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

Draft Scope

October 30, 2019

Background

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 highly associated with the metabolic syndrome with or without type 2 diabetes mellitus (T2DM) and NAFLD and metabolic syndrome have 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.[3] NASH has become a major cause of cirrhosis and, as effective treatment of hepatitis C is now available, it is expected to become the leading reason for liver transplantation.[2]

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]

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.[2,5] 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 2020. ICER had previously reviewed OCA as a treatment for NASH in 2016 and found the evidence insufficient at that time. That report can be accessed, here: https://icer-review.org/material/final-report-oca-nash/. Additional evidence has since become available for OCA as well as for other therapies for NASH.

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 preliminary calls with stakeholders and open input submissions from the public. A final 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.

Report Aim

This project will evaluate the health and economic outcomes of treatments with obeticholic acid for NASH with fibrosis. 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

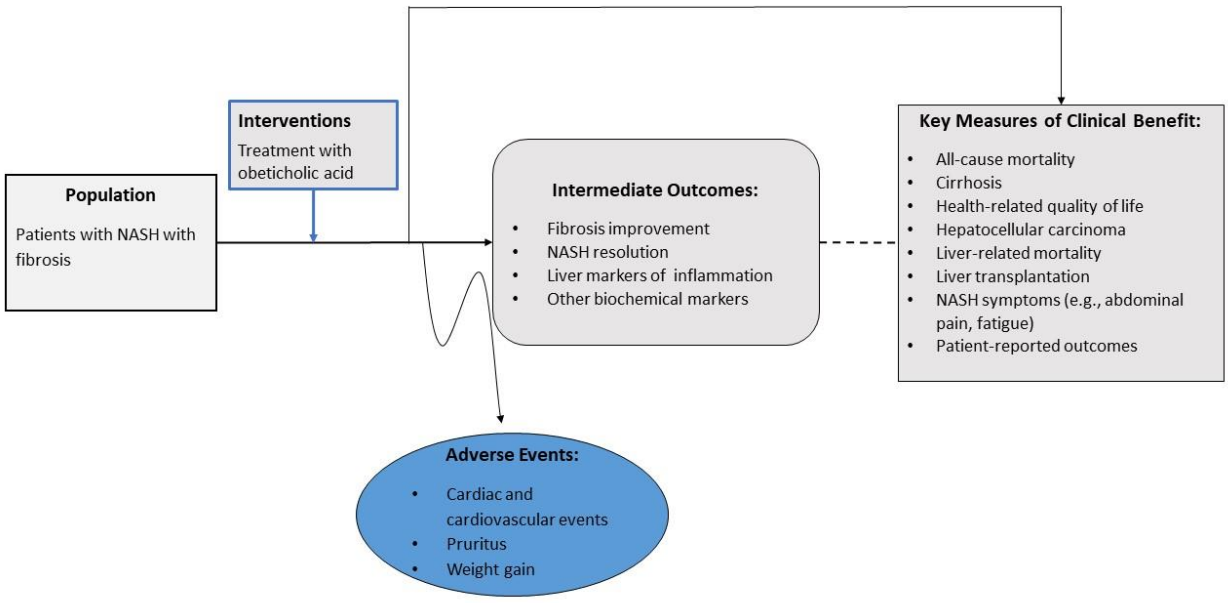
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative 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 https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/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 finalized scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The general analytic framework for assessment of obeticholic acid for nonalcoholic steatohepatitis (NASH) is depicted in Figure 1.1 below.

Figure 1.1. Analytic Framework: Anabolic Therapies for NASH



AE: adverse event, SAE: serious adverse event

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., fibrosis improvement), and those within the squared-off boxes are key measures of benefit (e.g., cirrhosis). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.[6]

Populations

The population of focus for the review is adults age ≥ 18 with NASH with fibrosis.

Interventions

The intervention of interest will be obeticholic acid administered as oral tablets plus usual care. Usual care includes lifestyle interventions, other treatments for NASH (including vitamin E), as well as usual care for associated metabolic comorbidities.

Comparators

Obeticholic acid will be compared with usual care (as estimated by the placebo arms of the clinical trials) and also to pioglitazone added to usual care as described above.

Outcomes

The outcomes of interest are described in Table 1.2 below.

Table 1.2. Key Outcomes and Harms

Outcomes	Harms
All-cause mortality	Cardiac and cardiovascular events
Cirrhosis	Pruritus
Health-related quality of life	Weight gain
Hepatocellular carcinoma	
Liver-related mortality	
Liver transplantation	
NASH symptoms (e.g., abdominal pain, fatigue)	
Patient-reported outcomes	

Additional intermediate and surrogate outcomes of interest include:

- Alterations in lipids
- Improvement in fibrosis
- Improvement in liver markers of inflammation
- Improvement in other biochemical markers
- NASH resolution

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 elements are listed in the table below.

Table 1.1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

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 a simulation 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, including the 2016 ICER review https://icer-review.org/material/final-report-oca-nash/. The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity losses and other indirect costs will be considered in a separate analysis using a modified societal perspective. The target population will consist of people 18 years or older with NASH with fibrosis. The model will likely consist of health states including NASH resolution, fibrosis stage 1, fibrosis stage 2, fibrosis stage 3, fibrosis stage 4, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), 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 may 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 decompensation events avoided, HCC avoided, liver transplants avoided, life-years, quality-adjusted life years (QALYs) gained, and equal value life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for each event and 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 losses and other indirect costs will be included in a separate scenario 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 liver transplant avoided.

In separate analyses, we will explore the potential health 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 simulation model for treatment costs and cost offsets. This potential 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 at: http://icer-review.org/wp-content/uploads/2018/05/ICER-value-framework-v1-21-18.pdf.

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-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by OCA (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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6. Woolf S. An organized analytic framework for practice guideline development: using the analytic logic as a guide for reviewing evidence, developing recommendations, and explaining the rationale. *Clinical Practice Guideline Development: Methodology Perspectives AHCPR Pub.* 1994(95-0009):105-113.