients with advanced fibrosis without cirrhosis (F3) at baseline who were treated with OCA 25 mg. Reductions in alanine aminotransferase (ALT) and liver stiffness with OCA 25 mg were observed in patients with no change in fibrosis on histology. Dose-	

	dependent reductions in ALT and liver stiffness were observed in OCA-treated patients out to 4 years.	
4.	In addition to this efficacy data, the safety profile of OCA is based on a robust safety assessment including more than 8,000 patient-years and ~1,000 patients with long-term exposure of at least 4 years. Our safety database is the largest in the NASH field, with the longest duration of patient exposure and shows a well-characterized safety and tolerability profile that supports the potential chronic administration of OCA.	
5.	In summary, we believe OCA's confirmed antifibrotic effect and robust safety profile supports a positive benefit:risk for the treatment of patients with pre-cirrhotic liver fibrosis due to NASH. Importantly, the Phase 3 study REGENERATE is ongoing and expected to continue while collecting data on the incidence of clinical outcomes for verification and description of clinical benefit. The end-of-study primary endpoint will compare the impact of treatment (placebo, OCA 10 mg or OCA 25 mg daily) on all-cause mortality and liver-related clinical outcomes, as well as on long-term safety.	
6.	In January 2023, the U.S. Food and Drug Administration (FDA) accepted Intercept's New Drug Application (NDA) for OCA in pre-cirrhotic liver fibrosis due to NASH. FDA has assigned a Prescription Drug User Fee Act (PDUFA) target action date of June 22, 2023, for the application, and we look forward to continuing our work with the FDA over the coming months as they review our NDA.	
Madrigal		
1.	Madrigal Recommends Patient Preferences Continue to Inform ICER's Value Assessment The consequences of NASH progression can be devastating for patients and their families, especially when a diagnosis comes too late. Madrigal appreciates ICER's efforts to capture patient input on the burden of the disease. There is an additional opportunity for published evidence examining patient treatment preferences to inform ICER's value assessment. In one study using accepted scientific methodologies for evaluating stated and unstated preferences for NASH treatments in an unbiased manner, NASH patients were asked to evaluate desired treatment effects of hypothetical products. "Improvement in their liver" (including the removal of liver fat and inflammation or	We thank Madrigal for their comment. While NASH resolution is important, fibrosis is the primary driver of disease progression and therefore the focus of our model. This structure has been used in many prior models in NASH, including Madrigal's own economic assessment, and has been the clinical pathway in models evaluated in other Health Technology Assessments. Furthermore, we do not have trial level data and utility inputs to inform NASH resolution states.

	NASH resolution) and fibrosis improvement were among the highest rated patient preferences for desired NASH treatment benefits. Resmetirom addresses both fibrosis changes, currently captured in ICER's model structure, and NASH resolution, not captured in ICER's model. Given the relevance of NASH resolution to patients, this treatment effect should be explicitly modeled in ICER's value assessment. Published examples of this approach are available, as shown in Chhatwal et al. A revised model structure, including both fibrosis and NASH resolution, will more accurately reflect patient-relevant endpoints.	
2.	Madrigal Recommends ICER Continue to Focus on atherogenic lipid Improvements We thank ICER for carefully considering the improvements in atherogenic lipids (e.g., LDLc) observed in our Phase 3 study. Given that cardiovascular disease is the leading cause of death in patients with NASH, we believe it is critical to consider potential measures of cardiovascular risk when assessing investigational medications for NASH. The FDA stated that NASH medications "should not worsen comorbidities, including cardiovascular disease, hyperlipidemia, metabolic disease, and diabetes, or cause liver injury." One recently published cost-effectiveness analysis specifically evaluated LDLc changes and compared resmetirom, OCA, and placebo; lifetime CVD event risks were 46.67%, 61.97%, and 60.28%, respectively. Per patient costs of CVD events were decreased by $5,785 with resmetirom and increased by $719 with OCA. Net monetary benefits of $21,029 and -$14,264 for CVD events were estimated for resmetirom and OCA, respectively.	Thank you for this suggestion.
3.	Madrigal Recommends ICER Recognize NASH as a Progressive Disease NASH is a progressive disease that can lead to liver failure, hepatocellular carcinoma and premature mortality. Although expected to increase further, NASH-related cirrhosis is already the leading indication for liver transplantation in women and those over 65 years of age and is on par with alcoholic liver disease as the leading indication overall. Rates of fibrosis progression can vary in patients with NASH and further research is needed to establish a more precise understanding of the natural history of the disease. We caution ICER to avoid overreliance on data from the placebo	Thank you for the comment. We certainly agree and our model captures net progression in liver disease over time including the development of cirrhosis, HCC, and death. We also agree with prioritizing patients with F2 and higher fibrosis for treatment: hence our explicit definition of these patients as the population of interest in our draft scope, final scope, and our draft report.

	arms of historical biopsy-based clinical trials when making assumptions about disease progression in NASH. The observation that many patients with early NASH do not progress to liver-related outcomes is not a justification for complacency and instead underscores the importance of careful risk-stratification. The recently published treatment guidance from the American Association for the Study of the Liver (AASLD) recommends prioritizing "at-risk" patients – those with metabolic comorbidities and F2 fibrosis or higher – for treatment because they have a demonstrably higher risk of liver-related morbidity and mortality.	
4.	Madrigal Recommends Opportunities for ICER to Enhance its Cost-Effectiveness Model <u>Future enhancement with Phase 3 data</u>: ICER's modeled results are likely to be further validated based on the full Phase 3 results from the MAESTRO-NASH trial, which may also capture additional benefits of resmetirom. In the MAESTRO-NASH trial, resmetirom helped patients achieve both NASH resolution and fibrosis improvement, two liver histological improvement endpoints that FDA proposed as reasonably likely to predict clinical benefit. Study integrity considerations and the timeline for ICER's value assessment have limited Madrigal's ability to provide ICER with additional data from MAESTRO-NASH, which read out topline results in December of 2022. While we understand the approach ICER used to account for the currently unavailable Phase 3 data, a more robust cost-effectiveness model using the broader Phase 3 dataset, including patient-reported outcomes, would have greater utility. Madrigal intends to continue to collaborate with ICER and share additional MAESTRO-NASH data once available, but notes that this is unlikely to occur during the current review window. Two key fibrosis change variables in ICER's model, (1) stable fibrosis and (2) worsened fibrosis, were based on weighted averages from a Phase 2 study of resmetirom. Additionally, the fibrosis improvement data used by ICER was from a Phase 3 composite endpoint ("≥1-stage reduction in fibrosis with no worsening of NAFLD Activity Score"). The reported Phase 2 fibrosis data are histologic evidence from paired biopsies performed at baseline and at 36 weeks. The Phase 3 evidence, when available, should be used to provide more robust estimates of treatment effect at 52 weeks; it includes	We appreciate the comment regarding the costs used in the model and the suggestion of a newer study. However, the study that is mentioned uses a measure (FIB-4) that is not readily usable given publicly available data. We welcome the manufacturer to provide data that would allow us to implement a FIB-4 based costing approach. On a similar note, we have decided to use updated costs from the GAIN study for early and advanced fibrosis.

	a much larger cohort of patients treated with higher doses of resmetirom. <u>Current enhancement with updated costs of care and PDFF information</u>: Beyond inclusion of additional resmetirom Phase 3 data, costs of care should be refreshed in the current cost-effectiveness model to avoid reliance on outdated data that underestimates the burden of the disease. The draft model currently utilizes costs from an analysis incorporating studies from up to 10 years ago. A more contemporary dataset that would be more appropriate for ICER's NASH model could be derived from a recent retrospective cohort study that provides an annual cost of NASH care in the US based on a patient's initial fibrosis stage. Importantly, ICER's report includes an inaccurate statement indicating that the resmetirom Phase 2 data is based on proton density fat fraction (PDFF) response. The evidence used in the ICER report, in the cited phase 2 resmetirom paper and in the cited published economic model is based on histology results from paired biopsies at 36 weeks that were further categorized by PDFF response. We encourage ICER to correct this in the Evidence Report.	
5.	Madrigal Recommends ICER Revise its Modeled Discontinuation Rate for Resmetirom ICER's current draft model overestimates the discontinuation rate of resmetirom, resulting in an underestimate of clinical benefit. Current treatment evidence suggests most patient who discontinue resmetirom do so within two months of treatment initiation, but ICER's model assumes a constant discontinuation rate (based on Phase 2 data at 36 weeks) that accumulates annually for the entire horizon modeled. In contrast to ICER's modeling of discontinuation rates for OCA, ICER assumes that a majority of patients treated with resmetirom would discontinue. This is shown in the results section of ICER's report and estimates that by year 5 only 39% remain on resmetirom, while 66% remain on OCA. Given the tolerability profiles of the two medications, the higher proportion of patients discontinuing resmetirom in ICER's model does not seem clinically plausible. Conversely, if an annual adherence rate of 83% was instead applied only to the first year, the estimated QALY for resmetirom could be doubled. In sum, ICER should adjust its model by using a	We appreciate the comment regarding the discontinuation rate used for resmetirom. ICER recently received Academic in Confidence data from Madrigal on early versus late discontinuation. Given that the available Phase 2 data is for a relatively short duration (36 weeks) and in a small sample of patients, we will keep our base case analysis that assumes a consistent annual discontinuation probability based on the 36 weeks of the Phase II trial. We will use the Academic in Confidence data as a scenario analysis, where the full 36 week discontinuation will be used for year one and late discontinuation data (Weeks 12-36) will be used for years two onwards. Regarding OCA's discontinuation rate, upon further review, we have revised this rate.

	more clinically feasible annual discontinuation rate for resmetirom and not a cumulative discontinuation rate.	
6.	Madrigal Recommends ICER Use More Rigorous Comparative Methodologies ICER's comparative methodologies could be improved by using more rigorous approaches for comparing treatments recommended by the Academy of Managed Care Pharmacy (AMCP) or the Professional Society for Health Economics and Outcomes Research (ISPOR). In the absence of a Phase 3 head-to-head trial - the gold standard for comparing treatments - evidence-based comparative methods should be employed for evaluating OCA and resmetirom. Specifically, a network meta-analysis or matched adjusted treatment comparison study would be better suited for making comparisons between the two medications, which is the best practice outlined by the AMCP and ISPOR, two leading authorities on healthcare payer-related economic evaluations. Therefore, we suggest clarifying this was a naïve or unanchored comparison methodology that was used in comparing OCA and resmetirom on Page 11 of ICER's report. Additionally, the limitations of this methodology should be noted in ICER's report.	As Madrigal suggested in our early discussions with them, the patient populations for the obeticholic acid and resmetirom studies differed sufficiently to preclude the use of a network meta-analysis and there are insufficient data available to allow for matched treatment comparisons (see paragraph three under uncertainties and controversies). Throughout the report, we intentionally kept analyses of obeticholic acid and resmetirom separate from each other and avoided statements comparing the two drugs. On page 11 of the Draft Report (ES2) there are no statements directly comparing the two drugs. The same is true on page 11 of the main report section of the Draft Report. In fact, at the bottom of page 11 we describe why indirect comparisons are inappropriate.
7.	Madrigal Recommends that ICER's Budget Impact Prediction Reflect the Real World Population for Treatment ICER's budget impact model overestimates the size of the likely treated population and rate of adoption for resmetirom. In its Value Assessment Framework, ICER notes that its budget impact predictions "are explicitly not meant to represent our assumptions of the budget impact of new interventions that are most likely in the real world," but any budget impact prediction for resmetirom should use realistic assumptions about the likely treated population and rate of adoption. Healthcare decision-makers focused on the potential budget impact of resmetirom should consider these key facts: 1. Resmetirom is not intended for all patients with nonalcoholic fatty liver disease (NAFLD) or NASH. Resmetirom is intended for patients with "at-risk" NASH (consistent with the Population in the PICOTS for this review), who are at higher risk of progressing to cirrhosis and its complications. Lifestyle intervention and co-morbidity management is an appropriate treatment strategy for patients with NAFLD or early NASH.	The intent of ICER's potential budget impact assessment is to serve as a policy trigger for health care payers and others when the potential budget impact of a new intervention is likely to be large. We estimated the size of the potential patient population based on a subset of patients with NASH (i.e., those with moderate and severe fibrosis). This subset of patients aligns with the anticipated indication for OCA and resmetirom and was the focus of ICER's clinical and cost-effectiveness analysis. The text in Section 7.1 of the ICER report has been revised for clarity. We would also like to emphasize that our estimate for the potential eligible population is intended to capture all patients who are considered eligible for the new treatment(s) regardless of the potential for underdiagnosis.

	2. Although at-risk NASH is a prevalent disease, low diagnosis rates will limit the initial uptake of new therapies. Madrigal estimates that approximately one million patients with NASH have been identified with ICD-10 codes in the U.S. Only a subset of these patients – those with at-risk NASH – would be candidates for resmetirom, if approved. Madrigal's field force will not be promoting resmetirom in the primary care setting. Madrigal's launch plan for resmetirom focuses on approximately 15,000 – 20,000 hepatologists, Oh oagastroenterologists and endocrinologists (and their affiliated advanced practice providers) who manage patients with NASH in the U.S.	
8.	Madrigal Recommends that Future Cost-Effectiveness Modeling in NASH Incorporate Noninvasive Tests (NITs) Given that biopsy is rarely performed outside of the clinical trial setting, future cost-effectiveness modeling in NASH should begin to incorporate the noninvasive measures of fibrosis and disease activity that are used to manage patients in real world clinical practice. The ordinal staging systems used to classify and measure NASH severity in histology trials create an incomplete picture of treatment response that NITs can help address. For example, a patient, who does not achieve a full 1-stage improvement in fibrosis at 52 weeks, may experience clinically meaningful improvements in NITs or other important measures of response. The Phase 3 MAESTRO trials of resmetirom are designed to generate a wealth of data to correlate changes in NITs with biopsy results and, ultimately, long-term outcomes.	We appreciate the comments regarding the use of NITs. However, the efficacy measures used in our model were based off of the available trials which used liver biopsy. If data become available which provide further insight on the use of NIT, we will consider their inclusion. However, we do note that prior analyses that evaluated the use of NIT for diagnosis (not monitoring) estimated negative impacts on outcomes due to misclassification.
9.	Madrigal Recommends that ICER Further Consider the Impact of NASH Treatment on Health Equity Madrigal believes improving care for patients with at-risk NASH will help improve health equity in the U.S., though access to pharmaceutical treatment is only one component of the larger public health response needed to support patients from underserved communities. Health inequity is a meaningful driver of NASH risk and adverse outcomes. Food insecurity is believed to play a role in the higher prevalence of advanced fibrosis among patient populations facing socioeconomic disadvantages. Additionally, patients with lower socioeconomic status have higher rates of liver cancer	Thank you for your comment. We have added details to the health equity section, but it is complex. A recent (2022) analysis of US data found that Caucasian people had a significant 42% higher overall prevalence of NASH, but all non-Caucasian people were combined. In other analyses Hispanics have a higher prevalence of NASH, while Black people have a lower prevalence of NASH. A separate analysis published in 2022 found no association between income and NASH in the US, but a significant decrease in NASH with higher levels of education.

	and an increased risk of dying on the waitlist for liver transplantation. NASH prevalence is higher in the Hispanic community and disease onset appears to occur at an earlier age in Hispanic patients. We thank ICER for acknowledging that Hispanic patients are well-represented in the Phase 3 MAESTRO-NASH trial of resmetirom. Improving racial diversity in NASH clinical research is a critical challenge for the field.	There are other disparities that arise in the care of patients with NASH. In particular, it is more challenging for low-income patients to access needed liver transplantations due to the need for time off of work, travel to transplant centers, and the support required to qualify for the transplant list. An oral therapy that prevents the need for transplant and is available to all patients may decrease disparities in long term outcomes. However, these new therapies must be priced at a level to allow for access to all patients.
10.	Madrigal is Committed to Future Clinical and Health Economic Research Madrigal intends to continue conducting and publishing health economics outcomes research examining the burden of NASH and the value resmetirom will bring to patients, healthcare providers and payers, if approved. When the data are available, we intend to publish an updated cost-effectiveness model with detailed results from the MAESTRO-NASH trial, which will also be shared with ICER, other modeling, and additional studies characterizing the real-world NASH patient population using NITs.	Thank you for this information. We look forward to reviewing your publication, once published.
Merck		
1.	On October 26th, 2022, we provided comments to the draft scoping document which included the following recommendations with its justification: a) To compare the natural history based on the early meta-analysis [1] that is being used in the ICER model versus recent trial data from the placebo arms of recent trials [2, 3] to assess which is a better representation of the baseline disease progression. b) To make fibrosis progression an independent parameter in the ICER CE model, with point estimates and uncertainty directly sourced from the trials. We would urge the ICER team to reconsider these comments along with the rationale as this report is finalized.	We thank Merck for these comments and for the draft scoping document. Regarding the use of the meta-analysis or placebo arms for baseline disease progression, we are in agreement of using the placebo arms of the trial data to model progression rates. The meta-analysis is not used for progression rates, but to inform progression weights. Regarding making fibrosis progression an independent parameter, we are in agreement and the current model uses progression as an independent parameter and is sourced directly from the trials.
2.	In addition to these two prior comments, we would like to provide additional comments on the draft evidence report released on February 16th, 2023. There are a few additional issues that we would like to note that are related to the cost	Thank you for bringing this to our attention. We have fixed this error in the revised version of the report.

	inputs presented in the section 'Cost inputs – non-drug costs': 1. Incorrect reference The costs for each fibrosis stage are based on the study by Younossi et al 2019. However, the corresponding reference #36 (Sayiner et al 2017) in the draft report seems to be incorrect: Sayiner M, Otgonsuren M, Cable R, et al. Variables Associated With Inpatient and Outpatient Resource Utilization Among Medicare Beneficiaries With Nonalcoholic Fatty Liver Disease With or Without Cirrhosis. J Clin Gastroenterol. 2017;51(3):254-260. The reference could be: Younossi ZM, Tampi R, Priyadarshini M, Nader F, Younossi IM, Racila A. Burden of Illness and Economic Model for Patients With Nonalcoholic Steatohepatitis in the United States. Hepatology. 2019 Recommendation*:* To update the reference.	
3.	Possibility of underestimation of annual costs in NASH patients with fibrosis stages F0-2 and F3 The GAIN study [4] indicated that the direct NASH-related resource use could be higher than that reported by Younossi et al., 2019. The GAIN study included procedures, treatment costs, surgery, consultation, and hospitalization for direct NASH-related resource use, which were obtained from the Medicaid NADAC database, Centre for Medicare and Medicaid Service, Physician Fee Schedule, and the American Medical Association. The study by Younossi et al. 2019 included primarily consultation, and blood/imaging tests for F0-F3, which were obtained from the Center for Medicare and Medicaid Services Fee Schedule 2017 and published data. The differences in annual NASH-related costs could be due to differences in included costs and/or cost data. After currency conversion, the GAIN study [4] estimated that the annual NASH-related cost for early stages (F0-2) is approximately $2300 and approximately $4200 for F3 while Younossi et al., 2019 (Table 2) estimated the annual NASH-related costs for early stages (F0-2) is $431 and $531 for F3 patients. Therefore, the F0-2 and F3 annual NASH-related costs in the US may be significantly higher than those in the ICER report. In addition, although F0-2 are bundled into the 'early stage' category and assigned with the same cost, a higher F stage may be associated with higher NASH-related cost. A recent study by Geier et al. [5] suggests	We appreciate this comment. We have decided to use the costs from the GAIN study for the fibrosis states. We have decided not to separate costs in the early stage category based on the figure provided, as it is not clear that utilization of services are significantly different between F0-2 and there is not a monotonic increase in utilization as severity increases.

	that the higher F stage is associated with higher numbers of certain tests and procedures (see Figure 1 cited from [5]). Recommendation*:* To consider using additional sources for annual cost data for NASH-related resource use for F0-F3 and to split costs for F0-2 based on the fibrosis stage to reflect the different levels of resource use.	

#	Comment	Response
Patient/Patient Groups		
American Liver Foundation		
1.	In the "Uncertainty and Controversies" section, ICER's draft report indicates that NASH is typically asymptomatic for most of its clinical course and refers to NASH as a condition that may never become symptomatic. While it is correct that progression will not occur in all patients diagnosed with NASH, we feel that the draft report insufficiently takes into consideration the large population living with NASH and the fact that up to 20-25% of adults with NASH may have or will develop cirrhosis. As such, NASH is one of the leading causes of cirrhosis in adults in the United States and is expected to become the leading cause of liver transplantation in the United States in the next two years.	Thank you for your comment. Many patients who we spoke with highlighted the fact that they were asymptomatic until late in the disease course of NASH and your website calls NAFLD and NASH "silent liver diseases." We agree that NASH is an important public health problem in the US due to its high prevalence and serious consequences. Indeed, we cited evidence that NASH is already the leading cause of liver transplantation in the US in the last sentence of the second paragraph of the Background: "NASH has become a major cause of cirrhosis and, as effective treatment of hepatitis C is now available, it has become the leading reason for liver transplantation."[1] Our budget impact analyses reflect the large population of patients living with NASH. This analysis highlights the fact that only a small proportion of patients with NASH and moderate or severe fibrosis can be treated without triggering affordability issues for payers. The large number of patients needing treatment and thus the large potential budget impact is one of the key messages from our report.
2.	We appreciate that the draft report includes a "Patient and Caregiver Perspectives" section. Our many interactions with patients, caregivers and medical professional confirms the report's perspective that halting the progression of fibrosis would be the most important outcome for patients with NASH, as well as the willingness of NASH patients to tolerate side effects of effective therapy to prevent progression of their disease. However, we feel that this patient voice is not reflected in other sections of the report and overall assessment in the ICER draft report.	We are glad to have accurately captured the most meaningful outcome for patients within the Patient and Caregiver Perspectives section. This patient-important outcome is also reflected in the summary of our clinical analysis (pg. 13-14). We look forward to patient testimony and participation at the public meeting and plan to further highlight the patient voice in our Contextual Considerations (Chapter 5) as

		well as our Key Policy Recommendations (Chapter 8) of the Final Report.
3.	The draft report did not identify any potential benefits regarding "Society's goal of reducing health inequities". We would like to point out that in the United States, NAFLD and NASH disproportionately affects communities of color and communities underserved by the health system. Thus, we feel that the draft report should address the possibility that the availability of oral medications leading to improvement in fibrosis or NASH resolution could provide potential benefits in reducing health inequities especially if drug costs are lower.	Thank you and we agree with your comment that if the drugs are fairly priced, they have the potential to reduce disparities. However, the epidemiology of NASH disparities is complex. Please see our response to Madrigal's comment number 9 above and our additions to the health equity section.
4.	Finally, regarding both the incidence and diagnosis of the disease, we would like to make ICER aware of ALF's Think Liver Think Life national public health campaign that aims to ensure that every American understands their risk for liver disease, receives the appropriate diagnostic testing and care coordination, and feels well-informed and supported throughout their journey living with liver disease. Preliminary data from our program screenings of at-risk adults in Alabama and nine other states, indicates that more than 60% of those screened have some form of NALFD or fatty liver disease. While it would be premature to include these results in ICER's report, we believe that our campaign will significantly contribute to the future landscape of NAFLD and NASH epidemiology and highlight the need of patients and caregivers affected by these diseases.	Thank you for sharing this helpful resource.
Fatty Liver Foundation		
1.	Incorporating SDOH for a Holistic NASH Cost-Effectiveness Assessment We appreciate the attention that ICER has given to evaluating the cost-effectiveness of OCA and resmetirom. While ICER's cost-effectiveness methodology offers valuable insights for evaluating the clinical and economic aspects of interventions, it may not fully capture the broader context of social determinants of health (SDOH) faced by NASH patients. Health disparities arising from factors such as income, education, and access to healthcare can lead to varying outcomes among different patient populations. By not accounting for these disparities, the cost-effectiveness analyses may not accurately reflect the benefits and outcomes for diverse NASH patient groups. Accessibility, affordability, and treatment adherence can also be influenced by SDOH. The cost-effectiveness analyses often focus on average costs and outcomes, but they may not capture potential barriers to accessing or affording new treatments faced by patients due to socioeconomic factors. Moreover, factors like transportation, time constraints, or	Thank you for your comment. We have added details to the health equity section, but it is complex issue. A recent (2022) analysis of US data found that Caucasian people had a significant 42% higher overall prevalence of NASH, but all non-Caucasian people were combined. In other analyses Hispanic people have a higher prevalence of NASH, while Black people have a lower prevalence of NASH. A separate analysis published in 2022 found no association between income and NASH in the US, but a significant decrease in NASH with higher levels of education. There are other disparities that arise in the care of patients with NASH. In particular, it is more challenging for low-income patients to access needed liver transplantations due to the need for time off of work, travel to transplant centers, and the support required

	cultural beliefs can affect a patient's ability to follow prescribed therapies, which may result in an over- or underestimation of the real-world impact of new treatments on the overall health of NASH patients. To provide a more holistic and patient-centered assessment, it is crucial to incorporate SDOH into the evaluation of cost-effectiveness for NASH treatments. Incorporating these factors can help ensure that the unique needs and challenges faced by different patient populations are considered, leading to more targeted interventions, policies and resource allocation to address the specific needs of various NASH patient groups.	to qualify for the transplant list. An oral therapy that prevents the need for transplant and is available to all patients may decrease disparities in long term outcomes. However, these new therapies must be priced at a level to allow for access to all patients.
2.	Factoring Patient Diversity into Cost-Effectiveness Models The ICER model's assumptions of uniform treatment effects for "improvement" and "worsening" across all fibrosis stages may not fully capture the diverse experiences of NASH patients. The comparison between the improvement in fibrosis with and without NASH worsening may not accurately represent the real-world outcomes, potentially leading to an imprecise estimation of the long-term cost-effectiveness of OCA and resmetirom. The model overlooks the effects of diabetes, a common comorbidity among NASH patients, which is crucial to assess the accuracy of long-term cost-effectiveness estimates. The emphasis on cost-effectiveness in the model might not reflect the complex risk-benefit trade-offs that NASH patients with fibrosis encounter when considering these drugs. Patients' individual circumstances and risk tolerance play a significant role in how they perceive the potential benefits and risks associated with the treatments. A more patient-centered evaluation should incorporate these perspectives to provide a comprehensive understanding of the drugs' overall impact.	We acknowledge that every patient will experience drugs and effects differently. The intent of a disease model is to evaluate population level effects and to inform decision making at the population level.
3.	Navigating the Complexities of NASH SOC and Emerging Treatments We believe there are significant limitations in ICER's assumptions that resmetirom and OCA will be added to the standard of care (SOC) without displacing any existing SOC treatments in the eligible NASH population, potentially impacting the accuracy of cost-effectiveness evaluations for these new pharmacotherapies. NASH is a heterogeneous disease, and the assumption that new treatment will simply be added to SOC may not accurately represent real-world treatment scenarios, as some patients may benefit more	We appreciate this comment and agree individual patients may use and be prescribed treatments differently. As previously mentioned, our goal was to model population level effects. We have already included specific components that the comment mentions such as adherence to the model.

	from switching to the new treatment entirely or a combination of therapies. Currently, SOC mainly consists of lifestyle modifications and management of comorbidities[5], making the comparison between SOC and new treatments challenging. Patient adherence and individual responses to the new treatments can vary greatly, which could lead to over- or underestimation of cost-effectiveness when assuming a simple addition to SOC. With multiple NASH pharmacotherapies in development[6], the rapidly evolving treatment landscape might not be captured by the assumption of simply adding new treatments to SOC. This may not reflect real-world treatment patterns, where clinicians might opt for a more personalized approach based on patient characteristics, preferences, or other factors, potentially resulting in a different cost-effectiveness profile. By assuming no SOC treatments would be displaced with the entrance of new treatments, ICER may not capture potential cost savings and changes in resource utilization that could result from patients shifting to new therapies. This assumption could lead to an overestimation of the incremental cost associated with new treatments.	
4.	Real-World Societal Costs of NASH The GAIN study provides valuable insights into the cost landscape for NASH patients across the U.S. and EU5 countries[7], but in our view, ICER's assessment of annual societal costs using this data has limitations that may impact its conclusions. Firstly, the reliance on self-reported data for resource use and cost estimation could lead to recall bias by survey respondents, affecting the accuracy of the assessment and potentially misrepresenting the true burden faced by NASH patients and their families. Secondly, the differences in diagnostic practices between the U.S. and the EU5 countries, as observed in the GAIN study, may influence the cost estimates and make direct comparisons challenging. Another concern is that the GAIN study did not measure tangible costs, such as pain, suffering, and decreased quality of life, which significantly contribute to the overall burden experienced by NASH patients. Including these tangible costs would provide a more comprehensive assessment of the societal impact of NASH	We agree that there are differences in diagnostic practices. We have used US-specific estimates from the GAIN study. Intangible costs are difficult to measure, and we are not aware of any sources or data to include these in our model. We do incorporate quality of life in our model as part of the QALY calculation. We agree that while heterogeneity is important, the purpose of our cost-effectiveness analysis is to provide a population-level estimate of the value of medical interventions. The epidemiology of NASH disparities is complex. It is challenging to predict whether the availability of these new therapies will improve health equity. Please see our response to Madrigal's comment number 9 above and our additions to the health equity section for more details.

	and highlight the need for more effective interventions to improve patients' quality of life. Lastly, the ICER's method may not fully account for the heterogeneity of NASH and its differential impact on various demographic groups, such as race, ethnicity, socioeconomic status, and geographic location. We would encourage an approach that considers health equity and the long-term health consequences of NASH including progression to cirrhosis, liver failure, and hepatocellular carcinoma, to better inform policy decisions and resource allocation for the benefit of all NASH patients.	
5.	In conclusion, we understand that the cost-effectiveness of OCA and resmetirom depends on their pricing and that the short-term budget impact of newly approved treatments could be a concern. However, we believe that addressing the unmet needs of NASH patients should remain a priority, and we support the ongoing exploration of innovative therapies that can improve the quality of life for those living with NASH and fibrosis. By considering the diverse experiences, comorbidities, and SDOH that affect NASH patients, we can strive for a more inclusive and accurate assessment of cost-effectiveness and overall impact of emerging therapies. Incorporating patient perspectives and real-world societal costs is crucial to ensure that interventions and resource allocations are tailored to the unique needs of various NASH groups. As patients and patient advocates, we urge decision makers to prioritize a holistic approach that considers health equity and the long-term health consequences of NASH, ultimately improving the lives of those affected by this complex and often misunderstood condition.	Thank you for this comment.
Global Liver Institute		
1.	Methods to describe NASH incorrectly represent the disease as having no progression, when NASH is a progressive disease by definition with patients at high risk of cirrhosis, liver cancer, and organ failure. We strongly disagree with the repeated assertion that NAFLD and NASH are not progressive diseases. NASH is a chronic, progressive, and prevalent disease with patients at-risk for cirrhosis, decompensated liver failure, hepatocellular carcinoma, liver transplantation, and death, as cited repeatedly in this draft report. ICER risks incorrectly assessing the value of the study drugs on patient outcomes when assuming that NASH does not progress. Prevention of	Thank you for the comment. However, we think that you are misreading our review. As described above, we cited evidence that NASH is already the leading cause of liver transplantation in the US in the last sentence of the second paragraph of the Background: "NASH has become a major cause of cirrhosis and, as effective treatment of hepatitis C is now available, it has become the leading reason for liver transplantation.[1]" We also highlight the prevalence of the disease in the background section.

	disease progression significantly impacts patient quality of life and leads to improved health outcomes. The draft report also presumes that someone in need of a liver transplant is able to acquire a successful transplant. Unfortunately, the number of patients waiting for new livers has been and is larger than available donor livers. Only a fraction of liver patients on the list for a liver transplant have a liver available and receive that transplant. NASH patients have the lowest likelihood of receiving a liver transplant while also having the highest mortality while waiting. Thus, as a progressive disease, the progression to end-stage liver disease is significantly more severe for NASH patients than others on the transplant waiting list. Without factoring this into the model, any results will underestimate the value of delaying NASH patients' progression to later stages of the disease and devalue the potential positive impact of the study drugs. We request ICER revise this to accurately reflect NASH as a chronic, progressive, and prevalent disease so that impact of the study drugs may be better assessed.	The entire premise for our review and the core of the economic model is that NASH, on average, is a progressive disease. The benefits of the drugs in the model come from the prevention of progression to cirrhosis and its consequences (HCC, transplant, decompensation, hospitalization, hepatic encephalopathy, and poor quality of life). We agree that the supply of livers is a bottleneck in liver transplantation. However, this issue applies equally to those receiving new therapies and those receiving the standard of care in the model, so that the incremental differences are minimized. We have added text to the health equity section highlighting greater challenges faced by patients with fewer resources in accessing liver transplantation. We also noted that new therapies that reduce the risk for end stage liver disease, if available equitably, may help to reduce this health disparity. Finally, as noted earlier, our budget impact analyses reflect the large population of patients living with NASH. This analysis highlights the fact that only a small proportion of patients with NASH and moderate or severe fibrosis can be treated without triggering affordability issues for payers. There is an enormous number of patients potentially needing treatment and thus the large potential budget impact is one of the key messages from our report.
2.	ICER should work closely with NASH patients and providers to incorporate their perspectives and lived experiences at all levels. We commend ICER for its discussion of the patient and caregiver perspective at the beginning of this report. However, caregivers should also be more thoroughly incorporated into the ICER review model. Caregivers for those with liver disease often show a lower quality of life, higher levels of anxiety, and face a higher economic burden than non-caregivers. Answers from caregivers on a	We appreciate the comment. As part of the scoping phase of our analysis, we worked closely with NASH patients, providers, and patient groups to incorporate their perspectives. We will continue to work with them, and they will be part of the review process at the public meeting.

	questionnaire designed to measure depression also suggested that 34% of caregivers suffered from clinical depression. As stated above, ICER incorrectly presumes certain aspects of NASH. This leads to an underestimation of the importance of treatment and a flawed model for evaluation. Mistakenly, ICER asserts that NASH is not a progressive disease and that NASH patients who are asymptomatic are not impacted by the disease. Neither of these assertions is accurate or consistent with patient experience. Often symptoms are masked by other conditions such as diabetes, obesity, or metabolic syndrome. Despite patients not experiencing externalized symptoms, the cell damage that occurs with NASH, even while patients may be otherwise asymptomatic, can lead to cirrhosis. Once a patient has progressed to cirrhosis, if not treated, cirrhosis can lead to liver failure.	
3.	ICER should reconsider biopsy as the diagnostic standard for its model and instead include alternative noninvasive diagnostics, especially as it relates to cost. Liver biopsy is a risky, invasive procedure that is often subject to sampling variability. As such, it should be a diagnostic test of last resort. Liver biopsy plays a role in unnecessarily high costs associated with the care for NASH independent of its metabolic comorbidities. Also, 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. Liver biopsy can artificially inflate the cost of care for NASH and unnecessarily lengthen treatments with an extra burden on the patient. 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. The largest increases in healthcare utilization and costs in NASH are represented by liver biopsies and hospitalizations. GLI understands there currently is no consensus around a single noninvasive to diagnose NASH and replace liver biopsy. However, 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.	We appreciate the comments regarding the use of biopsy and non invasive tests (NIT). However, the efficacy measures used in the model were based off trials which used liver biopsy. If data become available which provide insight on NIT measures, these could be added. However, we do note that prior analyses that evaluated the use of NIT for diagnosis and not monitoring estimated negative impacts on outcomes due to misclassification.

	From initial diagnosis to monitoring treatment change and deciding the length of treatment, noninvasives can play a valuable role throughout the entire NASH care pathway. A noninvasive diagnostic pathway should be prioritized within this ICER cost-effectiveness model.	
4.	Methods to quantify the disease burden and cost-effectiveness of the study drugs may not adequately assess patient priorities and the impact of a drug to treat NASH with fibrosis on patient quality of life. We are concerned that subsequent information demonstrates a skewed understanding of patient priorities and the impact of a drug to treat NASH on quality of life. In particular, we strongly disagree with the assertion that the majority of patients with NASH are not impacted by their disease. The use of quality-adjusted life years (QALYs) may not adequately capture the impact of the study drug on patient quality of life. The appropriateness of the QALY calculation has been largely criticized while alternative models better capturing the multidimensional relationship between time and utility have been introduced. Additionally, QALYs are frequently used to discriminate against and deny care to patients who do not have ideal scores, posing ethical and equity problems. The use of QALYs in this report casts doubt on ICER's assumptions and conclusions, particularly those pertaining to the cost of the study drugs.	We believe we are correct that the majority of patients with NASH will not have their lives impacted by NASH, except, perhaps, through interactions with the medical system. Cost-effectiveness analyses are only one part of ICER reports. ICER has a Value Assessment Framework that includes flexibilities built into that framework for deliberation that can include key other benefits and contextual considerations (e.g., equity, severity, unmet need, etc.) specific to NASH that may not be possible to incorporate in the cost-effectiveness model. We are unaware of any instance in which QALYs have been used to discriminate against people with lower baseline quality of life, however because of the theoretical risk that this could occur with therapies that extend life in patients with severely reduced quality of life, ICER uses the evLY metric which cannot be discriminatory even in this unusual situation.
5.	The Cost of Not Treating NASH In any cost-effective analysis of a disease, it is important to pose the challenge of not treating the disease. With NASH there is an immense public health and economic burden that must be accounted for. NASH and NAFLD have far-reaching public health impacts that are not 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. 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	Thank you for this comment. Yes, we account for this in our model. We agree that there is a substantial burden of disease with NASH.

	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 occurrence. Diabetes also contributes to greater fibrosis progression of NASH and can accelerate the progression to cirrhosis and liver cancer. The rise in the prevalence of NASH and its complications carries significant economic costs. Costs associated with NASH include inpatient, outpatient, professional services, emergency department, and drug costs. As the severity of NASH and fibrosis increases, the cost associated with the disease increases as well. Furthermore, co-occurring conditions also contribute to costs not only in healthcare spending but also in indirect costs, such as lost work productivity. We must be cognizant of the unique issues and costs at each stage of NASH. The standard of care, the truth about liver biopsy, the need for a solution at every stage of the disease, and the outcome of not treating this life-threatening disease, are crucial factors that must be considered when painting the cost picture for NASH and considering other benefits offered by the intervention.	
NASH kNOWledge		
1.	The first paragraph of the Executive Summary states that "Obesity is a common risk factor in patients with NASH." It should be recognized that Type 2 Diabetes is also a significant risk factor. It has been estimated that about 80% of those with Type 2 Diabetes also have NAFL.	Thank you and we agree. However, this is a summary and necessarily leaves out some details. The association with diabetes is noted in the second paragraph of the background section.
2.	The fifth paragraph of the Executive Summary states that "NASH is typically asymptomatic for most of its clinical course, and that course can be long; in many patients, NASH does not progress." I believe it should be pointed out that for the population at which both drugs are targeted, NASH has in fact progressed. I do not believe that either drug is intended to be prescribed for early stage NASH patients.	Again, in the executive summary, we are necessarily brief. We agree that it is likely that the FDA indication for both drugs will focus on those with stage F2 or F3 fibrosis, but that is not yet clear. It is also clear from studies that some untreated patients with F2 or higher improve on subsequent biopsies (3rd paragraph of Background section).
3.	The second paragraph of the Background section states "The exact prevalence of NASH is uncertain since diagnosis requires liver biopsy….". I do not think this is the case. I, for example, progressed from NAFL to NASH to cirrhosis without ever having a liver biopsy. It should be recognized that physicians are increasingly diagnosing NASH through non-invasive methods. In my case, NASH was diagnosed based on ultrasound technology results.	We agree that progression can occur from normal to NAFLD to NASH to cirrhosis without a diagnosis. This is an insidious disease. We also agree that non-invasive technologies are increasingly being used to assess fibrosis in NASH and other liver diseases. However, we are not assessing

		the utilities of these new approaches in this review. In the end, the estimates for the prevalence of NASH currently remain somewhat uncertain. However, we all recognize that it is increasingly common and is an important public health issue.
4.	The third paragraph of the Background section states "….and while some patients with NASH and fibrosis do progress to advanced liver disease, many stabilize or improve without pharmacotherapy". I have an issue with use of the words "some" and "many". I think most would interpret "many" as being greater than "some", and I don't believe that to be the case in this situation.	Thank you for your perspective.
5.	The fourth paragraph of the Background section states that "Lifestyle changes that result in the improvement in the metabolic syndrome including diet, exercise, and weight loss can improve NASH….". While this statement is true, the demonstrated difficulty in achieving these changes should be recognized. The results of a TARGET-NASH study were presented at the 2019 Liver Meeting and reported that 25% of the people enrolled in the study achieved long-term weight loss. Other studies have indicated that only 10% of NASH patients lose the recommended 10% of weight and about an additional 12% achieve 5-7% weight loss.	We agree. Hence the potential importance of the new therapies considered in our review.
6.	In the Patient and Caregiver Perspectives section it should also be noted that patients who have had a liver transplant commented that post-transplant life can introduce new medical issues such as worsening of type 2 diabetes and kidney damage, both associated with post-transplant medication requirements.	Thank you. We have added the following paragraph to that section: "If patients do receive a liver transplant, the medications used to prevent transplant rejection can introduce new medical issues including new or worsening hypertension and diabetes as well as damage to the kidneys."
7.	The second to last paragraph in part 3.2 of the Comparative Clinical Effectiveness section states "For both drugs, it remains unclear whether the changes in the primary outcomes will translate into a reduction in cirrhosis, decompensated liver failure, HCC, liver transplantation and death or into improvements in quality of life." The lack of long-term clarity on drug impact could be said of virtually all new drugs and is not unique to the two drugs being reviewed. I believe that this document needs to reflect the need for balance between urgency and certainty. Patient lives have not been put on pause while this process unfolds. What is clear to me is that without a medical solution, even an imperfect one, patients are continuing to progress to advanced liver disease and its consequences.	We agree that this is a common situation for many new therapies, and we expect that the FDA will approve one or both of the drugs on the basis of the interim outcomes. However, the FDA has required the manufacturers of both drugs to follow patients in the randomized trials long enough to assess the more important clinical outcomes. Until those data are available, there will be uncertainties that factor into the assessment of the value of the therapies.
8.	Table 4.6 presents Annual Non-Drug Costs. I have two issues/questions regarding the information presented:	We thank you for this comment. We believe we have used a robust source in

	a. The Cost of the Liver Transplant Procedure seems low. A Milliman Research Report entitled "2020 U.S. organ and tissue transplants: Cost estimates, discussion and emerging issues" estimated the cost of a liver transplant, including 180 days of post-transplant care, to be $878,400. My recollection of the cost of my own procedure is that the costs were considerably higher than the end of the range cited in this document. b. It is not clear to me that the costs for Post Liver Transplant Procedure includes costs associated with the side effects of the anti-rejection drugs. As mentioned earlier, my own experience was that additional medical costs are being incurred due to the worsening of my Type 2 diabetes and the onset of kidney issues.	determining the cost of liver transplant specifically for NASH patients. The $878,400 number that is mentioned is a charge and not the healthcare cost. The post liver transplant procedure costs from the publication that we used were inclusive of all healthcare costs after liver transplant.

#	Comment	Response
Other		
Partnership to Improve Patient Care (PIPC)		
1.	The assertions ICER makes in it evidence matrix are confusing and ignore the patient perspective. The purpose of randomized controlled trials (RCTs) are to show a statistically significant difference in a clinically important primary outcome, which it clearly has in the case of *resmetirom*. It was shown in the MAESTRO-NASH trial to be better than the standard of care at achieving NASH resolution without worsening of fibrosis stage at 12 and 24 months with a p value of less than 0.0001, and with no statistically significant difference in terms of rate of adverse events. Therefore, we would assert that this conforms to the definition of ICERs A grade, which equals a high certainty of a substantial benefit (moderate to large) net health benefit, or at a minimum, its B grade, which equals a high certainty of a small health benefit. The evidence rating ICER selects for *resmetirom* is C. This is confusing as ICER describes *resmetirom* in its evidence rating section as, "*resmetirom appears to reduce progression, promote regression of fibrosis, and lead to resolutions of NASH compared with placebo.*" ICER alludes to the fact that the reason it falls short in terms of evidence is due to its assertion that *long-term benefits are uncertain*, and the '*importance*' of these benefits are uncertain. The reality is that if ICER continues to assess treatments at or before FDA approval, there will always remain a question as	Thank you for your comment. As noted above, the FDA is requiring the manufacturer of resmetirom to complete five years of follow-up for clinical outcomes because of remaining uncertainty given the current interim outcome measures. In addition, the results of the MAESTRO-NASH trial have not been published in a peer reviewed journal. Resmetirom has the potential to receive an A rating, but that awaits publication of their five year outcome data. If the argument being made by PIPC is that it is improper to comment on comparative effectiveness and fair pricing until decades of data become available, we strongly disagree. The information ICER provides is needed at the moment a drug is approved and used and pricing decisions are made. It is also important to note that we are considering the net health benefits, not just a single outcome. This is particularly important for our assessment of OCA where concerns about increasing LDL-cholesterol levels in patients whose primary cause of

	to long-term benefit. If ICER's evidence rating requires proof of long-term benefit beyond the duration of a clinical trial, then ICER must conduct its assessments later in the life-cycle of a treatment, when that evidence exists. If ICER is going to continue to conduct assessments at or before approval, ICER needs to reconsider how it weights its evidence matrix grades. The evidence matrix must have at least the possibility that any new technology can achieve a rating of A, which is currently not possible if it requires long-term evidence for treatments that have not yet been FDA approved. Another issue with this current paradigm is that ICER seems to imply that there is no cost to delaying the introduction of new therapies, but certainty and delay are a trade-off. Individuals living with diseases now, as well as their providers, know that some level of risk is worth not having to wait 20-30 years for a definitive answer when there is a chance they could be benefiting today from treatment. The second point ICER makes regarding the 'importance' of the clinical effect is also confusing. Experts agree, which ICER acknowledges in its assessment, that slowing or halting the progression of fibrosis in NASH patients is important. ICER noted in its patient review that there is "*consensus among patients with NASH that the most important outcome is halting the progression of fibrosis.*" Yet, ICER states in regard to its evidence matrix rating that it is uncertain whether halting the progression of fibrosis is important, a statement that is not just contradictory to the goals of treating NASH, but also outright ignores the patient perspective acknowledged by ICER that halting or slowing fibrosis is not just important but *the most* important outcome.	death is cardiovascular disease impact our judgement about the magnitude and level of certainty of the net health benefits.
2.	ICER should work closely with NASH patients and providers to update its model. ICER seems to mischaracterize certain aspects of NASH, which lead to an underestimation of the importance of treatment and a flawed model. ICER asserts that NASH is not a progressive disease and that NASH patients who are asymptomatic are not impacted by the disease. Neither of these assertions are accurate. Despite patients not experiencing symptoms, the cell damage that occurs with NASH, even while patients are asymptomatic, can ultimately lead to cirrhosis. Once a patient has progressed to cirrhosis, if not treated, cirrhosis can lead to liver failure.	Thank you for the comment. However, we think that you are misreading our review. As described above, we cited evidence that NASH is already the leading cause of liver transplantation in the US in the last sentence of the second paragraph of the Background: "NASH has become a major cause of cirrhosis and, as effective treatment of hepatitis C is now available, it has become the leading reason for liver transplantation."[1] We also highlight the prevalence of the disease in the background section. The entire premise for our review and the core of the economic model is that NASH,

		on average, is a progressive disease. The benefits of the drugs in the model come from the prevention of progression to cirrhosis and its consequences (HCC, transplant, decompensation, hospitalization, hepatic encephalopathy, and poor quality of life).
3.	ICER should incorporate caregiver burden in its base case model. A recent study of caregivers of patients with liver disease showed substantially lower quality of life than non-caregivers in categories. A similar study comparing caregivers to a normal population showed lower level of quality of life as well as a higher level of anxiety. Answers from these caregivers on a questionnaire designed to measure depression also suggested that 34% of caregivers suffered from clinical depression. In instances, like NASH, where caregivers are known to have an outsized burden, it is becoming commonplace in health technology assessments to incorporate caregiver utility into base economic models. The National Institute for Health and Care Excellence (NICE), which ICER leans heavily on for its approach to value assessment, regularly includes caregiver utility in its base-case models for diseases where caregiver burden is known to be high. Including caregiver utility is also the recommended perspective for cost-effectiveness models of the United States' Second Panel on Cost-Effectiveness, and the International Society for Pharmacoeconomics and Outcomes Research. ICER should follow this example and include caregiver burden in its models.	ICER uses the modified societal perspective as a "co-base case" when: 1) impact of treatment on patient and caregiver productivity, education, disability, and nursing home costs is substantial and, 2) these costs are large in relation to health care costs. For example, when incremental cost-effectiveness ratio changes by greater than 20% or by greater than $200,000/QALY. In the case of NASH, these pre-specified requirements were not met.
4.	ICER makes simplistic assumptions about disease progression and liver transplant. ICER appears to make an assumption in the model that if someone needs a liver transplant, they get one. In reality, the number of patients on the waiting list for transplants is always longer than the number of available donor livers in the United States, which means that only a fraction of patients who need one, get one. Most recent data from UNOS suggests between 20-60% of patients depending on MELD score. A recent study showed that NASH patients have both the lowest likelihood of receiving a liver transplant	We appreciate the comment regarding the waitlist for liver transplants. We understand that in actuality, a liver transplant procedure is more complicated than our model can account for. However, this issue applies equally to those receiving new therapies and those receiving the standard of care in the model, so that the incremental differences are minimized.

	while having the highest mortality while on the list.[1] Given this reality, progression to end stage liver disease is in fact significantly more severe for NASH patients than other patients on the liver transplant waiting list. Without factoring this into the model, any results will underestimate the value of delaying NASH patients' progression to later stages of disease.	
5.	ICER's model ignores the wide public health value of reduced demand for liver transplants. In addition to its faulty assumptions about the availability of liver transplants, the model also ignores the public health value of reducing (or delaying) the demand for liver transplants in the NASH population. Since demand outstrips supply for liver transplants, each transplant averted has value not just to that patient but also to other patients who now see an increased probability of successfully receiving a donor liver. When modeling the cost-effectiveness of vaccines, the public health benefit is factored in by incorporating the benefits from the accrual of herd immunity. In the case of NASH, the public health benefit of fewer patients ultimately needing or delaying the need for liver transplants should be factored into the model. This is especially true because NASH is quickly becoming the largest cause of end-stage liver disease in the United States.	Thank you. We have added a new row under potential other benefits: Reduction in the need for liver transplantation for patients with NASH. However, modeling the public health benefit of liver transplants as suggested is out of scope with our objective of assessing the cost-effectiveness of OCA and resmetirom.
6.	ICER oversimplifies disease heterogeneity and complexity. ICER's use of 'prior cardiovascular event' as an overarching category for patients is a simplification. The condition of prior cardiovascular event will likely make up a considerable proportion of patients suffering from NASH, but it will also hide a considerable variation in both type of patients and level of risk for both future cardiovascular events and for other co-existing conditions 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 very different from the risks associated with a previous myocardial infarction or stroke. In addition to these simplified assumptions about the patient population, another issue is that the Framingham Heart study was used to estimate the risk of cardiovascular events rather than real world data sources. The Framingham risk model has been criticized as a source for real world modeling of outcomes in populations with co-existing conditions, as it is far from representative of a true population of need in the	We agree that the use of "prior cardiovascular event" as an overarching category for patients may be a simplification and have only included those with serious CV events such as MI or stroke as you mention. We also note that the use of the Framingham risk model is a limitation in our report, but the importance of incorporating CV risk in NASH warranted its use.

[1] Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, Ahmed A. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015 Mar 1;148(3):547-55.

	United States as a whole. 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.	
7.	Conclusion PIPC urges ICER to go review its report alongside experts in the field of liver disease, including patients and providers to ensure that it is accurately representing NASH and its modeling choices can lead to an accurate representation of value to this community.	Thank you for this comment. The list of expert reviewers of the draft evidence report can be found on page iii. You can also refer to our key stakeholder list here. Furthermore, we will discuss the findings of the report with clinical and patient experts at the public meeting on April 28th. You can register for the meeting here.

References

1. Wang S, Toy M, Hang Pham TT, So S. Causes and trends in liver disease and hepatocellular carcinoma among men and women who received liver transplants in the U.S., 2010-2019. *PLoS One.* 2020;15(9):e0239393.