Resmetirom and Obeticholic Acid for Non-Alcoholic Steatohepatitis (NASH)

Draft Background and Scope

October 5, 2022

Background

ICER reviewed obeticholic acid for NASH in 2020. Much of the background information in this draft scoping document is updated from that report. Nonalcoholic fatty liver disease (NAFLD) is common in the general population. An estimated 24% of adults in the United States (US) have NAFLD.[1] NAFLD requires the presence of fat in the liver (hepatic steatosis [HS]) without another explanation such as significant alcohol consumption or use of medications that cause HS.[2] NAFLD can be subcategorized as nonalcoholic fatty liver (NAFL), in which there is HS but no injury to liver cells (hepatocellular injury), and as nonalcoholic steatohepatitis (NASH), in which HS is accompanied by hepatocellular injury.

The exact prevalence of NASH is uncertain since diagnosis requires liver biopsy and many patients with NAFLD do not undergo biopsy. It is estimated that the prevalence of NASH in the adult population is between 1.5% and 6.5%.[1] Patients with NASH may have liver fibrosis, and liver fibrosis can progress to cirrhosis. Patients with cirrhosis are at high risk of death from liver failure and liver cancer (hepatocellular carcinoma [HCC]), and may require liver transplantation.[2] NAFLD is associated with the metabolic syndrome with or without type 2 diabetes mellitus (T2DM) and NAFLD and metabolic syndrome share the common risk factor of obesity. Metabolic syndrome is a major risk factor for cardiovascular disease (CVD), and despite an increased risk of death from liver-related causes, CVD is the most common cause of death in patients with NAFLD.[1] 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.[3]

The prognosis of NAFLD is variable. Most patients with NAFL and with NASH without fibrosis do not progress, and while some patients with NASH and fibrosis do progress to advanced liver disease, many stabilize or regress without pharmacotherapy. A meta-analysis of the placebo arms of clinical trials in patients with NASH found that 25% showed improvement on a common measure of disease activity.[4] In unpublished results from one trial, similar percentages of patients receiving placebo improved and worsened (23.2% vs 20.9%); presumably more than half of patients showed stability in their degree of fibrosis.[5]

Lifestyle changes that result in improvement in the metabolic syndrome, including exercise and weight loss, can improve NASH, as can weight loss after bariatric surgery; bariatric surgery also improves T2DM and the metabolic syndrome.[2,6] There have been limited pharmacologic options for treating NASH, although many are now in development. Vitamin E and pioglitazone may have efficacy for the histologic changes of NASH.[2]

Obeticholic acid (OCA; Ocaliva™; Intercept Pharmaceuticals) is a bile acid analog that was approved for the treatment of patients with primary biliary cholangitis in 2016. OCA is under review as a treatment for NASH with fibrosis, with a Food and Drug Administration (FDA) decision expected in 2023. ICER had previously reviewed OCA as a treatment for NASH in 2020 and found the evidence insufficient at that time. The prior report can be accessed, here: https://icer.org/wp-content/uploads/2020/10/ICER_NASH_Evidence_Report_072120.pdf.

Resmetirom (Madrigal Pharmaceuticals, Inc.) is a small molecule agonist for the thyroid hormone receptor beta (THR-beta). When activated in the liver, THR-beta leads to the breakdown of stored fat. Resmetirom is under review as a treatment for NASH with fibrosis, with a Food and Drug Administration (FDA) decision expected in 2023.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during our prior reviews on this topic as well as preliminary calls with stakeholders and open input submissions from the public specific to this review. A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

We heard from patients and patient groups about the discomfort of dealing with a disease that was virtually unknown two decades ago, has become increasingly prevalent since then, and yet still has little awareness in the general public and seemingly little focus as an issue of concern among primary care clinicians. Patients described believing themselves healthy, developing some symptoms that required evaluation, and then rapidly learning that they had advanced liver disease with all its risks and complications. Some found they rapidly needed liver transplantation.

Patients described the fatigue and brain fog of cirrhosis, the loss of the ability to work, drive, or productively contribute to the home, and the depression and fear caused by suddenly learning of a devastating disease. Patients with decompensated cirrhosis described abdominal pain and hospital admissions for ascites requiring paracentesis (removal of fluid from the abdomen) and for delirium from hepatic encephalopathy. A common experience was of having been told years earlier that

they had fat in the liver but that it was nothing to worry about, only to next have the issue raised when diagnosed with cirrhosis.

Patients and patient groups described the strain on caregivers of having a family member become disabled and confused, as well as the potentially extreme financial strain of having medical bills for advanced liver disease mount at the same time that the patient became unable to contribute to the household income.

We heard conflicting opinions about whether NAFLD was typically symptomatic before the development of advanced liver disease. Some stakeholders felt that fatigue, liver pain, and some generalized pain were common in patients with earlier stages of NASH, while others believed NAFLD was asymptomatic until late in the disease course or that these symptoms were similarly common in patients with the metabolic syndrome with or without NASH.

We received additional input from patient groups highlighting the broad impacts on health from liver dysfunction, concerns about lack of insurance coverage for pioglitazone given its lack of an FDA indication for NASH, and that NASH has very different implications for patients at different stages of disease, including very different effects on quality of life. We also heard ongoing concerns about lack of knowledge of NASH both in the general public and among clinicians. Based on feedback we received from other stakeholders on ICER's prior report on NASH, we added decompensated cirrhosis as an outcome of interest, added subgroups of patients with more and less advanced fibrosis, and revised the descriptions of the comparators, the key outcomes, and the population of interest to improve clarity.

Report Aim

This project will evaluate the health and economic outcomes of resmetirom and obeticholic acid (Ocaliva, "OCA") for non-alcoholic steatohepatitis (NASH). The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers,

and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for the review is adults age ≥ 18 with NASH with significant fibrosis and not cirrhosis. As data allow, we will look at subgroups of interest including fibrosis stage, presence of diabetes, and race / ethnicity.

Interventions

The full list of interventions is as follows:

Obeticholic Acid (Ocaliva)
Resmetirom

Comparators

Data permitting, we intend to compare all the agents to each other and to usual care alone (as estimated by the placebo arms of the clinical trials).

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - All-cause mortality
    - Cirrhosis
    - Decompensated cirrhosis
    - Health related quality of life
    - Hepatocellular carcinoma
    - Liver-related mortality
    - Liver transplantation
    - Cardiac and cardiovascular events (heart attacks, strokes, etc.)
    - NASH symptoms (abdominal pain, fatigue)
    - Adverse events including
        - AEs leading to drug discontinuation
        - Serious AEs
        - Pruritis
        - Weight gain or loss
        - Diarrhea
        - Nausea
- Other Outcomes
    - Changes in lipid levels
    - Changes in blood pressure
    - Changes in NAFLD Activity Score (NAS)
    - Fibrosis stage
    - Liver markers of inflammation
    - Quantitative measures of liver fat content
    - Resolution of NASH

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, including inpatient and outpatient settings in the United States.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.2. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration*
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

Potential Other Benefit or Disadvantage*
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients' ability to manage and sustain treatment given the complexity of regimen
Society's goal of reducing health inequities
Other (as relevant)

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of the treatments of interest relative to relevant comparator treatments. 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.[7,8] The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. The target population will consist of adults 18 years or older with NASH with fibrosis. The model is expected to consist of two cardiovascular (CV) event history

sub models (No prior CV event and Prior CV event). Each sub model will include health states for no fibrosis, fibrosis stage 1, fibrosis stage 2, fibrosis stage 3, compensated cirrhosis (i.e. fibrosis stage 4), decompensated cirrhosis, hepatocellular carcinoma (HCC), post-liver transplant, and death. A cohort of patients will transition between states during predetermined cycles over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., five years).

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using data from the relevant clinical trials and the clinical evidence review.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of progression to advanced liver disease (lifetime decompensated cirrhosis, HCC, and liver transplant) and CV events (myocardial infarction and stroke), life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per advanced liver disease avoided.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by OCA or resmetirom (e.g., hospitalization for decompensated cirrhosis), as these services will be captured in the economic model. Rather, we are seeking services used in

the current management of NASH beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

References

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