REPORT AT A GLANCE: **NON-ALCOHOLIC STEATOHEPATITIS**

MAY 2023

KEY FINDINGS

Intervention	Evidence Rating	Annual WAC*	Health-Benefit Price Benchmark	Change from Annual Price to Reach Threshold Price
Resmetirom (Madrigal Pharmaceuticals, Inc.)	Comparable or better to the standard of care (C++) for patients with NASH with F2 or F3 fibrosis	$19,011	$39,600 to $50,100 per year	No discount needed
Obeticholic acid (Ocaliva®, Intercept Pharmaceuticals, Inc.)	NASH with F2 fibrosis: insufficient ("I") NASH with F3 fibrosis: promising but inconclusive ("P/I")	$85,111	$32,600 to $40,400 per year	38%-47%

*WAC: wholesale acquisition cost; based on placeholder prices

"NASH is increasingly common and lacks good therapies. While many with NASH will remain asymptomatic, some individuals will progress to severe liver disease and experience the complications of cirrhosis, hepatocellular cancer, and/or require liver transplantation. NASH is also a marker for increased cardiovascular risk and one of these therapies, resmetirom, improves lipids, while the other therapy, obeticholic acid, worsens lipids and also causes itching in many patients. If these drugs receive FDA approval, while awaiting long-term liver and cardiovascular data, patients and doctors will need to balance the risks, burdens, and potential benefits of each of these therapies."

– ICER's Chief Medical Officer, David Rind, MD

THEMES AND RECOMMENDATIONS

- All stakeholders have an important role to play in ensuring that new treatment options for patients with NASH are introduced in a way that addresses health equity. This includes fair pricing for drugs, outreach to and coverage for screening in underserved communities, and integrated coverage of NASH treatments with broader approaches to coverage for programs and treatments for obesity.
- Payers should require that the prescription of initial therapy with resmetirom or obeticholic acid be done by a hepatologist. It is reasonable to limit prescribing to hepatologists or gastroenterologists until more is known about safety and efficacy in real world use. Once sufficient experience is gained with the initial management of these therapies, it would be reasonable to establish systems for diagnosis and management of NASH by primary care physicians in consultation with hepatologists, including electronic or virtual consultation.
- Once the FDA has approved the first therapy for NASH, there will likely be an increase in advertising about NAFLD and NASH as silent diseases and for patients to ask their doctors about screening. Given the number of patients that have NAFLD, this should be done in a measured way to avoid overwhelming the healthcare system. In addition, the messaging should highlight that only patients with significant fibrosis require treatment and that most patients with these conditions do not progress to clinically significant liver disease.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

An estimated 24% of adults in the United States (US) have nonalcoholic fatty liver disease (NAFLD). NAFLD can be subcategorized as nonalcoholic fatty liver (NAFL), in which there is hepatic steatosis (HS) but no injury to liver cells, and as nonalcoholic steatohepatitis (NASH), in which HS is accompanied by hepatocellular injury. It is estimated that the prevalence of NASH in the adult population is between 1.5% and 6.5%. Patients with NASH may have liver fibrosis, and liver fibrosis can progress to cirrhosis placing patients at high risk of death from liver failure or liver cancer. Some patients may need liver transplantation. Despite an increased risk of death from liver-related causes, cardiovascular disease (CVD) is the most common cause of death in patients with NAFLD. Obesity is a common risk factor in patients with NASH. Lifestyle interventions, including exercise and weight loss, can improve NASH, as can weight loss after bariatric surgery. There are currently no FDA approved medications for NASH.

Two oral medications are currently being evaluated as treatments for NASH with fibrosis. Resmetirom is a small molecule agonist for the thyroid hormone receptor beta (THR-beta). Obeticholic Acid (OCA) is a bile acid analog that was approved for the treatment of patients with primary biliary cholangitis (PBC) in 2016. ICER had previously reviewed OCA as a treatment for NASH in 2020 and found the evidence inconclusive at that time.

Topline data from a phase 3 trial found that more patients treated with resmetirom 80 mg or 100 mg than placebo had ≥ 1 stage improvement in fibrosis without worsening of NASH (24% and 26% vs. 14%) and more had NASH resolution without worsening of fibrosis (26% and 30% vs. 10%). The most frequent adverse event was diarrhea (28% to 34% vs. 16% placebo); LDL-cholesterol decreased with resmetirom compared with placebo.

More patients treated with OCA 25 mg for 18 months than placebo had achieved ≥ 1 stage improvement in fibrosis without worsening of NASH (22% vs. 10%) without significant differences between groups in NASH resolution without worsening of fibrosis. The discontinuation rate because of adverse events was higher with OCA than placebo (21.6% vs. 11.3%) with pruritus seen in 55% of patients receiving OCA; pruritus was the most common adverse event leading to treatment discontinuation. LDL-cholesterol increased initially with OCA; these increases came down over time, but it is unclear whether this improvement was due to initiation of treatment with cholesterol-lowering medication.

NASH is typically asymptomatic for most of its clinical course, and that course can be long; in many patients, NASH does not progress. Since the existing trials are relatively short, there are important uncertainties about their actual long-term benefits. For both drugs, it remains unclear whether the changes in the primary outcomes will translate into a reduction in cirrhosis, decompensated liver failure, hepatocellular carcinoma (HCC), liver transplantation and death or into improvements in quality of life. Treatments for a condition that may never become symptomatic must necessarily be quite safe and tolerable if they are to be used for many years. There are concerns about the safety of OCA because of the initial increases in LDL-cholesterol levels and because of reports of hepatic decompensation and death in patients with PBC treated with OCA. Tolerability is a concern because of pruritus, although patients may decide to continue therapy and manage their pruritus. We have fewer concerns about the safety and tolerability of resmetirom.

Clinical Analyses

As such, for resmetirom we conclude that there is moderate certainty of comparable to substantial net health benefits with high certainty of at least comparable benefits compared with standard of care (C++) for individuals with NASH with F2 or F3 fibrosis.

For OCA, we judge the evidence for OCA in NASH with F2 fibrosis to be insufficient ("I") and with F3 fibrosis, where patients are at higher risk of progression to cirrhosis, to be promising but inconclusive ("P/I").

Economic Analyses

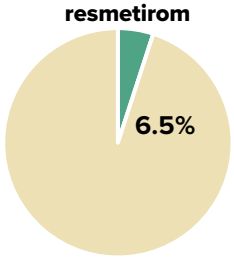
LONG-TERM COST EFFECTIVENESS

In our lifetime economic model, treatment of patients with NASH with fibrosis with either resmetirom or OCA resulted in small gains in QALYs, evLYs, and life years along with reductions in disease-related costs. The cost-effectiveness of both drugs will depend on their price. If the price of OCA is not substantially reduced from the price of the approved (lower) doses used for PBC, it will not meet typical cost-effectiveness thresholds. ICER's Health Benefit Price Benchmark (HBPB) for resmetirom is $39,600 to $50,100 and the HBPB for OCA is $32,600 to $40,400. Because of the large number of adults in the US with NASH, the short-term budget impact of newly approved treatments may be a concern even for treatments that are cost-effective in the long run.

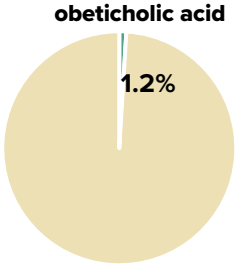
POTENTIAL BUDGET IMPACT

At the placeholder prices for resmetirom and obeticholic acid, assuming a 20% uptake of resmetirom and obeticholic acid each year approximately 6.5% and 1.2% US patients eligible for NASH treatment could be treated within five years without crossing the ICER potential budget impact threshold of $777 million per year.

ICER is issuing an access and affordability alert for resmetirom and obeticholic acid in the management of NASH. The purpose of an ICER access and affordability alert is to signal to stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services, creating pressure on payers to sharply restrict access, or causing rapid growth in health care insurance costs that would threaten sustainable access to high-value care for all patients.



Percent of eligible patients with NASH that could be treated in a given year before crossing the ICER potential budget impact threshold



Percent of eligible patients with NASH that could be treated in a given year before crossing the ICER potential budget impact threshold

Public Meeting Deliberations

VOTING RESULTS

For adults with non-alcoholic steatohepatitis (NASH) with significant fibrosis (i.e., stage 2 and stage 3 fibrosis) and not cirrhosis.

- A slight majority of panelists (8-7) found that current evidence is **adequate** to demonstrate a net health benefit for resmetirom when compared to lifestyle management alone.
- A majority of panelists (14-1) found that current evidence is **not adequate** to demonstrate a net health benefit for obeticholic acid when compared to lifestyle management alone.

During their deliberations, panel members also weighed potential benefits and disadvantages beyond the direct health effects, and broader contextual considerations. Voting highlighted the following as particularly important for payers and other policymakers to note:

- The acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability;
- The magnitude of lifetime impact of NASH on individual patients is substantial.

Consistent with ICER's process, because there is no firm estimate yet of a potential launch price for both treatments, the panel did not take separate votes on the treatments' long-term value for money.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer.org).