

## **Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis: Effectiveness, Value, and Value-Based Price Benchmarks**

### ***Draft Background and Scope***

**March 23, 2016**

#### **Background:**

Nonalcoholic steatohepatitis (NASH) is form of nonalcoholic fatty liver disease (NAFLD) that can progress to cirrhosis, liver failure, and cancer. It is defined by an accumulation of triglycerides in the cells of the liver with inflammation and ballooning of the liver cells, with or without fibrosis. A liver biopsy is needed to make a diagnosis of NASH. Other causes such as excessive alcohol consumption, viral hepatitis, and other liver disease must be excluded.<sup>1</sup>

NAFLD is estimated to be present in up to 30% of the population (or 80 million adults) and NASH in around 10%, or 30 million adults, in the United States alone.<sup>2</sup> In one widely cited study of patients undergoing bariatric surgery, NAFLD was present in 91% and NASH in 37% of patients.<sup>3</sup> Lifestyle is an important factor for developing NAFLD and NASH. High fructose intake coupled with a sedentary lifestyle are associated with higher incidence rates, especially for NASH. NASH is closely linked to metabolic syndrome, defined by the presence of 3 or more of the following: abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) levels, hypertension, and an elevated fasting plasma glucose.<sup>2</sup> The rise in obesity and diabetes is contributing to an increase in NASH incidence worldwide.<sup>4</sup>

The natural history of NASH is highly variable between individuals. In a longitudinal study of 103 patients with sequential liver biopsies in the absence of effective treatment, fibrosis stage progressed in 37%, remained stable in 34% and regressed in 29% with a mean interval of around 3 years between biopsies.<sup>5</sup> Around 11% of NASH patients progress to cirrhosis over a 15-year period, and NASH-related liver disease is expected to become the leading indication for liver transplantation in the United States by 2020.<sup>2</sup> Overall, NASH patients have a doubling of cardiovascular risk and a more than 10-fold increased risk of liver related death.<sup>6</sup>

Current treatment of NASH includes lifestyle interventions, control of metabolic syndrome, and liver-directed pharmacotherapy.<sup>6</sup> In a prospective study of 293 patients with biopsy-proven NASH, NASH resolved in 58% of patients who lost more than 5% of body weight over a period of 52 weeks. In patients who lost more than 10% of their body weight, NASH resolved in 90%, and fibrosis regressed in 45%.<sup>7</sup> Definition of resolution of NASH is based on the NAFLD activity score in liver biopsy of the Pathology Committee of the NASH Clinical Research Network.<sup>8</sup> Dyslipidemia, hypertension, and insulin resistance, aspects of metabolic syndrome, can be managed with specific pharmacotherapy, but there is no evidence of effect on liver histology. Pioglitazone, a drug used in the treatment of diabetes, has shown to be useful for treating NASH in non-diabetic patients, but the long term safety and efficacy of this approach has not

been established.<sup>1</sup> Vitamin E is considered the liver specific first line treatment of NASH, but does not improve fibrosis and may increase the risk of prostate cancer.<sup>1,2</sup>

A US based phase II trial of treatment of NASH with obeticholic acid (FLINT trial, NCT01265498) has shown an improvement in liver histology including fibrosis over a period of 72 weeks. A 5-year phase III trial was started in September 2015 (REGENERATE trial, NCT02548351). A combination trial of obeticholic acid and statins is also currently underway (NCT02633956) to study both liver-related outcomes as well as dyslipidemia (a known side effect of obeticholic acid). In January 2015, obeticholic acid received a breakthrough designation for treatment of NASH with concomitant liver fibrosis ([bit.ly/1pGh9jE](http://bit.ly/1pGh9jE)) but interim findings from the phase III trial are not expected to be available until March 2017. However, clinical interest in potential off-label use of obeticholic acid is likely to be great, given the lack of available treatments with liver-specific effects.

### Report Aim:

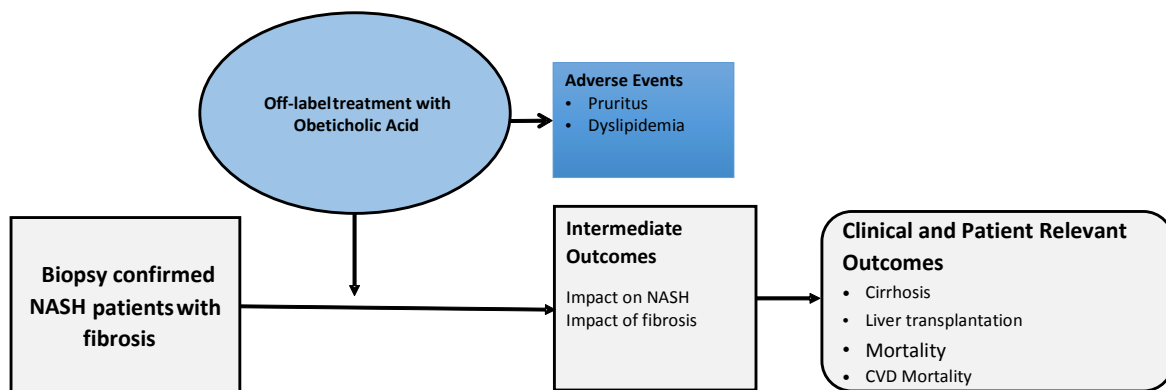
This project will evaluate the health and economic outcomes of obeticholic acid as an off-label treatment for adults with nonalcoholic steatohepatitis with fibrosis.

### Scope of the Assessments:

The proposed scope for these assessments is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be culled from phase II or III randomized controlled trials and comparative cohort studies as well as high-quality systematic reviews and meta-analyses where available. We will supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see <http://www.icer-review.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/>).

### Analytic Framework:

Figure 1: Analytic Framework: Obeticholic Acid for the treatment of Non-alcoholic steatohepatitis



### Populations

The population of focus for the review will include adults age  $\geq 18$  with biopsy confirmed NASH and fibrosis.

### Interventions

The intervention of interest will be treatment with obeticholic acid administered as oral tablets in doses of 10 or 25 mg once daily.

### Comparators

The comparator will be usual care, including lifestyle interventions and treatment with vitamin E.

### Outcomes

This review will examine key clinical outcomes related to NASH and its treatment, including surrogate outcomes in available clinical trials. Outcomes of interest will include:

- Impact on NASH (improvement, resolution)
- Measures of liver fibrosis
- Cirrhosis
- Liver transplantation
- Survival
- Health-related quality of life
- Adverse events (e.g., pruritus, effects on blood lipids)

### Timing

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

### Settings

All relevant settings will be considered, including inpatient, clinic, and outpatient settings.

## **Economic Evaluation & Simulation Models Focusing on Comparative Value:**

As a complement to the evidence review and to estimate long-term impact, we will develop a simulation model to assess the lifetime cost-effectiveness of OCA relative to standard treatment. Model structure will be based in large part on previously published data regarding the natural history and a previously published model of NASH.<sup>9</sup> The population modeled will be patients 18 years or older with histologic evidence of NASH following a liver biopsy and histologic evidence of fibrosis stage 1, stage 2 or stage 3. Key model inputs and estimates will differ to reflect varying levels of disease severity and risk of progression cirrhosis. Risks of side effects and quality of life for patients in different disease states will also be incorporated into the model. OCA efficacy will be estimated based on analysis of available trial results.

Key model outputs will include rates of clinical response and disease progression as well as time spent in each health state, treatment-related adverse events, disease-related survival, and the impact of these measures on health-related quality-of life. Costs will include those of current and subsequent treatment, management of adverse events, and ongoing NASH-related care. The time horizon will be lifetime. Results will be expressed primarily in terms of the incremental cost per quality-adjusted life year (QALY) gained (ICER) relative to the standard treatment strategy.

We will also assess the potential budgetary impact of each regimen over a 5-year time horizon, utilizing information on treatment costs and cost offsets from extended response and/or time off treatment. Potential budgetary impact analyses will assume a product “uptake” rate over the 5-year period based on ICER criteria. Finally, we will develop a “value-based price benchmark” for OCA, reflecting prices aligned with long-term cost-effectiveness thresholds and below a threshold for potential budgetary impact that would exceed growth targets for national health care costs.

More information on ICER’s methods for estimating product uptake and calculating value-based price benchmarks can be found at: <http://www.icer-review.org/wp-content/uploads/2014/01/Slides-on-value-framework-for-national-webinar-new-slide-19.pdf>.

## References:

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