October 26, 2022

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

**Re: ICER Seeks Public Input for Draft Scoping Document for Non-Alcoholic Steatohepatitis**

Dr. Pearson:

On behalf of patients with liver disease across the nation, the Global Liver Institute (GLI) writes to comment on the Institute for Clinical and Economic Review's (ICER's) recently released draft scoping document for Non-Alcoholic Steatohepatitis (NASH). GLI looks forward to continuing our engagement throughout this process.

However, we hold strong reservations about several aspects of ICER's current methodology, and whether it will lead to accurately and precisely reflecting the needs of the millions of patients living with liver disease in the U.S. As such, GLI recommends ICER consider GLI's concerns shared below and, in turn, adopt our recommended principles into ICER's review process for NASH.

Namely, we are concerned about ICER's assumption that liver disease does not tend to progress, as well as ICER diverting patient perspectives into "policy" discussions instead of incorporating them into the core analysis. GLI clarifies that liver disease diagnosis is no longer limited to biopsies[1] and recommends a review of updated guidelines on risk stratification approaches for liver diseases.[2,3] Further, GLI stresses the importance of weighing and considering cardiovascular factors as they are intimately related to liver disease.[4] Lastly, GLI urges that ICER not assume real patients experience care and outcomes as do participants in controlled clinical placebo-based trials, underlining the need for patient perspectives.

## In the Case of NASH

Treatments and new approaches to managing liver disease cannot come more quickly and at a more critical time. For instance, one study suggests a 36.6 percent prevalence

[1] *See* Noureddin, M., et al. Screening for Nonalcoholic Fatty Liver Disease in Persons with Type 2 Diabetes in the United States Is Cost-effective: A Comprehensive Cost-Utility Analysis. Gastroenterology (2020), 159(5):1985-1987. https://doi.org/10.1053/j.gastro.2020.07.050

[2] *See* Cusi, K., etal, American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings. Clinical Practice Guidelines (May 2022), 28(5):528-562

[3] *See also* Cusi, K. Time to Include Nonalcoholic Steatohepatitis in the Management of Patients With Type 2 Diabetes. Diabetes Care 2020;43(2):275–279. https://doi.org/10.2337/dci19-0064

[4] Nonalcoholic Fatty Liver Disease and Cardiovascular Risk: A Scientific Statement From the American Heart Association. https://doi.org/10.1161/ATV.0000000000000153

in the U.S. for NAFLD[5] with another study estimating that 1.5 billion persons have chronic liver disease worldwide.[6] However, with liver diseases too often going undiagnosed, many of these patients face exacerbation to later stages of liver disease, including liver cirrhosis and liver failure, due to non-treatment. 36.6 percent of one study's participants had NAFLD, but only 4.4 percent were aware that they had liver disease. Unfortunately, this dire figure is not just the consequence of low awareness by patients, but also their healthcare providers, who too often lack the understanding and tools to easily diagnose Americans for liver disease.

The failure to test for, diagnose, and treat liver conditions early can lead to costly, life-or-death situations. For example, liver disease is the progression through the various stages of liver disease - starting from fatty liver, ending at liver failure. This is particularly problematic when coupled with the fact that patients with earlier stage liver disease are often asymptomatic, leading to exacerbation to a later stage with much more severe symptoms. Unfortunately, patients suffering from liver disease may eventually progress to severe cirrhosis or liver failure, and face a situation where a costly liver transplantation may be the only option.

Further, there are strong equity concerns among patients with liver disease, with prevalence being higher within certain ethnicities and with other groups having a genetic proclivity to getting liver disease. In fact, certain patient groups face more challenges when attempting to get a liver transplantation.[7, 8, 9]

Therefore, we remain concerned about the public health and clinical impacts that an ICER final report may have if it does not incorporate many of the nuances and challenges associated with identifying and treating patients with various stages of liver disease. As such, GLI provides several recommendations below to help guide ICER towards a patient-informed endpoint.

## Recommended Principles

***Take a measured, flexible approach, rather than one rooted in ordinal measures, to reflect the nuances and challenges that exist in treating patients with liver disease.*** ICER must acknowledge and reflect the particular challenges faced by and nuances involved in the care of patients with liver disease by relying more on qualitative factors based on direct patient feedback and less on ordinal measures that offer some guise of accuracy and precision.

***Meaningfully incorporate patient needs and values through a transparent, systematic approach, rather than using an ad hoc approach, and incorporate patient needs and values into every aspect of its analytical approach.*** ICER must use a systematic and transparent approach to incorporate patient perspectives, needs,

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[5] Alqahtani, S.A., Paik, J.M., Biswas, R., Arshad, T., Henry, L. and Younossi, Z.M. (2021), Poor Awareness of Liver Disease Among Adults With NAFLD in the United States. Hepatol Commun, 5: 1833-1847.

[6] Moon AM, Singal AG, Tapper EB. Contemporary Epidemiology of Chronic Liver Disease and Cirrhosis. Clin Gastroenterol Hepatol. 2020 Nov;18(12):2650-2666.

[7] Mathur AK, Ashby VB, Fuller DS, et al. Variation in access to the liver transplant waiting list in the United States. Transplantation 2014;98:94–99.

[8] Bryce CL, Angus DC, Arnold RM, et al. Sociodemographic differences in early access to liver transplantation services. Am J Transplant 2009;9:2092–2101.

[9] Warren C, Carpenter AM, Neal D, Andreoni K, Sarosi G, Zarrinpar A. Racial Disparity in Liver Transplantation Listing. J Am Coll Surg. 2021 Apr;232(4):526-534.

and values, rather than relying on ad hoc communications and discussions with the patient community. Further, ICER should use this approach to solicit input, adjust based on that input, and then test out every aspect of the analytical process. Further, rather than relegating patient perspective discussion as part of the policy roundtable, ICER must incorporate them into the analysis itself.

***Fully acknowledge and then leverage its influence on health systems and payers to create a more equitable tool for discussions and negotiations about patient access to appropriate treatments - especially high value, high cost care.*** ICER must acknowledge the influence that its reports have on the creation of barriers and challenges that patients face when trying to access care. This is especially so when looking at treatments that have high value to patients, but come with a high cost as well (as opposed to ICER's more positive treatments of low value, low cost care). Given that ICER reports and recommendations often lead to such restrictions, meaningfully and systematically fusing the patient perspective into every aspect of the analytical process becomes that much more critical.

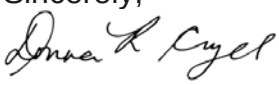
***Carefully distinguish medications that treat different stages and/or severities of liver disease, possibly treating them differently altogether.*** ICER must take a nuanced view of liver disease. Even with NASH, different levels of severity create very different clinical, economic, and quality-of-life considerations. As such, ICER must evaluate each indication for every drug analyzed differently and within its own particular sets of context. Melding the various stages and severity levels into one amalgam would lead to creating critical structural flaws in ICER's analytical approach.

***Carefully investigate equity concerns, particularly among certain ethnic groups with a high proclivity for liver disease.*** ICER must also take a measured approach at identifying ethnic groups with a high risk for liver disease (e.g., Latinos, Asians) within the data, and conduct an analysis of the health equity impacts with effective treatment.

***Consider comorbidities and their impact on treating liver disease, especially in light of recent findings and statements.*** ICER must also take into consideration the impact that cardiovascular disease and other chronic conditions have on liver disease. This is especially important in light of a recent American Heart Association's statement on liver disease, which indicates that among those with NAFLD, the primary cause of morbidity is atherosclerotic cardiovascular disease.[10]

We appreciate ICER reaching out to and involving GLI early on in the process. We look forward to engaging you further on this process. If you have any questions, please do not hesitate to contact Daniel Nam, Vice President of Policy at dnam@globalliver.org.

Sincerely,



Donna R. Cryer, JD
President and Chief Executive Officer
Global Liver Institute

[10] See footnote 4

October 26, 2022

Institute for Clinical and Economic Review (ICER)
14 Beacon St, 8th Floor
Boston, MA 02108

Dear ICER Review Team:

Thank you for the opportunity to comment on the draft scope for the assessment of obeticholic acid (OCA). Intercept is dedicated to developing innovative treatments for progressive, non-viral liver diseases with high unmet need, and we are committed to working with healthcare stakeholders, including ICER, to ensure access for patients who can benefit from our medicines.

We have provided below some important considerations for ICER's review of OCA.

**Fibrosis is the most robust, evidence-based predictor of negative clinical outcomes [1-3] and therefore the most important measure of efficacy when assessing treatments for nonalcoholic steatohepatitis (NASH).**

NASH is a serious progressive liver disease that may result in liver scarring or fibrosis, which can progress to cirrhosis, cancer, and death. While other assessments being considered in this review are important to patients with NASH, fibrosis is the strongest predictor of liver-related adverse outcomes and should be weighted accordingly in the review. 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]. There is an urgent need to treat patients with fibrosis due to NASH prior to their progression to cirrhosis.

**Longer-term data on OCA safety and efficacy are now available.**

In the 2020 Evidence Report for Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis with Fibrosis, ICER determined that "for people living with NASH with fibrosis, OCA appears to reduce progression and promote regression of fibrosis compared with placebo," and that "it is likely that OCA will reduce progression to cirrhosis" [5]. Since then, a second interim analysis of the ongoing pivotal Phase 3 REGENERATE trial of OCA in patients with liver fibrosis due to NASH has demonstrated the antifibrotic effect of OCA with an independent methodology, and has additionally provided a larger, more robust safety database of 2,477 patients with up to 4 years' exposure to obeticholic acid, allowing for better characterization of the long-

term safety and tolerability of OCA [6]. Below is a summary of topline results from the new efficacy interim analysis and substantially increased safety database for ICER to consider for this review.

A new interim analysis of the potential antifibrotic benefit for the intent-to-treat population from REGENERATE (n=931) was recently completed. The population in this new U.S. Food and Drug Administration (FDA) requested analysis mirrored the original analysis population from 2019 but used a consensus panel approach to histology reads, in line with recent FDA guidance, while the original analysis relied on results from individual central readers. In this analysis, 22.4% of subjects randomized to once-daily oral OCA 25 mg met the primary endpoint of achieving at least one stage of fibrosis improvement with no worsening of NASH at month 18 on liver biopsy compared with 9.6% of subjects on placebo ($p<0.0001$). These results are consistent with the original positive analysis announced in February 2019, which also showed that, at 18 months of exposure, OCA 25 mg demonstrated double the response rate of placebo and achieved a statistically significant improvement in liver fibrosis (≥1 stage) without worsening of NASH as compared to placebo (23.1% vs 11.9%, respectively; $p=0.0002$). A numerically greater proportion of individuals in the OCA 25 mg treatment group compared to placebo achieved the endpoint of resolution of NASH with no worsening of liver fibrosis, but the results were not statistically significant. For the primary objective to be met, the study was required to achieve only one of the two primary endpoints.

Safety was evaluated in 2,477 subjects who took at least one dose of study drug (placebo, OCA 10 mg, or OCA 25 mg). Compared to the original analysis, the safety population in this new interim analysis had substantially longer exposure to study drug (median 42 months vs. 15 months), yielding more than 8,000 total patient-years and 3.4 times more exposure. Nearly 1,000 subjects had been on study drug for four years. Topline safety results showed that treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and deaths were generally balanced across the treatment groups in this new safety population.

Independent groups of experts reviewed certain categories of safety events to provide a blinded adjudication as specifically requested by FDA. These included events pertaining to hepatic safety (excluding clinical outcomes), cardiovascular safety and renal safety. For adjudicated core major adverse cardiovascular events and adjudicated acute kidney injury events, frequency of events was low and balanced across treatment groups**.** Consistent with its mechanism of action as an FXR agonist, OCA treatment was associated with an increase in low-density lipoprotein (LDL) at Month 1, which then returned to near baseline values by Month 12**.** Topline analysis through four years (Month 48) of treatment showed a numerically higher number of adjudicated hepatic safety events for OCA 25 mg, the majority of which were mild in severity, and included laboratory changes such as serum alanine transaminase (ALT) elevation in the absence of increased bilirubin; this is consistent with Farnesoid X Receptor (FXR) mediated effects. Among the hepatic safety

events adjudicated to be probably or highly likely related to study drug, the total number of events was in the single digits.

We believe these substantially longer-term data are important for ICER to consider in the evaluation of the benefit:risk profile of OCA. The specific assumptions around cardiovascular events in ICER's economic model should be reconsidered.

We look forward to working with you throughout this review. Please do not hesitate to reach out with any questions.

Sincerely,

Leona Bessonova, PhD, MBA
Senior Director, Medical Research
Leona.Bessonova@interceptpharma.com

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5. Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis with Fibrosis. ICER Evidence Report, July 21, 2020.

6. Intercept Announces Positive Data in Fibrosis due to NASH from a New Analysis of its Phase 3 REGENERATE Study of Obeticholic Acid (OCA) - Intercept Pharmaceuticals, Inc. July 07, 2022.

Madrigal Pharmaceuticals

Dear ICER Review Team:

Thank you for the opportunity to comment on the draft scope for the assessment of resmetirom and obeticholic acid.

Nonalcoholic steatohepatitis (NASH) with significant fibrosis and without cirrhosis is a serious condition that places a heavy burden on patients and health systems. There are currently no approved medications to treat the disease. Madrigal's goal is to address this unmet need by developing resmetirom, a once-daily, oral, liver-directed thyroid hormone receptor (THR) β-selective agonist designed specifically to treat the underlying causes of NASH.

In a Phase 2 study, resmetirom helped patients achieve marked reductions in liver fat, resolved NASH on biopsy, improved biomarkers of fibrosis and lowered LDL-C and other atherogenic lipids and lipoproteins.[1] In the Phase 3 MAESTRO-NAFLD-1 safety and efficacy study, the data showed resmetirom was well-tolerated and improved noninvasive measures of efficacy that are used in real-world clinical practice to manage patients with NASH with significant fibrosis.[2]

As a leader in NASH drug development, we recognize and embrace our responsibility to comprehensively evaluate the benefits and risks of resmetirom, improve NASH disease education and ensure appropriate patients are able to access and afford resmetirom, if approved.

We are also committed to studying the cost-effectiveness of resmetirom. Building on ICER's previous work in value assessments of obeticholic acid, Madrigal has conducted and published a preliminary cost-effectiveness analysis of resmetirom using Phase 2 data.[3,4]

Before commenting on the PICOTS criteria outlined in ICER's draft scoping document, we would like to outline several key considerations that we believe will be important throughout the value assessment process:

**1. Consider the Patient Burden of NASH Throughout the Value Assessment.** NASH with significant fibrosis places a severe burden on patients and their families. A NASH diagnosis can cause significant emotional distress for patients, especially when they learn there is no approved medication to treat the disease.[5] NASH is associated with decreased health-related quality of life, depressive symptoms and fatigue.[6-8] Even patients with early-stage NASH can feel burdened by worry about the risk of future liver-related complications and need for transplant.[5] When patients do experience complications of advanced cirrhosis (such as hepatic encephalopathy, ascites and variceal bleeding) or receive a diagnosis of hepatocellular cancer, the results can be traumatic and have a devastating impact on quality of life that is difficult to capture in pharmacoeconomic modeling.

We hope that input from patient advocates will play a central role in this review and that ICER will incorporate patient perspectives in its overall value assessment of resmetirom.

**2. Detailed Phase 3 MAESTRO-NASH Data May Not Be Available During ICER's Published Review Period.** MAESTRO-NASH, the pivotal Phase 3 biopsy study evaluating resmetirom for the treatment of NASH with significant fibrosis, remains ongoing with a topline data readout expected in Q4 2022.[9] Detailed results from the study, including patient-reported outcomes, may not be fully available during the current ICER review window, creating a missed opportunity to assess resmetirom cost-effectiveness using the most robust dataset. A value assessment using Phase 2 data exists in published form[3]; one using Phase 3 data would offer the most accurate and incrementally useful information for payers.

**3. The Real-World Population Likely to be Treated is Limited.** ICER should consider the real-world NASH with significant fibrosis population likely to be treated with resmetirom throughout the value assessment process, as it has implications for appropriate data sources and budget impact estimates.

Data Sources: ICER's inclusion and evaluation of a real-world population should carefully consider the variation of utility and cost data available for economic modeling, ensuring the data sources accurately reflect only ICER's stated population of interest: patients with NASH with significant fibrosis and without cirrhosis. To avoid confounding modeling results, Madrigal recommends ICER explicitly exclude evidence and data sources that include patients with generalized NAFLD, early NASH or cirrhotic NASH.

Budget Impact Estimates: Madrigal estimates that about 800,000 non-cirrhotic NASH patients are currently identified and coded, a small fraction of the approximately 8 million patients with non-cirrhotic NASH.[10] This is consistent with recent prevalence estimates using medical claims data, where the newly coded non-cirrhotic NASH incidence was estimated to be ~100,000 annually. We expect diagnosis and treatment rates over time will be similar to other asymptomatic chronic diseases.[10] Since only identified and coded patients are likely to receive treatment, this upcoming review provides an important opportunity for ICER to provide health system decision-makers with an accurate view of the potential budget impact of resmetirom by using realistic assumptions about the likely treated population and rate of adoption.

**4. NASH with Significant Fibrosis is a Disease Treated by Specialists.** NASH with significant fibrosis is a complex disease that is managed in the outpatient setting by specialists (e.g., gastroenterologists/hepatologists and endocrinologists that focus on NASH). Madrigal's disease education and commercial planning efforts for resmetirom focus on these specialists focused on the treatment of NASH. The AASLD and EASL guidelines recommend referral of patients with suspected significant fibrosis to liver specialists.[11,12]

**5. Noninvasive Tests Are Used for Patient Identification and Monitoring.** Although liver biopsy remains the regulatory standard for pivotal studies supporting accelerated approval of medications for NASH, biopsy is performed infrequently outside the clinical trial setting for the management of patients with NASH. Noninvasive tests (NITs) are used to identify and monitor patients in real world clinical practice.[13] Thus, the NASH with significant fibrosis patient

population likely to be treated will be identified by specialists using the NIT-based algorithms established by medical societies such as the AGA,[14] EASL[12] and AACE.[15]

**6. NASH is Strongly Associated with Cardiovascular Risk.** ICER's focus on cardiovascular risk in its review of therapies for NASH with significant fibrosis is warranted. Patients with NASH, especially those with more advanced metabolic risk factors (hypertension, concomitant type 2 diabetes), are at increased risk for adverse cardiovascular events and increased morbidity and mortality.[16] NASH is also an independent driver of cardiovascular events, even after controlling for confounding factors such as type 2 diabetes, obesity, and smoking.[17] As noted in ICER's draft scoping document, cardiovascular disease is the leading cause of death in patients with NASH.[18]

## Comments on PICOTS Criteria

We appreciate ICER's efforts to collect feedback from Madrigal and other key stakeholders on the draft scoping document. ICER made meaningful revisions to the PICOTS criteria that improve on the 2020 review of obeticholic acid and bring key elements of the scope closer to the current thinking in the NASH field.

*Populations.* We agree that the focus for the review should be adults age ≥ 18 with NASH with significant fibrosis and without cirrhosis. We also agree the review should examine subgroups of interest including fibrosis stage, presence of diabetes, and race/ethnicity.

*Comparators.* We recommend that ICER consider real-world data when comparing resmetirom to usual care instead of relying solely on the placebo arms of clinical trials. Placebo arms of clinical trials may provide an augmented standard of care and may show responses related to the Hawthorne effect and other confounders. We appreciate the removal of pioglitazone as a comparator; the studies evaluating pioglitazone for the treatment of NASH vary in quality and pioglitazone is not widely used in clinical practice.

*Outcomes.* We agree with the outcomes listed in the draft scope. The inclusion of liver fat reduction as an outcome is particularly relevant given the resmetirom mechanism of action and the medication's ability to reduce liver fat in patients with NASH with significant fibrosis.

Sincerely,

Stephen Dodge, PharmD, MBA

SVP, Global Medical Affairs
Phone (cell): 908.455.1755
Four Tower Bridge
200 Barr Harbor Drive, Suite 200
West Conshohocken, PA 19428

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Oct 26, 2022

Steven D. Pearson, MD, MSc, FRCP
President Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

**Public comments to ICER Draft Scoping Document for the Assessment of Resmetirom and Obeticholic Acid for Non-Alcoholic Steatohepatitis (NASH)**

Dear Dr. Pearson:

Thank you for the opportunity to provide comments on the proposed ICER analysis of Non-Alcoholic Steatohepatitis treatments. At this time, we would like to provide feedback on the draft scoping document released on October 5, 2022.

Please find below our comments on the draft scoping document. There are 2 key comments that we would like to highlight at this time:

**1- Clinical inputs for economic model**

The scoping document states that "The model structure will be based in part on a literature review of prior published models of NASH, particularly the model developed for the ICER review of OCA in 2020, as well as other models that have been published since the previous ICER review."

ICER's OCA assessment [1] as well as the mentioned CEA study of Resmetirom using its Phase 2b data [2] focused on fibrosis progression and regression to predict long-term outcomes. More specifically, the ICER assessment took the probability of fibrosis improvement and no change from REGENERATE trial and then the relative risk for fibrosis improvement and no change between OCA and natural rate [1]. Whereas the probability of fibrosis worsening is the remainder of improvement and no change probabilities. The Resmetirom CEA study [2] used a similar approach except that the fibrosis improvement/no change probabilities are derived from estimated fibrosis status based on MRI-PDFF responder data in the Resmetirom Ph2b trial.

This setting leads to some seemingly counter-intuitive findings. For example, despite a relatively lower efficacy in % fibrosis improvement for Resmetirom compared to OCA, the Resmetirom CEA showed much more desirable cost-effectiveness than the OCA CEA (Res: $53,930/QALY [2] vs OCA: $1,482,000/QALY [1]). In addition, the one-way sensitivity analysis showed that the key parameters are relative risks/probabilities for fibrosis improvement/no change; it is interesting that fibrosis improvement has almost equivalent size of influence on cost-effectiveness ratio as fibrosis no change and fibrosis regression is not the key driver in the model.

Although one can argue that using the remainder percentage as fibrosis progression is mathematically sound, there is a lack of transparency in the modelling of fibrosis progression which may become an issue for the following reasons:

1. Fibrosis progression as the key value driver parameter can't be fully or correctly assessed if it continues to be evaluated as a hidden parameter in the model. In both one-way and probabilistic sensitivity analyses, the hidden parameter of fibrosis progression can't be directly altered. Altering fibrosis improvement/no change parameters is likely to distort the range of underlying uncertainty around fibrosis progression.

2. As mentioned, the Resmetirom CEA [2] used fibrosis improvement/no change based on a conversion of MRI-PDFF to fibrosis status. Details of the conversion were not provided in the publication, partially because no change was considered a less important input [2]. However, we believe that this parameter with limited disclosed information was the primary reason for distinctively different cost-effectiveness ratios in the two studies. In addition, probability of fibrosis progression was not provided in either ICER's evidence report or Resmetirom CEA.

3. Assessments may potentially favor compounds with direct antifibrotic mechanism of action (MoA) over anti-steatotic and anti-inflammatory MoAs that may stop fibrosis progression but may take longer to achieve fibrosis regression. Based on the current model, it is mathematically possible that a drug can be highly cost-effective even when the effect size of fibrosis regression is zero, as long as it stops fibrosis progression and this needs to be acknowledged.

***Recommendation:***

1. ICER should make fibrosis progression an independent parameter, with point estimates and uncertainty directly sourced from the trials. Fibrosis progression input need to be displayed and discussed, rather than as a hidden parameter. If the fibrosis progression data is not available in a trial study (as is the case in existing publications), ICER should make effort to contact authors for original data, instead of using calculated values for this key input.

2. ICER did not provide calibration info in the OCA report. It would be desirable to provide calibration results against trial-observed fibrosis regression/progression rate.

3. ICER should discuss the economic implications for fibrosis regression versus stopping fibrosis progression. Emerging NASH drugs will achieve these two endpoints through different MoAs and in turn by varying degrees. The key value driver(s) need to be discussed in comparison of compounds of different MoAs.

**2- Natural history of fibrosis progression**

Although not specified in the scoping document which set of inputs to use for fibrosis natural progression rate, the OCA report and the Resmetirom CEA used the rates calculated from a 2015 meta-analysis by Singh et al [3]. The natural progression rate is a critical input to the model, as the faster progression will lead to high economic value of NASH drugs, and the opposite is also true. We believe that the 2015 meta-analysis may not be the ideal option, for two reasons. First, the meta-analysis included eight observational study spanning 2000-2012 [3], which are relatively outdated. Second, the meta-analysis has a limited number of patients with significant fibrosis (F2 n=25, F3 n=16) and compensated cirrhosis (F4 n=5) [3], which leads to a high level of uncertainty.

Third, fibrosis progression in the placebo arms of recent trials [4, 5] is shown to be faster than the meta-analysis. Of relevancy is that, from simtuzumab trials [6, 7], a 20% rule is suggested [8]: approximately 20% of patients with NASH with advanced NAFLD Fibrosis Score (NFS) (F3) fibrosis or compensated cirrhosis will progress to cirrhosis or develop decompensation, respectively, over a 2-year time period. The 2015 meta-analysis yields a lower progression rate than what 20% rule indicates.

***Recommendation:*** ICER may compare the natural history based on early meta-analysis versus recent trial data to assess which set of inputs better represent the baseline disease progression.

Thank you again for this opportunity to provide comments and we look forward to continuing this engagement. If you have any questions, please feel free to contact me.

Sincerely,

Gail Fernandes

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