November 20, 2019

Institute for Clinical and Economic Review (ICER)
2 Liberty Square
Boston, MA 02109

Dear ICER Review Team:

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

Detailed comments follow; however, we highlight these important topline considerations:

- The target population for obeticholic acid is real-world patients with **Advanced Fibrosis due to NASH without cirrhosis**, a narrower population than suggested in the draft scope.
- Non-invasive tests are the preferred methods of diagnosis in actual clinical practice, so we expect the majority of patients to be identified without a liver biopsy.
- Obeticholic acid, if approved, will be the first proven pharmacologic treatment for fibrosis due to NASH. Although patients currently may receive care for co-morbid conditions, there are no approved medications for NASH and therefore the natural history of the disease should be the comparison for obeticholic acid.
- The epidemiology and natural history of NASH are uncertain, affecting scope descriptions for population, outcomes and timeframes.

**Background:** Uncertainty in prevalence rates and the associated diagnostic challenges with liver biopsies and histology will generate a range of estimates of cost-effectiveness and budget impact. The challenges created by this uncertainty are not adequately considered in the scope. We suggest that ICER reconsider its observation that “many [patients] stabilize or regress without pharmacotherapy” and that placebo improvement rates in clinical trials provides evidence of this. Much of the “placebo improvement” seen in trials is likely due to measurement error, life-style modifications and the general health benefits of receiving care in a clinical trial setting.¹²³ In the presence of substantial measurement error, actual drug effects are more challenging to detect, making the positive efficacy results with obeticholic acid even more meaningful.⁴⁵

**Recommendation:** Do not conflate placebo response rates from clinical trials with the natural history of the disease.⁴⁵

**Population:** The population of most interest to payers is those patients who are likely to be treated in a real-world clinical practice. While the draft scope states that the population of focus is adults
≥18 with NASH and fibrosis, the treatment population in practice will be much narrower. Those most likely to be treated with obeticholic acid are patients at highest risk of adverse liver-related outcomes, i.e., those patients with “Advanced Fibrosis due to NASH” (without cirrhosis, as obeticholic acid will not have sufficient evidence in cirrhosis at launch). Intercept’s disease education campaigns, the size/structure of our field support teams, our public comments during investor presentations and our initial interactions with payers all focus on Intercept’s commitment to position obeticholic acid as a treatment for the Advanced Fibrosis due to NASH without cirrhosis population. Intercept has made a clear strategic decision to focus on this population because:

1) The unmet need and clinical benefit of obeticholic acid is greatest in patients with Advanced Fibrosis due to NASH without cirrhosis;\(^8\)
2) Market research with health care providers indicates they are planning to prioritize treating patients with Advanced Fibrosis due to NASH without cirrhosis vs. early fibrosis;
3) We are highly sensitive to health system cost concerns when a specialty medication is introduced for a chronic disease with a potentially large and poorly defined prevalence.

For these reasons, our disease education efforts are focused on Advanced Fibrosis due to NASH without cirrhosis with specialist prescribers (e.g., hepatologists and gastroenterologists). There is substantial evidence supporting the use of obeticholic acid as a treatment for Advanced Fibrosis due to NASH without cirrhosis; however, if ICER instead uses the broader NASH patient population in its model, the assessment will significantly overstate utilization and budget impact while under-estimating the cost-effectiveness of OCA.

**Recommendation:** ICER should define the assessment population as diagnosed patients with advanced fibrosis due to NASH without cirrhosis under specialist care.

**Intervention:** The draft scope is not clear in this regard. The management of co-morbid conditions in NASH patients should not be conflated with treatments for NASH.

**Recommendation:** ICER should clarify the intervention to be evaluated as obeticholic acid.

**Comparators:** There are no targeted treatments available and no treatments routinely provided in real world practice for patients with NASH. Therefore, the comparator is the untreated natural history of NASH. Lifestyle changes are the standard of care in NASH; obeticholic acid, if approved, will be used in addition to, not in lieu of, lifestyle changes.\(^9,10\) Pioglitazone is used and indicated as a treatment for diabetes, which is often a co-morbidity for patients with NASH. However, it is not indicated for, nor broadly used in the treatment of NASH.\(^11\) In fact, the major study of pioglitazone in NASH showed no benefit and no fibrosis improvement.\(^12\) Pioglitazone should not be considered a comparator in this assessment. In its 2016 review of NASH, ICER concluded that there was insufficient data on pioglitazone, and that conclusion still applies today.\(^13\) Treatments for co-morbid conditions, including pioglitazone, are not treatments for NASH and therefore are also not appropriate comparators.
Recommendation: ICER should use natural history of the disease as the comparator.

Outcomes: While we appreciate the list of outcomes, we note that cardiac and cardiovascular events and weight gain are listed under “Harms.” In the REGENERATE interim analysis of obeticholic acid, the incidence of cardiovascular adverse events and serious adverse events was low and similar across treatment groups, and there was a net weight reduction with treatment, as well as OCA-associated improvements in other markers of CV risk (e.g., reduction in triglycerides).14

Recommendation: ICER should not include cardiac or cardiovascular outcomes as harms.

Timing: This is ambiguously described in the scope and is not consistent with the intent in subsequent sections that suggest ICER will construct a lifetime cost-effectiveness model. This will require projection beyond the 18-month study timeframe currently described in the REGENERATE interim analysis. Time-to-events and time of progression are critical to a lifetime simulation model where estimates are highly variable.15

Recommendation: ICER should use a lifetime model.

Setting: Treatment of NASH with obeticholic acid in patients with advanced fibrosis without cirrhosis due to NASH will occur predominantly within specialist hepatologist and gastroenterologist outpatient clinics.

Recommendation: ICER should use specialist outpatient clinics as the model setting.

Scope of Comparative Value Analyses: Fibrosis stages are histological, descriptive categories—NOT clinical health states used to guide medical practice. Existing published economic models in NASH have used histological fibrosis stages given that this data predominates in the literature. We believe obeticholic acid will be used in the health state known as “Advanced fibrosis due to NASH” (excluding compensated cirrhotic patients). In this health state, there is an urgency to treat because of its chronological proximity to the development of cirrhosis (compensated and decompensated) as well as HCC, liver transplant and death, as ICER has noted. Notably, non-invasive tests rather than biopsy will likely be used in clinical practice.

Concerning the budget impact, we appreciate the desire to use published literature on potential populations; however, literature is lacking. We encourage you to review Intercept’s public comment on ICER’s 2020 Value Assessment Framework for additional background on the challenges of estimating budget impact in a condition like NASH.

Yours sincerely,

Dr. Bruce Wong MD, MSc, FRACP
Vice-President, Medical Affairs Research
References:


11. Intercept (data on file). ~1% of patients were treated with thiazolidinediones at baseline in the REGENERATE study.


14. Younossi et al. Positive Results from REGENERATE: A Phase 3 International, Randomized, Placebo-Controlled Study Evaluating Obeticholic Acid Treatment for NASH. EASL 2019. Vienna, Austria

November 20, 2019

Via Electronic Mail

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

RE: Comments on Draft Scoping Document for “Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis (NASH) with Fibrosis”

Dear Dr. Pearson:

On behalf of Allergan plc, we are submitting this letter in response to your current assessment of “Obeticholic Acid for the Treatment of NASH with Fibrosis”. We are pleased to note that ICER recognizes the importance of NASH and its significant burden on patients and healthcare systems. The evidence base is rapidly evolving with new diagnostic technologies and treatments in development that will continue to shape our understanding of how NASH can be diagnosed and managed effectively to avoid significant complications. Allergan is committed to the development of novel medicines to improve outcomes in patients with NASH and as such, would like to provide comments for consideration in your review.

**Comment 1: NASH is a more severe form of NAFLD and should be the clear focus of the review**

The background section of the draft scoping document opened with NAFLD and discussed NAFLD and NASH interchangeably throughout the section on epidemiology and clinical implications. Since obeticholic acid (OCA) is under the U.S. FDA review as a treatment for NASH with fibrosis, we recommend that ICER revises the background section of the scoping document so that the review is clearly focused on NASH, the fibrotic/progressive form of NAFLD.
Comment 2: “Pioglitazone added to usual care” is not an appropriate comparator for obeticholic acid for NASH

The use of pioglitazone for NASH is limited in clinical practice due to uncertainty regarding its clinical benefit and concerns regarding safety and tolerability. As such, it would seem inappropriate to consider it as a comparator for this review. The safety and efficacy of pioglitazone has not been robustly established, nor is it approved by the U.S. FDA for the treatment of NASH. While small sample size proof-of-concept studies reported a modest positive effect of pioglitazone, larger and more robust studies are needed to confirm this effect and to further characterize safety. Among safety and tolerability concerns well-documented with the use of pioglitazone in type 2 diabetes is weight gain. This is a concern both because weight loss plays a key role in improving the histopathological features of NASH and a high proportion of patients with NASH are overweight or obese.

We appreciate your consideration of our comments for the review of “Obeticholic Acid for the Treatment of NASH with Fibrosis”. Should you have any questions, please contact Jason Wang, PhD, Executive Director – U.S. Health Outcomes and Value via e-mail at Jason.Wang@allergan.com, or Jonathan Kowalski, PharmD, Vice President – U.S. Health Outcomes and Value via e-mail at Jonathan.Kowalski@allergan.com.

Best regards,

Zhixiao Jason Wang, PHD
Executive Director

Jonathan W. Kowalski, PharmD, MS
Vice President
Nov 20, 2019

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 Treatments for Non-Alcoholic Steatohepatitis

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 30, 2019.

There are several limitations to determining the value of a NASH treatment currently which should be stated as limitations for any assessment of treatment in NASH. These include but are not limited to: paucity of published data on health utility measures, healthcare resource utilization and cost of NASH.

Please find below our comments on the draft scoping document. There are 3 key comments that we would like to highlight that will help this evaluation:

1- The choice of the interventions and comparators for NASH:

Please clarify in the report how vitamin E will be evaluated in the usual care arm. It looks like vitamin E will be included as part of the placebo arm, so patients with vitamin E will be included from the RCT in the usual care. This is reasonable but vitamin E should not be included as a treatment for NASH as suggested in the language on pg. 4. It is important to note that there are no approved treatments for NASH so including vitamin E as a treatment for NASH would be incorrect and misleading. In addition, vitamin E is not recommended for NASH in diabetic patients (Chalasani et al. Hepatology, 2018). A recent systematic literature review and meta-analysis reported that the prevalence of NASH among patients with type 2 diabetes mellitus (T2DM) was 37.3% (95% CI 24.7–50.0) when diagnosed via liver biopsy, and the prevalence of advanced fibrosis among biopsied patients with NAFLD and T2DM was 17.0% (95% CI 7.3–34.9) (Younossi et al, 2019). Results from Bril et al, 2019 in patients with NASH and T2DM showed that vitamin E alone was not different from placebo in achieving improvement in the primary liver
histological outcome or the proportion of patients achieving improvement in steatosis, inflammation, ballooning, or fibrosis.

In addition, including pioglitazone as comparator for NASH would be incorrect and misleading. The efficacy data for use of pioglitazone to treat NASH are limited. The largest study has been the PIVENS trial (Sanyal et al, 2010) which was relatively small. It included 247 adults with nonalcoholic steatohepatitis to receive pioglitazone at a dose of 30 mg daily (80 subjects), vitamin E at a dose of 800 IU daily (84 subjects), or placebo (83 subjects), for 96 weeks. People with Type 2 diabetes were excluded and nearly 20% of the study population did not have liver fibrosis. Results from the PIVENS trial showed that both vitamin E and pioglitazone were associated with reductions in hepatic steatosis (P=0.005 for vitamin E and P<0.001 for pioglitazone) and lobular inflammation (P=0.02 for vitamin E and P=0.004 for pioglitazone) but not with improvement in fibrosis scores (P=0.24 for vitamin E and P=0.12 for pioglitazone). Though pioglitazone did demonstrate favorable impact on NASH activity, the small study size and discrepancies between the study population and the anticipated target pre-cirrhotic NASH population (F2-3 and including T2DM) preclude conclusions regarding the efficacy of pioglitazone for NASH treatment.

Pioglitazone has known adverse events such as edema and congestive heart failure and is potentially associated with increased fracture risk in women and increased risk of bladder cancer. In part due to these safety issues, the use of pioglitazone for its approved indication of T2DM is quite limited. For the rolling 12-month period ending in August 2019, pioglitazone accounted for 3.7% of the total prescriptions in the US for Type 2 Diabetes oral antidiabetic and GLP-1 agonists market (TRx volume pioglitazone was 6,011,973 and the total OAD+GLP-1 market volume was 160,841,215) (IQVIA NPA August 2019, extracted from OneView).

Given the limited assessment of pioglitazone efficacy in NASH, its safety liabilities, and its very limited use for its established T2DM indication, pioglitazone does not appear to be a relevant benchmark comparator for future agency-approved NASH treatments including OCA.

**Recommendation:** Provide a clear clarification on how vitamin E is going to be included and clear justification for including pioglitazone as comparator for treatment for NASH as this is not approved for use in the treatment of NASH.

### 2- Outcomes of interest:

Weight gain is not in itself a harm as listed in Table 1.2 as the clinical impact of weight gain depends on both the magnitude and nature of the weight gain. Several studies have shown the protective effect of increased muscle mass. While increased adiposity is generally associated with increased insulin resistance and its consequences (hyperglycemia, hyperlipidemia, steatosis), increased adiposity occurring with thiazolidinedione (pioglitazone, rosiglitazone) treatment is associated with improved insulin sensitivity and metabolic benefits. This illustrates the need to assess the health implications of weight gain based on specific clinical consequences, which may depend on the drug mechanism of action. Therefore, we would agree that unfavorable effects on lipid profiles and glycemic control should be considered harms. Weight gain of a magnitude likely to be associated with unfavorable consequences (e.g., by predisposing to worsening arthritic or
orthopedic conditions) might also be considered a harm, though this will require a clear, data-based rationale. We also suggest that liver decompensation events (bleeding varices, ascites, encephalopathy) be added to Table 1.2. as outcomes. This is noted on Page 7, but not in Table 1.2.

**Recommendation:** We strongly recommend that weight gain be assessed as a harm only if it has, or is likely to have, unfavorable clinical consequences such hyperlipidemia, hyperglycemia, steatosis, and/or worsening arthritic or orthopedic conditions. We also suggest that liver decompensation events (bleeding varices, ascites, encephalopathy) and glycemic control be added as outcomes.

### 3- Population

Studies have shown that subgroups of the NASH patient population are more likely to progress and should be considered as higher need for treatment. Increasing age, male sex, impaired insulin sensitivity, Hispanic ethnicity, obesity, and T2DM have been consistently identified as risk factors for fibrotic progression to cirrhosis (Estes et al 2018, Younossi et al 2019).

**Recommendation:** Consider that there are subgroups of the F1-F2 population that are fast progressors to outcomes and there may be value of early treatment as no drug has shown efficacy in the F4 population to date.

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

Director | CV/Metabolic Diseases | Center for Observational & Real-World Evidence (CORE)
351 N Sumneytown Pike, PO Box 1000, 2MW10B | North Wales, PA 19454-1099
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References


November 20, 2019

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

VIA Electronic Delivery

RE: Draft Scope: Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis with Fibrosis: Effectiveness and Value

Request for Comments

Dear Sir or Madam:

The undersigned organizations appreciate the opportunity to comment on the Institute for Clinical and Economic Review (ICER) draft scope entitled “Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis with Fibrosis: Effectiveness and Value.”

Central to understanding the impact of NASH are 8 core issues that must be considered and addressed equally within the draft scoping document:

1. Lack of public and clinician awareness of NASH
2. The intrinsic link to other diseases
3. NASH impact on quality of life
4. Unique issues at each stage of the disease
5. Challenges in diagnosing NASH
6. Risks of adverse outcomes, including liver cancer
7. Lack of treatment options
8. Liver transplantation and complications

With the required length limitation we will focus this letter on 3 of the topics above.

First, there is a lack of public and clinician awareness of NASH, leading to underreported and varying prevalence. Symptoms of NASH are non-specific and often misinterpreted. NASH is typically only detected once it has progressed to cirrhosis or liver cancer, therefore most people live for years unaware of the damage. Existing data is derived from people with NAFLD selected for biopsy. Given that liver biopsy is rarely
performed outside of a specialist setting, this is not truly representative of the scope of the NAFLD population, and plays a role in the under-reporting of NASH in primary care settings.\(^5\)

Second, there are major concerns with the “gold standard” for NASH diagnosis, liver biopsy. The risky, invasive, and expensive procedure can also be subject to sampling variability and should be a diagnostic test of last resort.\(^2\)\(^6\) Biopsy also plays a role in the high costs associated with NAFLD care, independent of metabolic comorbidities. The largest increases in health care utilization and costs in NAFLD are represented by liver biopsies and hospitalizations.\(^7\) Currently, acceptable and relatively accurate non-invasive tests (NIT) exist are being developed to assess liver fibrosis.\(^8\)\(^9\)\(^10\)\(^11\)

Third, the risk of adverse outcomes and mortality increases with fibrosis progression. NASH patients have a seven year mortality rate of 7.9%, almost twice that of the general population.\(^12\)\(^13\)\(^14\)\(^17\) Presence and degree of fibrosis are main factors in determining disease outcome of NASH.\(^12\)\(^13\)\(^14\) The rate of disease progression is not uniform; some patients experience fast fibrosis progression while others follow a slower, or regressive, course.\(^16\) CVD is the most common cause of death, followed by cancer outside the liver and liver-related complications (due to cirrhosis and liver cancer).\(^12\)\(^13\)\(^15\) Approximately 2–12% of NASH patients develop liver cancer annually.\(^18\) For people with end-stage liver disease and/or NASH-related liver cancer liver transplantation is the only option.\(^19\)

**NAFLD and NASH Progression**

- **25%** People with NASH have an overall mortality rate of almost twice that of the general population.
- **20%** People with NASH can progress to fibrosis stage 3 and cirrhosis.
- **2-12%** People with NASH cirrhosis that will develop liver cancer per year.

The rise of NASH, its complications and comorbidities carry significant economic costs for health systems and society. The efficacy and side effects of OCA or any other pharmacologic intervention should be evaluated against the cost of disease progression and cost as well as efficacy of current standard of care (weight loss). Existing analyses show increasing costs with increasing severity of disease.\(^17\)\(^20\) Including inpatient, outpatient, professional services, emergency department, and drug costs, the lifetime direct costs of the total U.S. NASH
population is $222.6 billion. Advanced NASH patients are estimated to be 20% of the total NASH population, but account for almost half of the cost total ($95.4 billion).21 22

Each critical point highlighted in this letter must be considered across each stage of NASH, and when looking at potential other benefits offered by the intervention not considered as part of the evidence on comparative clinical effectiveness.

We look forward to continuing to work together on a report that correctly captures the costs associated with this life threatening disease.

With appreciation and respect,

American Gastroenterological Association
Global Liver Institute
Endnotes

November 19, 2019

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

VIA Electronic Delivery

RE: Draft Scope: Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis with Fibrosis: Effectiveness and Value

Request for Comments

Dear Sir or Madam:

The Fatty Liver Foundation appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) draft scope entitled “Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis with Fibrosis: Effectiveness and Value.”

A key concern of the foundation is that NASH is comorbid with a wide range of other chronic non-communicable diseases. As we seek to analyze the benefit value of a NASH therapy it is important to keep in mind that liver dysfunction has wide ranging impact so therapies that improve liver status will almost certainly have secondary impacts that are likely of value.

The risk of obesity, type 2 diabetes, cardiovascular disease (CVD), cancer and chronic kidney disease is elevated in people with NAFLD. The global prevalence of NASH has increased in the past 15 years and is projected to continue rising parallel to the growth in obesity and type 2 diabetes. In people with obesity and type 2 diabetes, NAFLD prevalence is approximately 50–70% and NASH prevalence is approximately 56%. NASH has a bidirectional relationship with type 2 diabetes, such that once developed, diabetes can promote NASH progression to cirrhosis and liver cancer. People with type 2 diabetes and other metabolic conditions appear more likely to have more progressive stages of disease compared to people with few or no metabolic conditions.

Currently there are no FDA approved treatments available for NASH. A weight loss of 10% or more, which is the threshold shown to induce the highest rates of NASH resolution and fibrosis regression, is the only current recommended option. Also the utility of pioglitazone in NASH has insufficient evidence at this time and without a specific indication for NASH, a lack of coverage may make access to this problematic in real world application.
With appreciation and respect,

Wayne Eskridge

Wayne Eskridge CEO
November 20, 2019

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

VIA Electronic Delivery

RE: Draft Scope: Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis with Fibrosis: Effectiveness and Value
Request for Comments

Dear Sir or Madam:

NASH kNOWledge appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) draft scope entitled “Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis with Fibrosis: Effectiveness and Value.”

Central to understanding the impact of NASH are eight core issues that must be considered and addressed equally within the draft scoping document:

1. Lack of public and clinician awareness of NASH
2. The intrinsic link to other diseases
3. NASH impact on quality of life
4. Unique issues at each stage of the disease
5. Challenges in diagnosing NASH
6. Risks of adverse outcomes, including liver cancer
7. Lack of treatment options
8. Liver transplantation and complications

With the length limitation for responses we will focus on point 3.

Patients with NASH experience a range of symptoms that negatively affect their quality of life including major depressive disorder, generalized anxiety disorder, fatigue, feeling bloated, having discomfort or pain around the liver, sleeping problems and lethargy. Due to the lack of public awareness of liver health, and NASH in particular, patients with NASH find it difficult to differentiate between symptoms related to NASH and other health issues or comorbidities. Patients also feel a lack of adequate educational support from their physicians, and healthcare professionals may also not think to screen for NASH in high-risk patients.

Work performance was considered to decline as the disease progressed. Patients with a more severe disease stage mentioned taking frequent time off work due to medical appointments, ultimately leading to job changes. Work absences are also an issue with caregivers, causing lost time, lost wages and sometimes even job loss. One can imagine the economic burden placed on families when they can least afford it.
NASH is typically only detected once it has progressed to cirrhosis or liver cancer. As a result, most people live with the disease for years without being aware of the damage accumulating in their liver. Early detection coupled with effective medical treatment will benefit patients’ quality of life and save enormous amounts in our healthcare system. Transplant simply cannot be the ultimate solution for the treatment of this disease.

We applaud ICER for listening to the NASH patients who have been neglected for far too long, and look forward to continuing to work together on a final report that correctly captures the burden and costs associated with this life-threatening disease.

With appreciation and respect,

Anthony Villiotti
President, NASH kNOWledge

Notes:

November 20, 2019

Steven D. Pearson, M.D., M.Sc. FRCP
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

DELIVERED ELECTRONICALLY

RE: 2019 Nonalcoholic Steatohepatitis with Fibrosis Draft Scoping Review

Dear Dr. Pearson:

On behalf of Gilead Sciences, we would like to provide input into ICER’s scoping exercise for its review of Nonalcoholic Steatohepatitis (NASH) products.

Gilead, a science-based and patient-driven company, is committed to the development of new therapies that offer meaningful benefit for people living with advanced fibrosis due to NASH and other serious liver diseases. Gilead is advancing a pipeline of novel investigational agents for advanced fibrosis due to NASH, addressing multiple targets.

We encourage ICER to consider the following changes to its draft scoping document:

- **Interventions and Comparators.** We recommend that the interventions for this analysis should be obeticholic acid + standard care (intervention) versus standard of care (comparator) as well as obeticholic acid + standard care (intervention) versus placebo (comparator). In defining standard care, current American Association for Study of Liver Disease (AASLD) standard treatment guidelines recommend diet and exercise. Pioglitazone may be considered for diabetic patients with biopsy-proven NASH and Vitamin E (RRRa-tocopherol) may be considered when administered at a daily dose of 800 IU/day for non-diabetic adults with biopsy-proven NASH. AASLD guidelines caution that risks and benefits should be discussed with each patient before starting therapy. The guidelines, however, note that “until further data support its safety and efficacy, pioglitazone should not be used to treat NAFLD without biopsy-proven NASH.” Moreover, since the current phase 3 trials did not include pioglitazone endpoints in the trials, we believe pioglitazone should not be used as a comparator for this assessment. We would also like to note that current NASH standard care is limited and not sustainable for weight loss, as demonstrated in real-world NASH registry of over 4,500 patients. In a prospective cohort study, 293 patient with biopsy-proven NASH were encouraged to adopt recommended lifestyle changes to reduce weight, and weight status and NASH parameters were evaluated at week 52. In this study, less than 10% of the population had achieved sufficient weight loss [i.e., 10% weight loss] required to affect fibrosis. Given
the lack of long-term data on sustained weight loss outcomes, we believe placebo-only should also be considered as a comparator for this assessment.

- **Outcomes of Interest:**
  - **Key Measures of Clinical Benefit:** We believe ICER should add decompensated cirrhosis (DCC) as a key measure in this analysis. The progression from cirrhosis to DCC can occur in 10-31% of cases and its presence indicates a dire need for a liver transplant to prevent death from liver failure as there are currently no approved therapeutic interventions for DCC. The AASLD maintains that for clinical trials in subjects with cirrhosis, development of clinical decompensation is a recommended primary endpoint. DCC is a distinct health state that is accompanied by higher costs and a significant outcome of advanced liver disease. Compared to the general population, risk of death from DCC is 10 times higher. In addition, one-year and five-year survival for decompensated cirrhosis is 67% and 45%, which are 20% and 12% less, respectively, than for patients with compensated cirrhosis. Mortality due to NASH versus NASH with DCC also jumps from 13% to 51% and is associated with a higher comorbidity burden. 

  - **Intermediate Outcomes:** We also believe ICER should add "no worsening of fibrosis" as an intermediate outcome. AASLD recommends that "no worsening of fibrosis" be captured as an important endpoint in studies in subjects at risk of progression to cirrhosis. Progression of fibrosis to cirrhosis occurs in approximately 15% of cases. In a study of patient outcomes incorporating the SF-36, patients with cirrhosis reported worse physical functioning than patients with bridging fibrosis. In addition, health utilities between the two subgroups were lower on SF-6D and EQ-5D for patients with cirrhosis. Thus, advancement to cirrhosis is linked to a lower quality of life such that preventing the worsening of fibrosis would be a fundamental outcome for patients.

- **Model - General:** We encourage ICER to employ microsimulations to capture heterogeneity. Good modeling practice would suggest patient-level modeling to capture variances in comorbidities, genetic issues, performance status, etc. ICER should incorporate the most recent data and understanding of NASH to address differences across patients for a more accurate analysis. NASH inter-individual differences include clinical-histologic phenotypes such as NASH with non or early stage disease (stage 0-2), NASH with advanced fibrosis or cirrhosis (stage 3-4), cryptogenic cirrhosis, decompensated cirrhosis, and recurrent NASH post liver-transplant.

- **Costs:** To best capture the financial consequences associated with progressed liver disease, ICER should assess costs based on real-world data (RWD), with particular focus on real-world healthcare resource use in Medicare and the commercial population. There are significant differences in patient costs dependent on stage of disease. For example, Medicare DCC patients average $74,000 annually, $47,000 more than patients with compensated cirrhosis, largely due to inpatient services. Moreover, in 93% of cases, a patient’s first cirrhosis diagnosis is identified with a decompensated event. There are similar differences in commercially insured populations.

- **Health States:** We encourage ICER to use updated NASH-specific data sets, not hepatitis C, with special attention to the latest research to inform transition probabilities. The most recent publication on natural history of progression in advanced fibrosis published by Sanyal
et al shows that in a well-controlled CT with biopsy-proven NASH one out of 5 patients progressed to the next stage of disease in two years or less. Similarly, ICER should consult the most recent publication on updated mortality data, including Sanyal (2019) and Chattwaal (2018).

Overall, we appreciate ICER’s steps towards increasing transparency in modeling and look forward to a transparent, data-based dialogue. The way cost-effectiveness models are developed to capture value has evolved over time. We believe that the proposed draft scoping document can be improved to capture the real value of NASH treatments. We appreciate this opportunity to make some initial comments in such a dialogue and look forward to future interactions.

Sincerely,

Bill Guyer
Senior Vice President and Head of Medical Affairs

REFERENCES


v Calzadilla Bertot L, Adams LA. The natural course of non-alcoholic fatty liver disease. International journal of molecular sciences. 2016 May;17(5):774. Available at: Link


