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Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis: Comparative Clinical Effectiveness and Value

Draft Evidence Report

May 25, 2016

Institute for Clinical and Economic Review

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We would also like to thank Erin Lawler, MA and Shanshan Liu, MS, MPH for their contributions to this report.

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Stakeholder Input

The following stakeholders provided input and feedback that helped guide the ICER team as we shaped our scope and report. None of these stakeholders is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

Stakeholders

Harvard Pilgrim HealthCare
Indiana University School of Medicine
Intercept Pharmaceuticals
Massachusetts General Hospital
Mayo Clinic

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List of Acronyms Used in this Report

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CEA	Cost-effectiveness analysis
CC	Compensated cirrhosis
CT	Computed tomography
CRN	Clinical Research Network
FDA	US Food and Drug Administration
FLINT	Farsenoid X Receptor Ligand Obeticholic Acid in Nonalcoholic Steatohepatitis Treatment
GGT	Gamma-glutamyl transferase
HCC	Hepatocellular carcinoma
HDL	High-density lipoprotein
HOMA-IR	Homeostasis model assessment of insulin resistance
ICER	Increased cost effectiveness ratio
ITT	Intention-to-treat
LDL	Low-density lipoprotein
NAFLD	Nonalcoholic fatty liver disease
NAS	NAFLD activity score
NASH	Nonalcoholic steatohepatitis
OCA	Obeticholic acid
PBC	Primary biliary cholangitis
PBO	Placebo
PDUFA	Prescription Drug User Fee Act
PICOTS	Population, Intervention, Comparator, Outcome, Timing, Setting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomized controlled trial
SF-36	36-Item Short Form Health Survey
US	United States
UPSTF	United States Preventive Services Task Force
VA	Department of Veterans Affairs
VLDL	Very low-density lipoprotein

Executive Summary

Background

An executive summary will be provided as part of the full Evidence Report.

1. Background

1.1 Introduction

Background

Nonalcoholic steatohepatitis (NASH) is a 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. Both NAFLD and NASH are highly prevalent. NAFLD is estimated to be present in up to 30% of the population (or 80 million adults) and NASH in around 5% or 15 million adults in the US alone.[1,2] Among the 25 million Americans with diabetes, around 18 million are thought to have NAFLD, and 63–87% of patients having both diabetes and NAFLD may have NASH.[3,4] High fructose intake coupled with a sedentary lifestyle are associated with higher incidence rates, especially for NASH. NASH is closely linked to the metabolic syndrome, defined by the presence of three or more of the following: abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) levels, hypertension, and an elevated fasting plasma glucose.[2] The rise in obesity and diabetes is contributing to an increase in NASH incidence worldwide.[5]

Current treatment of NASH comprises lifestyle interventions (e.g., diet, exercise, and/or behavioral change), control of the metabolic syndrome, and liver-directed pharmacotherapy.[6] Obeticholic acid is a selective agonist of the bile acid nuclear receptor FXR. Its activity on lipid and glucose metabolism and hepatic inflammation makes it interesting candidate as a pharmacologic agent for treating NASH.[7] 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. In January 2015, obeticholic acid (OCA) received a US Food and Drug Administration (FDA) breakthrough designation for treatment of NASH with concomitant liver fibrosis[8] and a 5-year Phase III trial was started in September 2015 (REGENERATE trial, NCT02548351) Interim findings from this Phase III trial are expected to be available around March 2017.

OCA for the treatment of primary biliary cholangitis (PBC) was given a priority review by FDA. The expected date for FDA to approve this indication under the Prescription Drug User Fee Act (PDUFA) is May 29, 2016. If OCA receives market access for PBC, the clinical interest in its potential off-label use for NASH is likely to be great given the unmet medical need and the lack of other approved treatments.

Scope of the Assessment

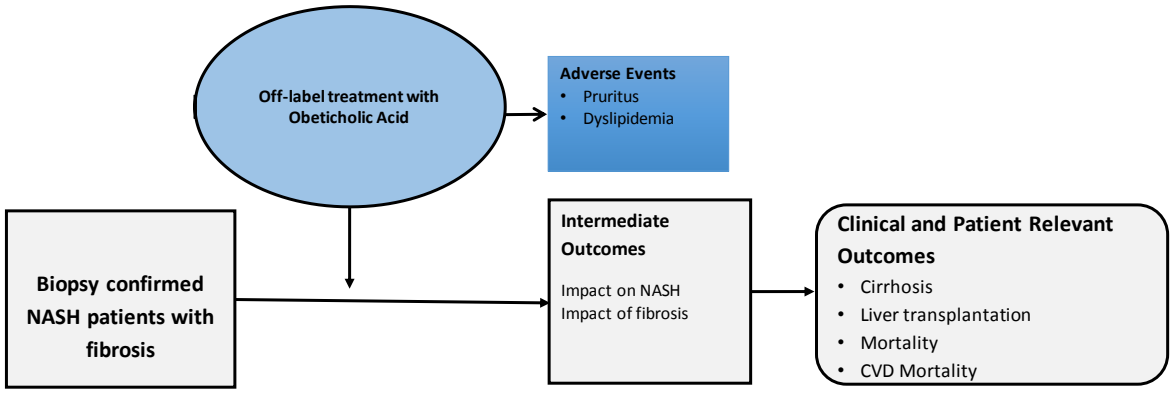
The proposed scope for this assessments is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was culled from

Phase II or III randomized controlled trials and comparative cohort studies as well as high-quality systematic reviews and meta-analyses where available. We supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.

Figure 1. Analytic Framework



Populations

The population of focus for the review included adults age ≥18 with biopsy confirmed NASH and fibrosis.

Interventions

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

Comparators

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

Outcomes

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

- 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 was derived from studies of any duration.

Settings

All relevant settings were considered, including inpatient, clinic, and office settings.

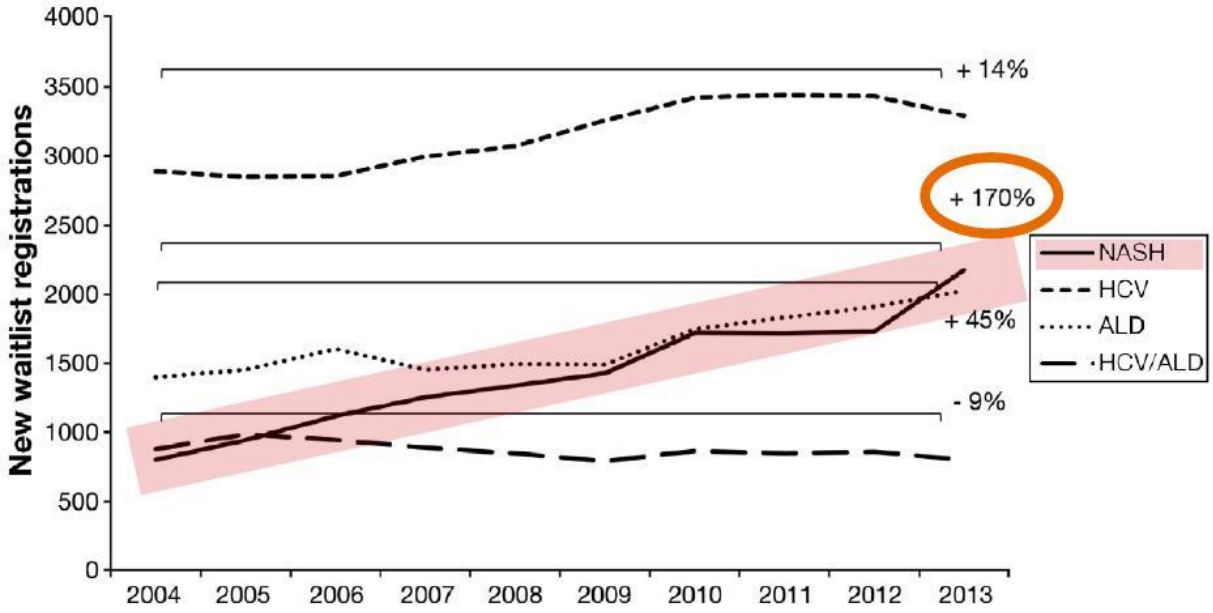
2. The Topic in Context

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 three years between biopsies.[9] Approximately 11% of NASH patients progress to cirrhosis over a 15-year period.[2] As NASH is largely asymptomatic,[2] cirrhosis can develop without any prior diagnosis. About 7% of patients with NASH cirrhosis will develop hepatocellular carcinoma (HCC) over 6.5 years of follow-up.[1] While the risk of developing HCC in cirrhotic NASH patients seems lower than in cirrhotic hepatitis C patients,[10] HCC can also occur in a substantial proportion of NASH patients in the absence of cirrhosis,[1] especially among diabetic patients.[11] Overall, NASH patients have a doubling of cardiovascular risk and a more than tenfold increased risk of liver-related death.[6]

Current treatment of NASH comprises lifestyle interventions (e.g., diet, exercise, and/or behavioral change), control of the metabolic syndrome, and liver-directed pharmacotherapy.[6] Weight loss does appear to be highly effective for treating NASH. 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%.[12] After bariatric surgery, steatosis, steatohepatitis, and fibrosis appear to improve or completely resolve.[13] 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.[13] 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.[2,13]

Data from the Centers for Disease Control and Prevention show that liver disease is the 12th leading cause of death in the United States.[14] This liver-related mortality results from complications of chronic liver disease. Between 1988 and 2008, NAFLD increased from 46.8% of chronic liver disease cases to 75.1%.[15] Between 2004 and 2013, NASH has become the second leading etiology of liver disease among adults awaiting liver transplantation in the United States (Figure 2) and is expected to become the most common indication for liver transplantation in the United States between 2020 and 2025.[16] Resource utilization for HCC is also largely driven by NASH, with NAFLD/NASH being the most common underlying etiologic risk factor (59%) for HCC in the United States between 2002 and 2008, followed by diabetes (36%) and hepatitis C virus infection (22%).[17]

Figure 2. Annual Trends in New Liver Transplant Waitlist Registrations in the US[18]



Considering the important disease burden of NASH, the evidence base for treatment is very poor compared to other chronic liver diseases.[19,20] However in recent years, clinical trials for NASH have increased dramatically.[21] The database ClinicalTrials.Gov contains currently 159 open studies for NASH including 16 Phase III trials.[22] Intercept and Genfit seem to be the only pharmaceutical companies with Phase III NASH drug candidates – respectively, OCA and elafibranor – with the elafibranor results expected first according to some business analysts.[23]

NASH's dynamic nature with spontaneous regression and slow asymptomatic evolution represents a great challenge for clinical trials.[24] The FDA and the American Association for Study of Liver Diseases (AASLD) jointly sponsored a workshop in September 2013 to discuss specific challenges and opportunities to facilitate development of therapeutics for NASH.[25] There are currently no validated surrogate endpoints that meet the evidentiary burden to qualify as a generally accepted endpoint for NASH trials.[26] The accelerated approval pathway used by FDA is based on surrogate outcomes that are "reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity."[27]

While there is a consensus to use histology-based endpoints as reasonable endpoints in NASH trials, the most appropriate choice of these endpoints is subject to debate, with trials using variations of outcome on NAFLD activity score (NAS) – based on steatosis, ballooning of hepatocytes and lobular inflammation – and outcomes based on fibrosis.[28] For example, the outcome of the Phase III trial of elafibranor uses a primary endpoint of NASH resolution without worsening of fibrosis (NCT02704403), while the co-primary endpoints of the Phase III trial for OCA are both a liver fibrosis

improvement with no worsening of NASH and NASH resolution with no worsening of liver fibrosis (NCT02548351). With fibrosis stage being the strongest predictor for disease-specific mortality in NASH,[29] the main author of the publication defining NAS in 2005[28] states 10 years later that "assessing fibrosis change as a primary outcome provides the clearest answer to the question of clinically relevant therapeutic response, although it may come at the cost of longer and/or larger trials."[30] NAS alone is not predictive of clinical outcomes, and therefore changes in NAS on therapy are probably not an adequate reasonable surrogate endpoint for drug approval.[31]

In the absence of disease-specific FDA approved therapeutics, the editors of the journal Hepatology consider the use of weight loss therapy in NASH to be "transformed from one of relatively ineffective lifestyle advice to providing evidence-based effective weight loss interventions, including dietician consultation, meal replacement, medications, and endoscopic intervention. This will change what is typically a relatively unsatisfying clinical interaction into a full plan for care with multiple visits, specific interventions, and the ability to monitor responses biochemically and via noninvasive assessment of fibrosis."[32] Dietary changes and lifestyle modifications are currently and will continue to be the first-line therapy for patients with NASH. Even with advances in lifestyle and weight loss interventions, those individuals with advanced liver disease or judged to be at high risk of progression to cirrhosis are in need of pharmacological therapy.[33]

If OCA receives market access for PBC, with an expected Prescription Drug User Fee Act (PDUFA) of May 29, 2016, this medication will become accessible for off-label use for NASH. While pharmaceutical companies are not allowed to promote their medications for off-label use, FDA does not limit or control how medications are prescribed by physicians once the medications are available on the market.[34]

A very large percentage of the 15 million adults in the United States alone who are estimated to be afflicted with NASH[1,2] ignore their condition. Among 127 patients with hepatic steatosis found incidentally on abdominal computed tomography (CT), only 29 (22%) patients had their diagnosis entered into their medical record by the primary care provider, none had documentation of the NAFLD fibrosis score, and none were referred for specialist evaluation or for liver biopsy. Fourteen patients (11%) at high risk for advanced hepatic fibrosis were identified by calculating the NAFLD fibrosis score.[35] Gastroenterologists and hepatologists also frequently diverge from published practice guidelines for the management of NASH. Although liver biopsy remains the gold standard to diagnose NASH, less than 25% of respondents routinely require it to make the diagnosis of NASH.[36]

In a primary care setting, the Michael E DeBakey VA Medical Center in Houston, Texas, 19,692 patients with elevated liver enzymes were identified from a total of 120,226 patients who consulted between 2004 and 2009. Of these, 450 were randomly selected for detailed chart review using the Computerized Patient Record System, and 251 patients were identified with probable NAFLD. For

only 99 patients (39.4%), the medical record mentioned abnormal ALT, with 54 patients (21.5%) identified as potentially having NAFLD. Thirty-seven patients (14.7%) were counseled on diet and exercise, and 26 (10.4%) were referred to a specialist. Among those at a high risk of fibrosis (NAFLD fibrosis score >0.675), only 3% of patients were referred to specialists.[37] This study indicates that only around 14% of probable NAFLD patients received some form of treatment in this primary care setting and that only 3% of high risk patients are seen by specialists.

The 2012 practice guideline for NAFLD recommends that "screening for NAFLD in adults attending primary care clinics or high-risk groups attending diabetes or obesity clinics is not advised at this time due to uncertainties surrounding diagnostic tests and treatment options, along with lack of knowledge related to the long-term benefits and cost-effectiveness of screening. (Strength – 1, Evidence -B)"[13] A cost-effectiveness analysis for screening for NASH in the high risk population of patients with type 2 diabetes concludes that "screening for NASH may improve liver related outcomes, but is not cost-effective at present, due to side effects of therapy. As better tolerated treatments for NASH become available, even with modest efficacy, screening for NASH will become cost-effective."[4]

3. Summary of Coverage Policies

FDA approval for obeticholic acid is pending at the time of this report. This section will be updated as coverage policies become available.

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the comparative clinical effectiveness of OCA as an off-label treatment of NASH, we abstracted evidence from available clinical studies, whether in published, unpublished, or abstract form. The intervention of interest was treatment with obeticholic acid administered as oral tablets in doses of 10 or 25 mg once daily.

As described previously in the Topic in Context section, the comparators of interest included usual care, including lifestyle interventions and treatment with vitamin E. Our review focused on key clinical benefits and surrogate outcomes of clinical benefit as well as potential harms and drug-related adverse events:

- Clinical Benefits
    - Fibrosis (as described by histologic assessment of biopsy specimens)
    - Cirrhosis
    - Liver transplantation
    - Survival
    - Impact on NASH (as described by NAFLD activity score and histologic assessment)
    - Other measures of liver function (AST, ALT, GGT, ALP, etc.)
    - Health-related quality of life (recorded with standardized and validated questionnaires administered at serial time points)
- Harms
    - Dyslipidemia
    - Incidence of pruritus
    - Other possible treatment-related events

Stratified results of these clinical benefits are provided within each reported outcome whenever possible, and other subgroup analyses (e.g., for diabetic patients) are presented separately.

4.2 Methods

We included evidence from Phase II and III randomized controlled trials (RCTs) and supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature that met ICER standards for review (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on OCA for NASH followed established best methods used in systematic review research.[38] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[39] The PRISMA guidelines include a checklist of 27 items, further detail of which is available in Appendix Figure A1.

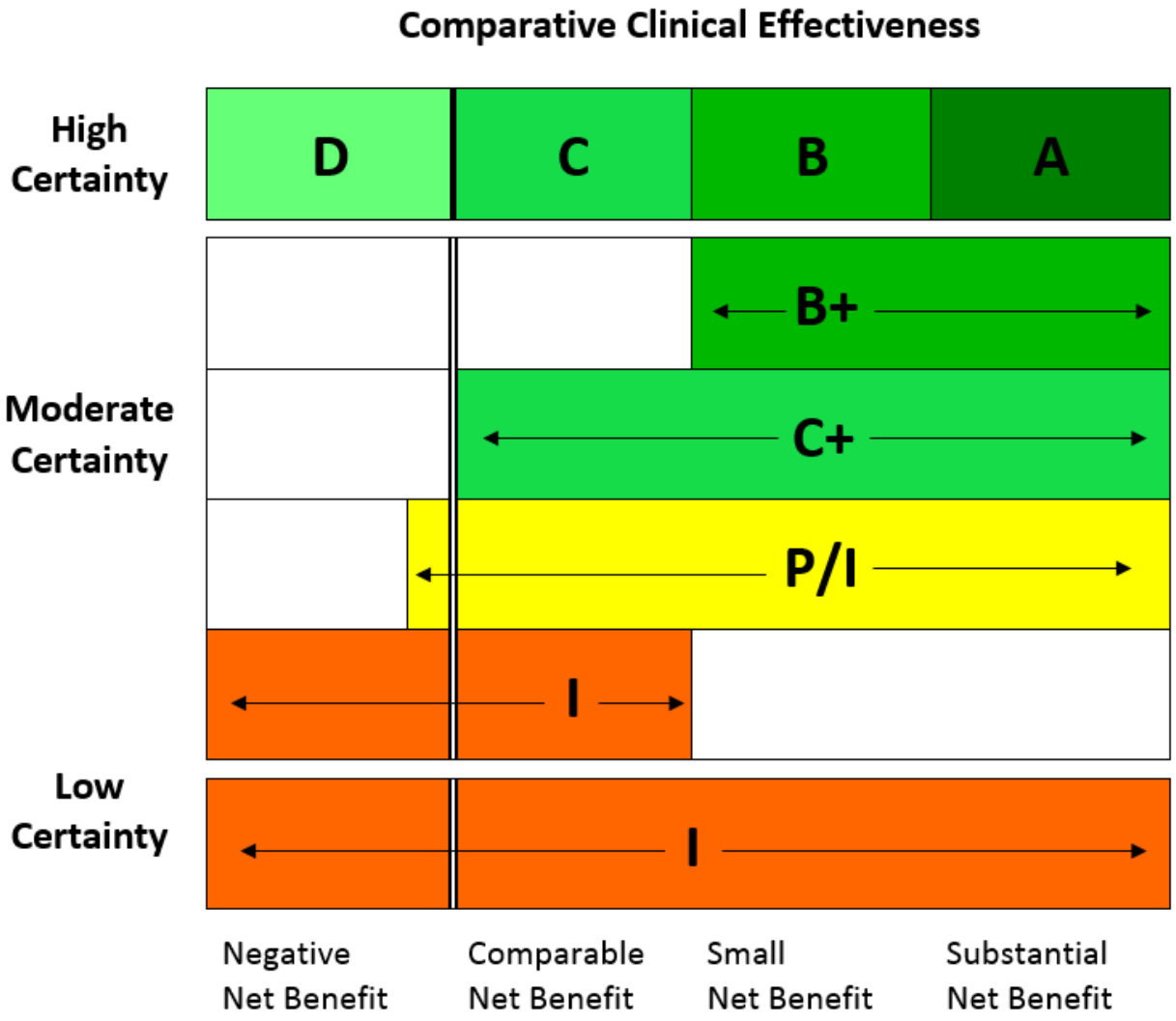
The timeframe for our search spanned the period from January 1996 to April 12, 2016 and focused on MEDLINE, EMBASE, and Cochrane-indexed articles. We limited each search to studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent relevant reviews and meta-analyses. Further details on the search algorithm, methods for study selection, data extraction, quality assessment, assessment for publication bias, and our approach to meta-analyses of the data are available in Appendix A.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 3) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[40]

Figure 3. ICER Evidence Rating Matrix



A = "Superior" **-** High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" **-** High certainty of a small net health benefit
C = "Comparable"**-** High certainty of a comparable net health benefit
D="Negative"**-** High certainty of an inferior net health benefit
B+="Incremental or Better" **–** Moderate certainty of a small net health benefit, with high certainty of at least incremental net health benefit
C+="Comparable or Better" **-** Moderate certainty of a comparable net health benefit, with high certainty of at least comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" **–** Either moderate certainty that the best point estimate of comparative net health benefit is comparable or inferior; or any situation in which the level of certainty in the evidence is low

4.3 Results

Study Selection

Our literature search identified 105 potentially relevant references (see Appendix A, Figure A1), of which two publications and three abstracts met our inclusion criteria; these citations related to two individual studies. Primary reasons for study exclusion included animal studies and absence of information on the outcomes of interest. Details of the included studies are described in Appendix E and the two key trials are summarized below in Table 1.

Key Studies

We identified two studies of interest for this review. Summarized in Table 1, these Phase II studies were double-blind, placebo-controlled, multicenter RCTs that examined OCA use among adults with NAFLD.

Farsenoid X Receptor Ligand Obeticholic Acid in NASH Treatment (FLINT) Trial[41]

The FLINT trial enrolled 283 patients with histologic evidence of non-cirrhotic, non-alcoholic steatohepatitis into a 72-week course of receiving either 25 mg daily OCA or placebo. Participants had baseline biopsies within 90 days of randomization into the study and again at the end of week 72, except for 64 patients who were excluded from the end-of-treatment biopsy when the data safety and monitoring board recommended not performing the biopsy after the superiority boundary was crossed (significantly different decrease in NAFLD activity score [NAS] – the primary outcome – between the OCA group and the placebo group: 43% vs. 21%; p=0.0024). All participants received recommendations on healthy lifestyle behaviors and appropriate management of hypertension, hyperlipidemia, and diabetes. Non-histologic outcomes were also assessed 24 weeks after the final dose was administered.

Efficacy and Safety of the Farnesoid X Receptor Agonist Obeticholic Acid in Patients with Type 2 Diabetes and Fatty Liver Disease[42]

A trial conducted by Mudaliar and colleagues[42] enrolled 64 patients with type 2 diabetes and NAFLD, which was defined by elevated aminotransferases, hepatomegaly detected with imaging, and/or histologic evidence from a biopsy done in the prior five years. Participants were randomly assigned to receive 25 mg OCA, 50 mg OCA, or placebo daily for six weeks. In order to determine glucose sensitivity, participants were admitted for a hyperinsulinemic-euglycemic clamp procedure before the first and after the last dose of the treatment. During the procedure, patients received first a low-dose infusion rate of insulin followed by a high-dose infusion rate of insulin while glucose measurements were taken every 5-10 minutes to maintain euglycemia. The resulting glucose infusion rate was the primary outcome for this trial.

Two key differences distinguish the populations in the FLINT and Mudaliar trials. In the former, all of the participants have NASH and 53% have diabetes, whereas in the Mudaliar trial, all of the participants have NAFLD and diabetes. Both trials examined changes in liver enzymes and cholesterol levels while on therapy as secondary outcomes; additional outcomes and study descriptors are provided in Appendix E.

Quality of Individual Studies

Using criteria from US Preventive Services Task Force (USPSTF), we rated one RCT publication, the FLINT trial, to be of good quality.[41] We judged this publication investigating OCA use among adults with NASH (n=283) to be of good quality because it was double-blind with comparable patient characteristics in each study arm at baseline, and the authors used valid instruments to evaluate outcomes with no differential attrition observed. Interpretation of the trial is limited by its having been stopped early when interim analysis suggested a benefit with OCA. This prevented 64 (23%) of the patients from receiving a post-treatment biopsy to assess fibrosis.

We rated the other publication of the NCT00501592 trial by Mudaliar et al. to be of fair quality because the study arms in this investigation of OCA use among diabetic patients with NAFLD (n=64) were not randomized evenly.[42] The male to female ratios, baseline glucose levels, and baseline concomitant medications in each of the treatment arms were dissimilar. In addition, the description of the analyses and results in the publication limited interpretation of the results (e.g., intention-to-treat analysis was not used in reporting primary outcome, and only 69% of the participants were retained for this outcome).

Three abstracts provided supplemental results to the FLINT trial, and these are unrated in keeping with the ICER grey literature policy (http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).[43-45]

Table 1. Key Trials

Key Trials	Patient Characteristics	Treatment	Comparator	Harms
FLINT[41] **Phase II** **Double-blind** **RCT** **Multicenter** **ITT analysis**	Mean age: 52 Percent male: 34% Mean weight: ~98kg Hyperlipidemic: 62% Diabetic: 53% Vitamin E last 6 mos: 22% Antilipidemic last 6 mos: 48% Definite steatohepatitis: 80% Mean NAFLD score: 5.2	OCA 25 mg daily (n=141; ITT* n=110)	Placebo (n=142; ITT* n=109)	Pruritus: 23% vs. 6% (p<0.0001)
		Administered for 72 wks w/ 24 wks follow-up Primary outcome: ≥2 point decrease in centrally scored NAS w/o worsening fibrosis 72 wks (OCA 45% vs. PBO 21%) RR 1.9 (95% CI 1.3-2.8); p=0.0002 Secondary outcomes: -Mean change in NAS (-1.7 vs. -0.7) RR -0.9 (95% CI -1.3 to -0.5); p<0.0001 -Patients w/ improved fibrosis (35% vs. 19%) RR 1.8 (95% CI 1.1-2.7); p=0.004 -Resolution of NASH (22% vs. 13%) RR 1.5 (95% CI 0.9-2.6); p=0.08		
		-Mean change (baseline to 72 wks): ALT -38 AST -27 ALP -12 GGT -37 Total cholesterol 0.16 HDL -0.02 HOMA-IR 15 Weight (kg) -2.3	-Mean change (baseline to 72 wks): ALT -18 (p<0.001) AST -10 (p=0.0001) ALP -6 (p<0.0001) GGT -6 (p<0.0001) Total cholesterol -0.19 (p=0.0009) HDL 0.03 (p=0.01) HOMA-IR 4 (p=0.01) Weight (kg) 0.0 (p=0.008)	
NCT00501592 by Mudaliar et al.[42] **Phase II** **Double-blind** **RCT** **Multicenter**	Mean age: 52 Percent male: 53% Mean weight: ~106kg Diabetic: 100%	OCA 25 mg daily (n=20) or OCA 50 mg daily (n=21)	Placebo (n=23)	Any AEs (OCA 25 mg vs. 50 mg vs. PBO): 45% vs. 76% vs. 61% Treatment-related AEs: 5% vs. 38% vs. 26% Pruritus: 0 vs. 5% vs. 9%
		Administered for 6 wks Primary outcomes: -Percent change in low-dose glucose infusion rate (OCA 24.5 vs. PBO -5.5); p=0.011 -Percent change in high-dose glucose infusion rate (OCA 15.0 vs. PBO -5.4); p=0.025		
		Secondary outcomes: change in mean values 25 mg/50 mg AST -2/5 ALT -10/10 ALP 14/27 GGT -37/-22 Total cholesterol 18/13 HDL -2/-6 Weight 1/1.9	Secondary outcomes: change in mean values (p-value 25 mg/p-value 50 mg) AST 5 (0.12/0.73) ALT 11 (0.003/0.84) ALP 0 (0.003/<0.001) GGT 5 (<0.001/<0.001) Total cholesterol 8 (0.08/0.15) HDL 0 (0.42/0.01) Weight (0.096/0.008)	

*ITT population was defined in FLINT trial as those 219 patients who received both baseline and 72-week follow-up biopsies

Clinical Benefits

A detailed review of each clinical outcome of interest is presented in the sections that follow. The most important clinical outcome, resolution of fibrosis, was reported in the FLINT trial publication as a secondary outcome but not in the other trial publication or affiliated abstracts. Although neither study shared the same primary outcomes (FLINT: decrease in NAS; Mudaliar: change in glucose infusion rate), both reported secondary outcomes of mean changes in liver enzymes, cholesterol, and weight.[41-45] Liver enzymes include aminotransferases, ALT and AST, and other enzymes, GGT and ALP, which are elevated when the liver is inflamed. They can indicate liver function and be used by clinicians to track disease progression.

These studies reported no data on cirrhosis, liver transplantation, or survival.

Resolution of Fibrosis

The ultimate goal of NASH therapy is to prevent cirrhosis from developing, which also means preventing fibrosis. Patients with NASH are at higher risk of developing significant fibrosis than patients with simple steatosis.[2] At the same time, some patients with NASH experience improvement or stabilization of fibrosis without intervention.[46] Resolution or improvement in fibrosis was presented in the FLINT trial as a secondary outcome (improvement for OCA: 35% vs. 19% for placebo; rate ratio [RR] 1.8; 95% CI 1.1-2.7; p=0.004).[41]

Among the patients in the FLINT trial who had the most severe NASH at baseline (stage 2-3 fibrosis or stage 1 with diabetes, obesity, or ALT ≥ 60 U/L), an accompanying poster by Neuschwander-Tetri examined changes in fibrosis within this subpopulation (OCA: n=85; placebo: n=77).[45] More patients in the OCA group experienced regression of fibrosis by at least one stage (39% vs. 22% for placebo; p=0.012). Similarly, fibrosis progressed for fewer patients treated with OCA than placebo (16% vs. 29%; p=0.047).

This outcome was not reported in other abstracts or publications included in the evidence review.

NAFLD Activity Score

The NAFLD activity score, or NAS, is based on histologic assessment of liver biopsies: it is the unweighted sum of scores given for steatosis (0-3), lobular inflammation (0-3), and hepatocellular ballooning (0-2). Fibrosis is measured separately as it the result of inflammation and damage to hepatocytes.[28] In the FLINT trial, these scores were given centrally by pathologists blinded to the treatment arm.[41] NAS scores were a key component of the primary outcome: ≥2-point decrease without worsening fibrosis after 72 weeks of OCA versus placebo (45% vs. 21%; RR 1.9; 95% CI 1.3-2.8; p=0.0002). When measured as a single outcome, patients in the OCA arm had greater mean change in NAS (-1.7 vs. -0.7 for placebo; p<0.0001). These statistically-significant improvements in

NAS are of unknown clinical significance, however, since improvement in NAS does not always lead to a reduction in NASH diagnoses.[41] Some patients in both treatment groups experienced histologic resolution of NASH by 72 weeks of therapy, but these changes were not statistically significant.

Among the patients in the FLINT trial with most severe NASH at baseline, a Neuschwander-Tetri poster reported that significantly more patients treated with OCA experienced two or more points of improvement in NAS compared with the placebo group (50% vs. 31%; p=0.001).[45] More of these patients in this subpopulation also experienced resolution of NASH if they were treated with OCA (18% vs. 6.5%; p=0.03).

Liver Enzymes

Serum aminotransferases (ALT and AST) and other liver enzymes (GGT and ALP) are elevated in liver inflammation, which is an earlier stage of the pathway to cirrhosis. However, elevations in these enzymes are not indicative of NASH by themselves, since they can be elevated in many other conditions and normal in patients with histologic evidence of NASH. While the FLINT patients were taking OCA, they had significantly lower levels of ALT, AST, and GGT than the patients receiving placebo.[41] This suppression of enzyme levels became indistinguishable between the two arms at week 96 when the drug was no longer being administered (stopped at week 72). An inverse of this relationship was seen with ALP, which was significantly higher among the patients receiving OCA and then indistinguishable from baseline at week 96. Although a secondary outcome in the FLINT trial, the clinical significance of altering liver enzymes by 12 to 38 U/L is uncertain beyond its use in tracking disease progression.

The trial by Mudaliar in which NAFLD patients with diabetes were treated with six weeks of OCA at 25 mg or 50 mg doses versus placebo also reported some small, but statistically-significant, decreases (-10 to -37 U/L) in ALT and GGT among patients receiving 25 mg OCA at day 43 compared to baseline measurements.[42] The patients receiving 50 mg experienced a mean decrease only in GGT (-22 U/L; p<0.001 compared to placebo). There was no significant change in levels of AST regardless of treatment arm. As in the FLINT trial, ALP levels increased for both OCA treatment groups compared to patients in the placebo arm (25 mg: +14 U/L; p=0.003; 50 mg: +27 U/L; p<0.001).

Weight

Body weight decreased while patients in the FLINT trial took OCA (mean change of -2.3kg vs. no change in the placebo arm; p=0.008), but this gravitated back to baseline once treatment was stopped at week 72.[41] Weight loss of this degree was associated with some benefit in lowering systolic blood pressure (mean change of -4mmHg vs. -1mmHg in the placebo arm; p=0.05). Similarly, diabetic patients with NAFLD in the Mudaliar trial lost more weight (-1.9% change in mean

body weight; p=0.008) if they had been treated with 50 mg OCA for six weeks compared to the placebo group.[42] This same relationship was not observed for the patients taking the 25 mg dose.

A subgroup analysis of the FLINT trial examined several clinical outcomes by presence or absence of weight loss during the trial. These outcomes were reported in affiliated abstracts.[43,44] The NAS was significantly lower for patients who experienced weight loss during the 72-week trial period, whether in the OCA or placebo treatment arm (mean change in NAS for OCA patients with weight loss -2.4 vs. without weight loss -1.2; p<0.001; placebo patients -1.4 vs. -0.4; p=0.006).[43] LDL levels were higher among patients who received OCA and lost weight during the trial compared to patients who did not lose weight (23 mg/dL vs. 0; no significance testing). However, patients who lost weight while taking placebo had lower LDL levels than patients on placebo who did not lose weight (-17 mg/dL vs. -2 mg/dL; no significance testing). Although the changes in LDL were not tested statistically within treatment arm, they were tested across treatment arm within the subpopulation who lost weight and found to be significantly different (+23 mg/dL vs. -17 mg/dL for OCA and placebo, respectively; p<0.001).[44]

Health-Related Quality of Life

Health-related quality of life measures were assessed in the FLINT trial using SF-36 questionnaires for physical and mental well-being.[41] Neither treatment nor placebo group showed a change from baseline over the course of the 72 weeks of treatment for either component of the SF-36. Of note, NASH, as with NAFLD, is often asymptomatic and identified incidentally when testing is performed for an unrelated condition, so these findings are unsurprising.[1]

Insulin Sensitivity

As an activator of the farsenoid X nuclear receptor, OCA can promote insulin sensitivity.[47] Diabetes is also an independent risk factor for advancing fibrosis and disease progression in NAFLD and NASH.[48] The FLINT trial included as a secondary outcome a fasting homeostasis model of insulin resistance (HOMA-IR).[41] Somewhat surprisingly, patients treated with OCA had a greater increase in hepatic insulin resistance than those in the placebo arm (p=0.01). This is contrary to the findings demonstrated in the six-week long Mudaliar trial of OCA treatment of NAFLD patients with diabetes.[42] The authors suggest that the difference may be accounted for by adaptive mechanisms in settings of longer-term farsenoid X receptor activation. The primary outcome was the percent change in low- and high-dose glucose infusion rates between the treatment arms. For both low- and high-dose glucose infusion rates, the percent increase was significantly larger for patients treated with 25 mg OCA compared to placebo (low-dose: 28.0 vs. -5.5; p=0.019; high-dose: 18.3 vs. -5.4; p=0.036) than it was for 50 mg OCA compared to placebo (low-dose: 20.1 vs -5.5; p=0.60; high-dose: 10.8 vs. -5.4; p=0.076).

Other Subgroup Analyses

In addition to the subgroup analyses presented within the Clinical Benefit subsections above, we review here the impact of OCA on the subpopulation of NASH patients with diabetes, which describes 53% of the patients in the FLINT trial.[41] As summarized, the results of the Mudaliar trial fit within this subpopulation, too, although histologic outcomes were not examined and the proportion of NASH patients was not reported.[42] The supplemental post-hoc analyses accompanying the FLINT trial revealed that of the patients in the ITT sample (n=219), the patients without diabetes at baseline (n=103) were less likely than the patients with diabetes (37% vs. 53%) to experience histologic improvement while taking OCA; histological improvement was defined as a decrease of at least two points in the NAS without worsening fibrosis at week 72.[41] Diabetes also had an impact on measures of treatment effect. The odds ratio (OR) for histological improvement with OCA versus placebo in patients without diabetes (OR 2.0; 95% CI 0.8-4.7) was not statistically significant, whereas the OR for patients with diabetes was significant (OR 4.6; 95% CI 2.0-10.6). Furthermore, only patients with advanced beta cell loss (n=60) had significantly improved histology (OR 5.3; 95% CI 2.1-13.3), whereas the ORs for the subpopulations with early beta cell loss (n=23), intact beta cells (n=69), and those who were insulin sensitive (n=17) were smaller and not statistically significant.

Harms

We describe the most commonly reported types of harms associated with OCA therapy: dyslipidemia, pruritus, and other treatment-related adverse events.

Dyslipidemia

When the lipophilic bile acid OCA binds to farsenoid X nuclear receptors, both hepatic gluconeogenesis and circulating triglycerides are inhibited. These helpful actions occur because the liver synthesizes fewer lipids and upregulates clearance of VLDL. Unfortunately, at the same time, activating the farsenoid X nuclear receptor also increases HDL clearance because it speeds up reverse cholesterol transport (through upregulation of hepatic scavenger receptors). As with the liver enzymes, patients in the FLINT trial experienced a small, but statistically significant, increase in total cholesterol and LDL and decrease in HDL while taking OCA.[41] This effect disappeared once the drug was stopped, and clinical experts differ about the clinical impact of worsening lipid profiles that might be managed with statin therapy.

For the subpopulation with most severe NASH at baseline in the FLINT trial, Neuschwander-Tetri reported in a poster that statin therapy initiated for those in the OCA treatment arm reduced LDL levels to those seen among the patients who were treated with statins at baseline.[45]

Among diabetic patients with NAFLD, Mudaliar found that patients treated with OCA (25 mg or 50 mg) for six weeks did not have statistically significantly elevated total cholesterol levels.[42] HDL levels, on the other hand, were significantly lower (-6 mg/dL; p=0.01) for patients treated with 50 mg OCA at day 43 than they were at baseline compared to patients in the placebo arm. Patients treated with 25 mg OCA had no change in HDL levels. It is not clear whether this is because patients with diabetes are less susceptible to the lipid effects of OCA, if more of these patients were taking statins at baseline, or whether the drug has an impact on lipids only after a longer course of therapy.

Pruritus and Other Adverse Events

OCA treatment is associated with increased pruritus among those in the treatment arms (FLINT: 23% vs. 6%; p<0.0001), but this reportedly led to little treatment discontinuation.[41] The Mudaliar trial of diabetic patients with NAFLD reported greater incidence of patients with any kind of adverse events among the patients treated with 50 mg OCA (76%) compared with 25 mg (45%) and placebo (61%).[42] Similar absolute differences were seen when *treatment*-related adverse events were reported, although incidence in the 25 mg OCA group was low: 50 mg OCA (38%) compared with 25 mg (5%) and placebo (26%). In either scenario, the lower dose of OCA was associated with fewer adverse events, including pruritus (25 mg: 0%, 50 mg: 5%, placebo 9%).

Controversies and Uncertainties

NASH is currently an off-label indication for OCA, which makes its use in this clinical setting more susceptible to hypothetical benefit and anecdotal supporting evidence. The published evidence base for using OCA in NASH is very slim and excludes the findings from a completed Phase II trial conducted among Japanese patients with NASH that failed to meet its primary endpoint (≥ 2-point improvement in NAS without worsening fibrosis). Data from that trial have not been published and are available only from press releases and online news aggregators.[49,50] This placebo-controlled trial was similar to FLINT in that daily OCA was administered (doses were 10 mg, 20 mg, or 40 mg) for 72 weeks. Additional trials are underway (REGENERATE and CONTROL) and should be examined carefully to further characterize the effectiveness of OCA activity on NASH.

The current studies do not directly describe the impact of OCA on cirrhosis. The clinical significance of several of the secondary outcomes is uncertain: what is the clinical impact of lowering liver aminotransferase or of raising HDL levels to the degree described in the sections above? Are there undesirable and unintended consequences of initiating patients on statin therapy to manage dyslipidemia associated with OCA therapy or are these offset by long-term gains in preventing end-stage liver disease? These are questions that remain unanswered given the limited evidence base.

Another consideration is that the side effect of pruritus is noxious, whereas the symptoms of NASH are quiescent for many years. This raises the question of long-term adherence to oral therapy taken daily to suppress a chronic condition with few symptoms until late stages of the disease.

Summary

Given the limited evidence base and uncertainty regarding the long-term clinical effects of changes in surrogate endpoints and conflicting physiological outcomes while taking the drug (e.g., insulin resistance in the Mudaliar vs. FLINT trials), we assign an ICER evidence rating of "Insufficient," or "I" for using obeticholic acid as an off-label treatment for adults with nonalcoholic steatohepatitis with fibrosis.

5. Other Benefits or Disadvantages

Our reviews seek to provide information on other benefits or disadvantages 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. Examples include but are not limited to:

1. Methods of administration that improve or diminish patient acceptability and adherence
2. A public health benefit, e.g., reducing new infections
3. Treatment outcomes that reduce disparities across various patient groups
4. More rapid return to work or other positive effects on productivity (if not considered a benefit as part of comparative clinical effectiveness)
5. New mechanisms of action for treatments of clinical conditions for which the response to currently available treatments vary significantly among patients for unknown reasons (substantial heterogeneity of treatment effect)

OCA offers the potential of oral therapy to slow or suspend the progression of NASH. Currently, best practices include lifestyle modification (e.g., weight loss) and managing cardiovascular risk. Other oral agents (e.g., vitamin E, pioglitazone) have unclear effectiveness given some safety concerns about their widespread use (i.e., increase in all-cause mortality and weight gain as a side effect). Approval of OCA gives practitioners an additional oral agent to deploy in preventing end-stage liver disease, but the data currently available do not demonstrate impact on long-term outcomes.

6. Comparative Value

6.1 Overview

The primary aim of this analysis was to estimate the cost-effectiveness of obeticholic acid (OCA) treatment for patients with NASH. We conducted a cost-effectiveness analysis (CEA) by developing a microsimulation model that simulated the long-term outcomes of patients receiving OCA as observed in the phase II FLINT study; as a comparator, we also simulated the placebo arm of the trial. Model parameters were estimated from published studies and calibrated where assumptions were required. The outcomes of the model included total costs, quality-adjusted life years (QALYs), incremental cost-effectiveness ratios, transplant-free survival, and cumulative incidence of advanced disease stages.

6.2 Prior Published Evidence on Costs and Cost-Effectiveness of Obeticholic Acid

We did not identify any published articles or public presentations pertaining to the cost and/or cost-effectiveness of OCA for treatment of NASH patients. To the best of our knowledge, this report is the first analysis that estimates the cost-effectiveness and long-term impact of OCA for the treatment of patients with NASH.

6.3 Incremental Costs per Outcome Achieved

Cost-Effectiveness Model: Methods

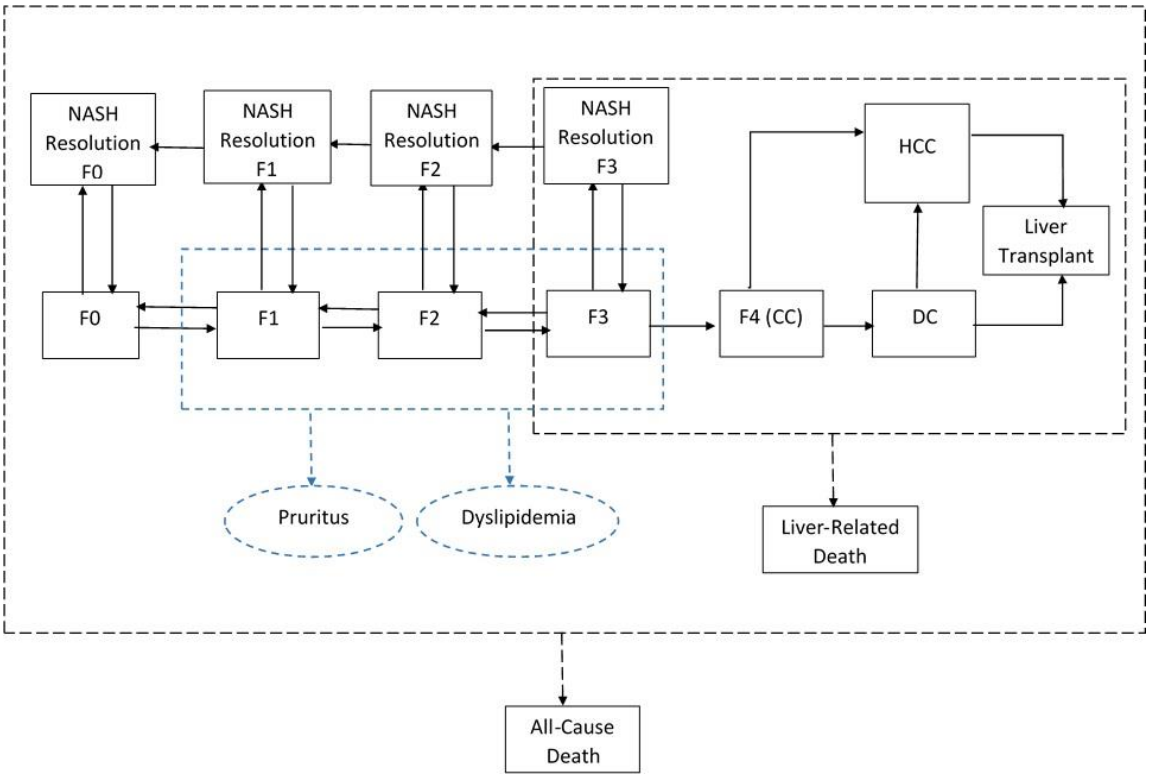
Model Structure

We developed an individual-level state-transition model (i.e., a microsimulation model) to assess two different strategies for treating NASH in hypothetical patients: OCA, and standard care, which could include treatment with Vitamin E in both the OCA and standard care strategies.

We simulated a hypothetical cohort of patients with fibrosis stages F1–F3 to estimate the CEA of OCA in NASH patients. Health states in our model included: NASH fibrosis states prior to cirrhosis (F0–F3), compensated NASH cirrhosis, decompensated NASH cirrhosis, HCC and liver transplant. Patients with decompensated cirrhosis and HCC would be eligible for liver transplantation. Possible causes of death included liver-related mortality, cardiovascular mortality, and all-cause mortality. Liver-related mortality can occur because of advanced fibrosis (F3), compensated cirrhosis, decompensated cirrhosis, HCC or liver transplantation. All patients with NASH have a higher cardiovascular mortality compared to the general population, which was based on published

studies[51] and incorporated into the model. Background mortality risk was based on patients' age and sex and estimated from US life tables.[52] Transplant patients have higher risk of mortality for the first year than in subsequent years.

Figure 4. Model Structure: Natural History of NASH Disease



Abbreviations: F0–F4=fibrosis stages; CC=compensated cirrhosis; DC=decompensated cirrhosis; HCC= hepatocellular carcinoma

For each treatment regimen, a hypothetical patient cohort began distributed across the three fibrosis states (F1–F3). Patients remained in their fibrosis state until they experienced: A) progression in disease toward cirrhosis, B) regression in disease, or C) death from all-cause mortality. Patients continued to receive OCA in the intervention group as long as they were in fibrosis stages F1, F2 or F3. Patients that progressed to compensated cirrhosis (CC, F4) stopped taking the treatment. We estimated overall average patient survival, total costs, and QALYs for each treatment strategy, as well as the incremental cost-effectiveness ratio (ICER) comparing the two strategies. Model cycle length was one year, except for the first cycle, which was assumed to be 72 weeks, to align with the duration of the FLINT study. To model the efficacy of OCA treatment, we used the primary endpoint used in the phase III REGENERATE trial. Consequently, the primary outcome in our model was the percentage of patients who achieved NASH resolution without worsening of fibrosis.

Target Population

The population modeled in the analysis will be patients 18 years or older with histologic evidence of NASH with fibrosis (F1, F2 or F3) diagnosed by a liver biopsy (Table 2). The baseline parameters in the model were based on data from the NASH Clinical Research Network (CRN) Study for patients who had definite steatohepatitis.[53] As it is likely that payer coverage of OCA will be contingent on a prior attempt at lifestyle intervention, we assumed that patients in the model had made an attempt at lifestyle intervention but did not achieve meaningful success.

Table 2. Model Cohort Characteristics

	Value
Mean age	49
NASH fibrosis stage distribution	
F1	39%
F2	27%
F3	34%
Sex: Female / male	66% / 34%

Source: NASH CRN Study[53]

Treatment Strategies

The interventions of interest were OCA compared to usual supportive care. The intervention of interest was treatment with OCA administered as oral tablets in a dose of 25 mg once daily. The comparator was usual supportive care, including treatment with vitamin E.

Key Model Choices and Assumptions

- The intervention of interest was treatment with OCA administered as oral tablets in a dose of 25 mg once daily.
- The natural history model of NASH progression to cirrhosis and liver-related death was constructed incorporating data from published sources.
- The model structure was adapted from a previously published model and published data regarding the natural history of NASH.[4]
- OCA efficacy was estimated based on analysis of one US-based Phase II trial (FLINT, NCT01265498), which showed an improvement in liver histology, including fibrosis, over a period of 72 weeks.
- There was no data to inform the model beyond week 72; therefore, we made biologically and clinically plausible assumptions beyond week 72, which were additionally confirmed by clinical experts.
- Key adverse events related to OCA are included in the model, including pruritus and dyslipidemia.

- The model included grade 3/4 adverse events only, as less severe events are not expected to substantially impact patient health or costs. The model therefore included all grade 3/4 events that occur in at least 5% of patients.
- Costs included those of current and subsequent treatment, management of adverse events, ongoing NASH-related care, and management of advanced disease outcomes such as hepatocellular carcinoma.
- We utilized a health system perspective (i.e., focus on direct medical care costs only) and a lifetime horizon, modeling patients from treatment initiation until death.
- Results were expressed primarily in terms of the incremental cost per quality-adjusted life year (QALY) gained relative to the standard treatment strategy.
- A 3% annual discount rate for both costs and QALYs, with a half-cycle correction, were used in the model analyses.

Clinical Inputs

The primary outcome in our model was resolution of NASH without worsening of fibrosis. From the post-hoc analysis of the FLINT study, 19% of patients in the OCA arm achieved the primary outcome versus 8% in the placebo arm.[54]

Adverse Events

The model includes pruritus and dyslipidemia as adverse events. In addition, we considered three levels of pruritus, defined as mild, moderate and severe. A decrement to quality of life was applied when a patient experienced pruritus. There was an additional cost for pruritus treatment, which included the cost of physician office visits and anti-pruritic drugs. Pruritus did not affect the transitions between health states. We also included dyslipidemia as an adverse event, which did not have impact on quality of life or transitions between health states. However, it did lead to additional costs for management of dyslipidemia, including a physician office visit and medication.

Table 3. Adverse Event Inputs

Adverse Event	Patients Affected	Reference
OCA		
Pruritus – mild	6.3%	FLINT Table 4 (OCA)
Pruritus – moderate	14.8%	FLINT Table 4 (OCA)
Pruritus – severe	2.1%	FLINT Table 4 (OCA)
Dyslipidemia	51%	FLINT Study
Standard Care		
Pruritus – mild	4.2%	FLINT Table 4 (Placebo)
Pruritus – moderate	2.1%	FLINT Table 4 (Placebo)
Pruritus – severe	0%	FLINT Table 4 (Placebo)
Dyslipidemia	35%	FLINT Study

Drug Utilization

The model used a 25 mg OCA dose, as this was the dosage used in the FLINT trial.

Costs

Health state costs associated with advanced stages of the disease were based on reported costs for patients with hepatitis C virus infection.[55] The cost of early stages of NASH was assumed to be similar to that of hepatitis C patients having mild, moderate and advanced fibrosis. Table 4 summarizes the costs associated with each health state. All costs were converted to a 2015 baseline using the medical care Consumer Price Index.

For patients who have pruritus, we assumed there will be additional costs for two primary care visits; these costs are based on the fees associated with HCPCS code 99213 in the physician fee schedule.[2] We also applied the cost of one year of hydroxyzine treatment, based on the Red Book value for a 25 mg dose three times per day for one year.[56]

Table 4. Cost Inputs Associated with Health States and Management of Adverse Events

Parameter	Values
Fibrosis stages F1–F3	$737
Compensated cirrhosis	$5,752
Decompensated cirrhosis	$40,141
Hepatocellular carcinoma	$88,383
Liver transplant-1st year	$179,080
Liver transplant-subsequent year	$44,074
Cost of OCA	Assumption
Dyslipidemia treatment	$191
Dyslipidemia doctor's office visit	$52
Cost of Pruritus (doctor's office visit)	$103
Cost of Pruritus (ongoing hydroxyzine treatment)	$712

Utilities

We assigned health-related quality-of-life (QOL) utilities to each patient in the model, with 0 denoting death and 1 denoting perfect health. Health state utilities from publicly available literature (Table 5) were used, with consistent values across treatments evaluated in the model. Because NASH-specific utilities by different stages of disease were not available, we used the utilities of health states for patients with hepatitis C. Specifically, we used health-state specific utility weights from a previously published study using the EuroQol-5D,[57,58] and adjusted these weights to the US population norm (Table 6).[59] We further applied a disutility for patients who experience pruritus; to

determine the overall utility for a patient with pruritus, we took the product of the health state utility and the pruritus utility.

Table 5. Utilities for Health States and Adverse Events

Health State	Base Case
Health States[57]	
Fibrosis F0–F3	0.93
Compensated cirrhosis	0.90
Decompensated cirrhosis	0.80
Hepatocellular carcinoma	0.79
Transplant-first year	0.84
Transplant-subsequent year	0.93
Adverse events (multiplicative factor)[60]	
Pruritus – mild	0.93
Pruritus – moderate	0.87
Pruritus – severe	0.79

Table 6. Health-Related Quality-of-Life Utilities of the United States Population

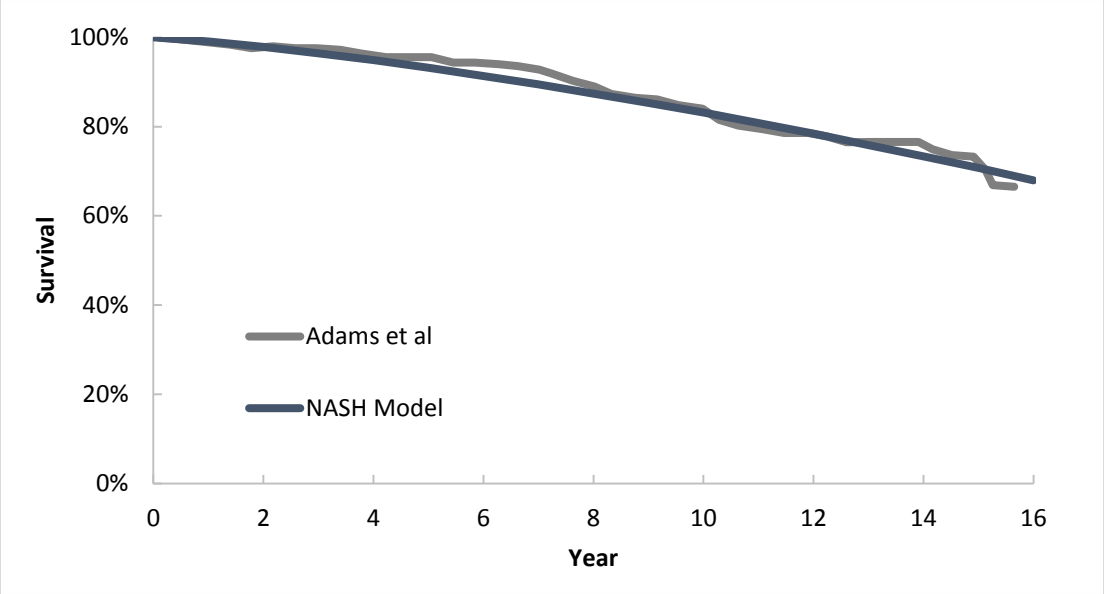
Age Group	Male	Female
20–29	0.928	0.913
30–39	0.918	0.893
40–49	0.887	0.863
50–59	0.861	0.837
60–69	0.84	0.811
70–79	0.802	0.771
80–89	0.782	0.724

Source: Hammer et al.[59]

Transition Probabilities

We used a meta-analysis by Singh et al.[61] to estimate progression and regression in NASH fibrosis stages. Because patients with NASH have higher cardiovascular risk compared to the general population, we calibrated background mortality such that the overall survival for the modeled NASH patients matched that of a cohort published by Adams et al. that followed patients for 16 years.[62] To do so, we simulated 16-year survival in patients followed in Adams et al. with the following baseline characteristics: age 50 years; 58% female, NASH fibrosis of F0 36%, F1, 18%, F2, 15%, F3, 18%, F4, 13%. We found that the model-predicted overall survival closely matched survival reported by Adams et al. (Figure 5). The mortality associated with decompensated cirrhosis, hepatocellular carcinoma and liver transplantation were assumed to be similar to that in patients with hepatitis C who developed these advanced outcomes.[63]

Figure 5. Comparison of Overall Survival of NASH Patients Predicted by the Model and Adams et al.



We estimated transition probabilities between health states from previously published studies. For progression and regression of fibrosis, we used a meta-analysis by Singh et al[61] which provided fibrosis progression/regression at the end of 7.1 years. We converted these probabilities to annual probabilities. Table 7 below provides the parameter values. For advanced stages of NASH, we extracted transition probabilities from published sources.

Table 7. Transition Probabilities in the NASH Model

Parameters	Annual transition probability
F0 to F1[61]	0.095
F0 to F2[61]	0.010
F0 to F3[61]	0.002
F0 to compensated cirrhosis[61]	0.095
F1 to F0[61]	0.049
F1 to F2[61]	0.077
F1 to F3[61]	0.034
F2 to F0[61]	0.021
F2 to F1[61]	0.165
F2 to F3[61]	0.051
F2 to compensated cirrhosis[61]	0.043
F3 to F1[61]	0.116
F3 to F2[61]	0.067
F3 to compensated cirrhosis[61]	0.118
Compensated cirrhosis to F3[61]	0.059
Compensated cirrhosis to decompensated cirrhosis[10,64,65]	0.058
Compensated cirrhosis to HCC[66]	0.026
Compensated cirrhosis to LRD[10,64,65]	0.021
Decompensated cirrhosis to HCC[66]	0.026
Decompensated cirrhosis to liver transplantation[67,68]	0.023
Decompensated cirrhosis to liver-related death[69]	0.130
HCC to liver transplantation[68,70]	0.040
HCC to liver-related death[71]	0.427
Liver transplant (first year for DC) to liver-related death[72,73]	0.094
Liver transplant (first year for HCC) to liver-related death[73]	0.101

Sensitivity Analyses

We performed one-way sensitivity analyses to identify the key drivers of model outcome variability.

Cost-Effectiveness Model: Results

Figures 6-10 show 15-year cumulative incidence of decompensated cirrhosis, hepatocellular carcinoma, liver transplants and liver-related deaths in the simulated cohort of patients treated with OCA versus placebo. In comparison with placebo, treatment with OCA would decrease the 15-year cumulative incidence of decompensated cirrhosis from 10% to 8.8%, hepatocellular carcinoma from 4.7% to 4.2%, liver transplant from 0.9% to 0.8%, and liver-related deaths from 12.9% to 11.3%, respectively. In addition, treatment with OCA increased 15-year transplant-free survival from 68.6% to 69.9% (Figure 10). Compared with placebo, treating 10,000 patients using OCA could

prevent 120 cases of decompensated cirrhosis, 50 cases of hepatocellular carcinoma, 10 liver transplants and 160 liver-related deaths.

Figure 6. Cumulative Incidence of Decompensated Cirrhosis in NASH Patients Treated with OCA versus Placebo

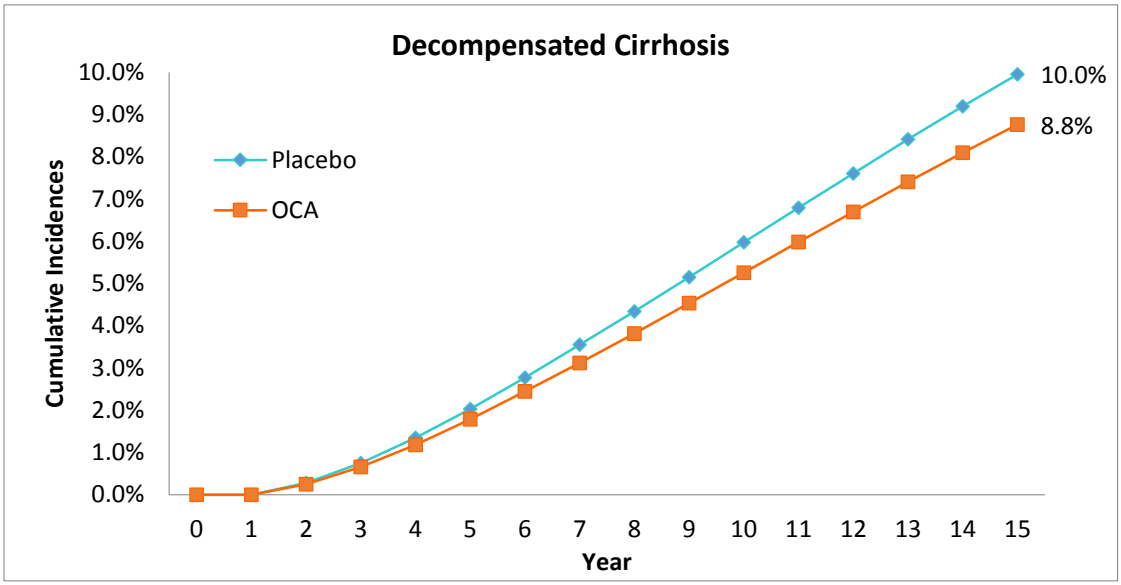


Figure 7. Cumulative Incidence of Hepatocellular Carcinoma in NASH Patients Treated with OCA versus Placebo

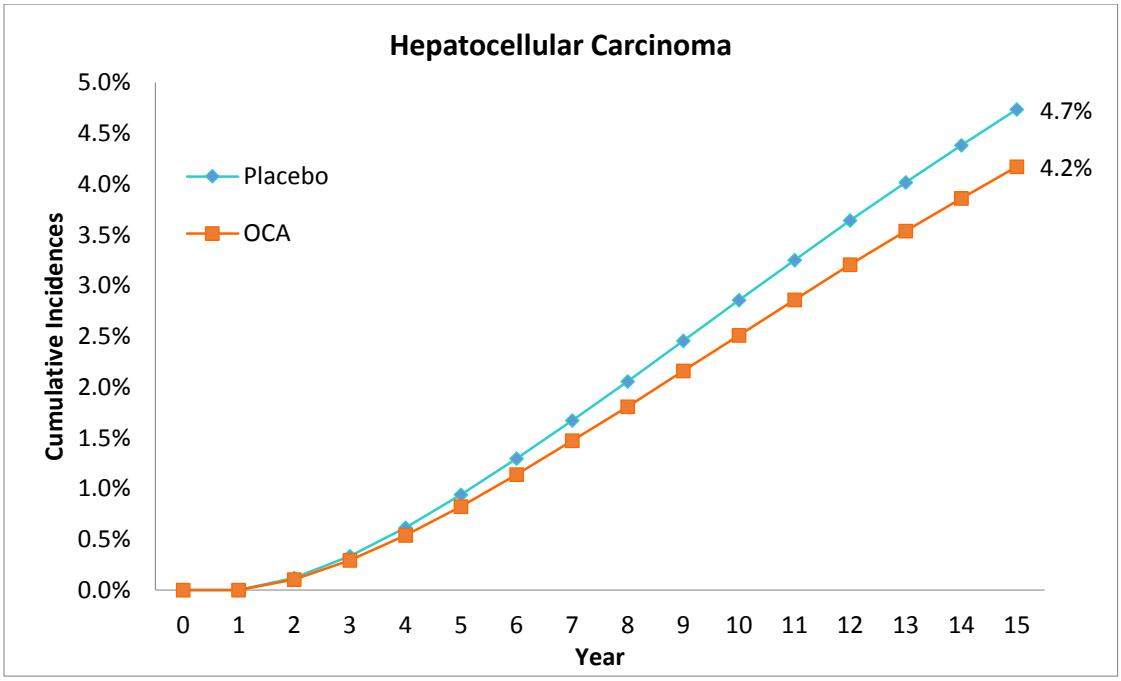


Figure 8. Cumulative Incidence of Liver Transplants in NASH Patients Treated with OCA versus Placebo

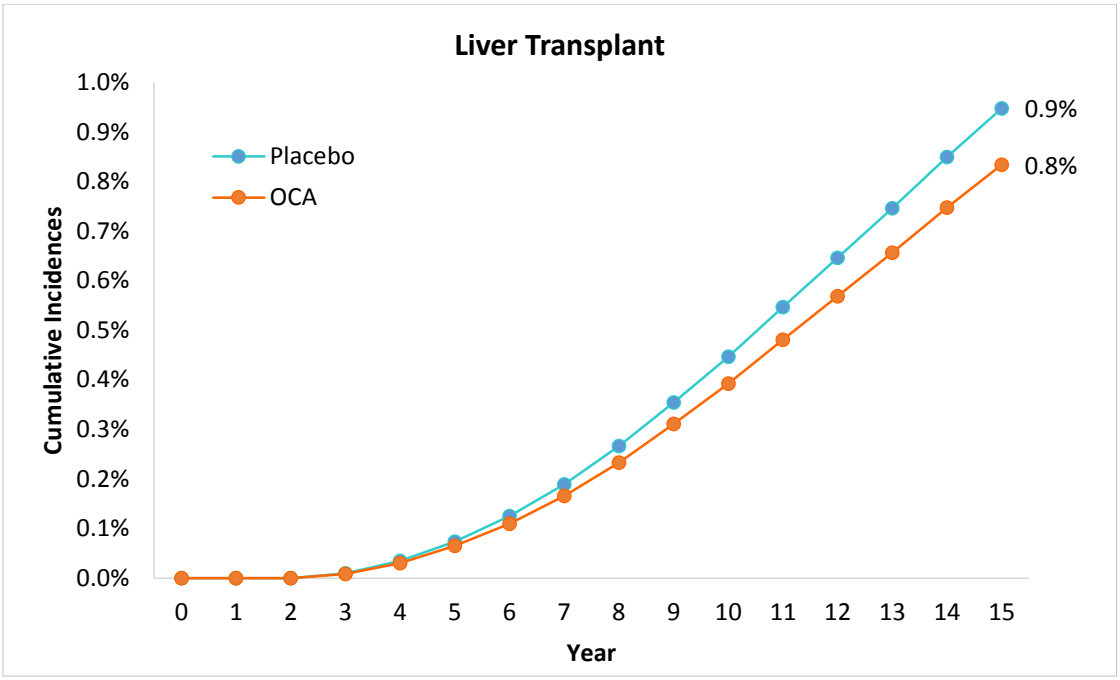


Figure 9. Cumulative Incidence of Liver-Related Deaths in NASH Patients Treated with OCA versus Placebo

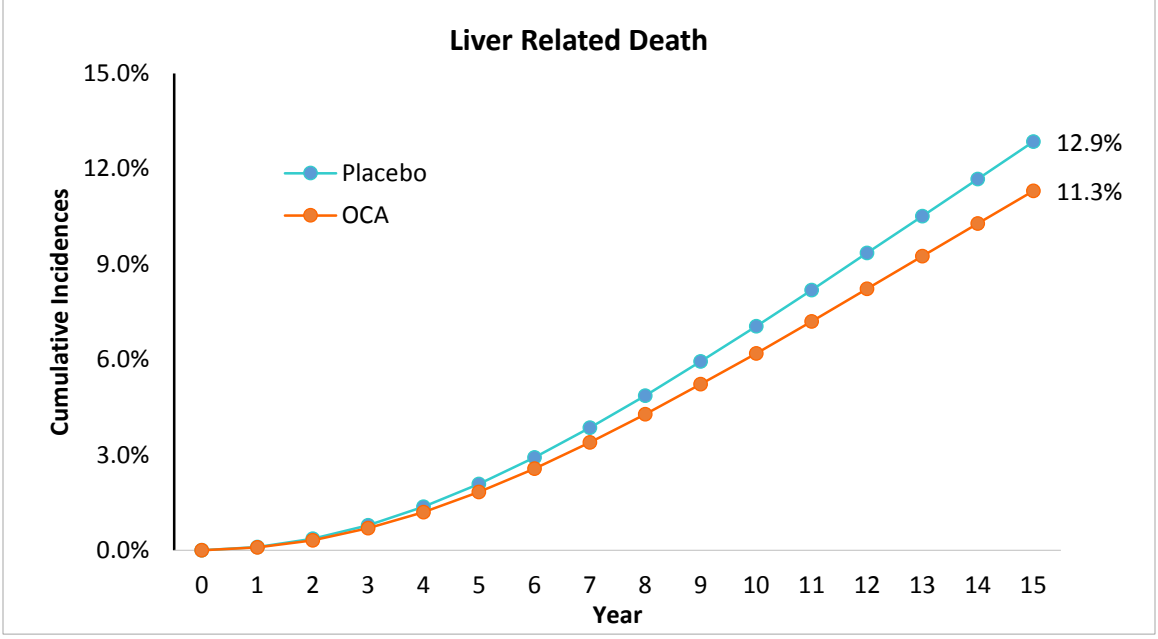
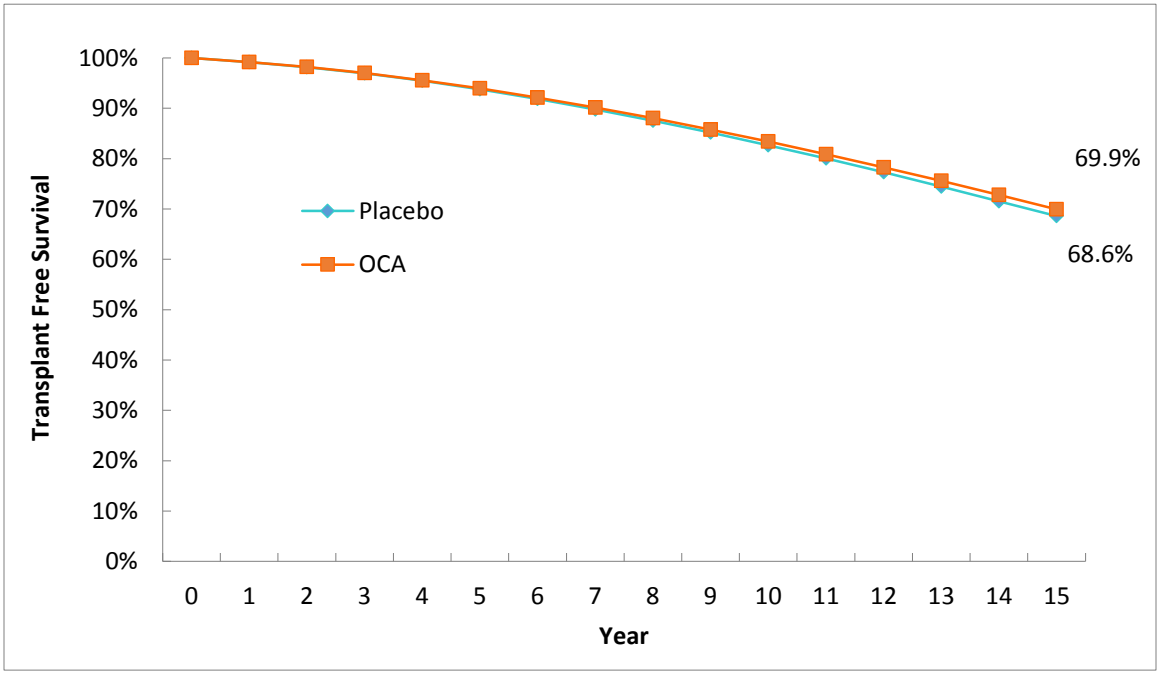


Figure 10. Transplant-Free Survival in NASH Patients Treated with OCA versus Placebo



The average (undiscounted) life years per patient in placebo versus OCA were 16.45 and 17.36 (increment = 0.91 years), respectively. The corresponding discounted QALYs were 10.91 and 11.02 (increment = 0.11 years), respectively. The average lifetime discounted cost per patient treated with placebo was $70,300. Assuming that the price of OCA is $65,000/year, average lifetime cost of patients in the OCA arm was $351,000 (increment of $280,700). The incremental cost-effectiveness ratio (ICER) of OCA was $2.57 million per QALY (Table 8). Using the willingness to pay threshold of $100,000 per QALY, OCA at $65,000/year is not a cost-effective option in NASH patients.

Table 8. Cost-Effectiveness of OCA When the Annual Cost of OCA is $65,000 per Year

	Placebo	OCA
Undiscounted Life Years	16.45	17.36
Discounted QALYs	10.91	11.02
Discounted Total Cost	$70,300	$351,000
ICER ($/QALY)		2,574,200

If the annual price of OCA is assumed to be $15,000/year, the average lifetime cost of OCA strategy was reduced to $131,000 and the ICER was $550,000 per QALY (Table 9), which remains above the $100,000 per QALY threshold.

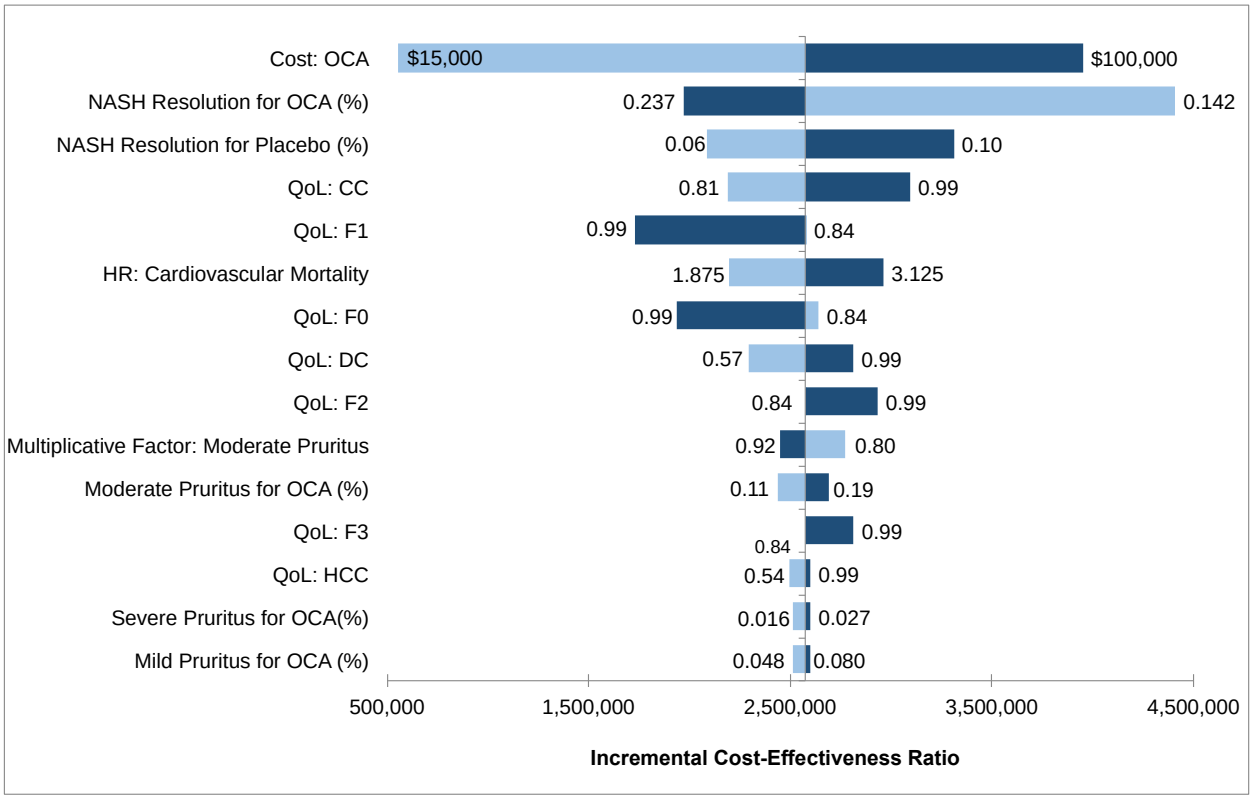
Table 9. Cost-Effectiveness of OCA When the Annual Cost of OCA is $15,000 per Year

	Placebo	OCA
Undiscounted Life Years	16.45	17.36
Discounted QALYs	10.91	11.02
Discounted Total Cost	$70,500	$131,000
ICER ($/QALY)		549,900

Sensitivity Analysis

We conducted one-way sensitivity analysis to identify the most sensitive model parameters. We plotted the tornado diagram showing 15-most sensitive parameters (Figure 11). We found that ICERs were most sensitive to the cost of OCA and percentage of patients who had NASH resolution in placebo and OCA arm. However, the ICERs remained above $500,000 / QALY.

Figure 11. Tornado Diagram Showing 15 Most Sensitive Model Parameters



6.4 Potential Budget Impact

We also used the cost-effectiveness model to estimate the potential total budgetary impact of OCA for NASH patients, based on assumed patterns of product uptake.

Potential Budget Impact Model: Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total incremental cost of the OCA therapy for the treated population, calculated as incremental health care costs (including drug costs) minus any offsets in these costs from averted disease progression. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time.

The potential budget impact analysis included the entire candidate population for treatment, which was considered to be adult NASH patients with fibrosis stages F1–F3. To estimate the size of the potential candidate population for OCA, we first applied the estimated prevalence of NASH in the United States. We used an estimate of NASH prevalence in the US from a review by Yeh et al.,[74] who found estimates in the literature of from 3.5% to 5%. For this analysis, we used the lower estimate of 3.5% of the US population having NASH. Applying this prevalence to the projected 2016 US population would imply approximately 11.3 million individuals with NASH. Because of the difficulty in definitively diagnosing NASH (requiring liver biopsy) and the current lack of effective medical treatments, we assumed that the vast majority of these patients would not be diagnosed at this time. We assumed that 5% of the population with NASH would have been diagnosed and therefore eligible for treatment. Applying this percentage resulted in a candidate population size of approximately 567,000 individuals in the US.

ICER's methods for estimating potential budget impact and calculating value-based benchmark prices are described in detail elsewhere. Briefly, our calculations assumed that the utilization of new drugs occurs without any payer, provider group, or pharmacy benefit management controls in place, to provide an estimate of "unmanaged" drug uptake by five years after launch.

In general, we examined six characteristics of the drug or device and the marketplace to estimate "unmanaged" uptake. These characteristics are listed below:

- Magnitude of improvement in clinical safety and/or effectiveness
- Patient-level burden of illness
- Patient preference (ease of administration)
- Proportion of eligible patients currently being treated
- Primary care versus specialty clinician prescribing/use
- Presence or emergence of competing treatments of equal or superior effectiveness

Based on our assessment of these criteria, we assigned a new drug or device to one of four categories of unmanaged drug uptake patterns: 1) very high (75% uptake by year 5); 2) high (50% uptake by year 5); 3) intermediate (25% uptake by year 5); and 4) low (10% uptake by year 5). In this analysis, we assumed a 10% uptake pattern for OCA in NASH patients. We assumed that uptake would be low for this drug because, while there is a lack of effective therapeutic alternatives for NASH patients, the use of OCA for these patients would be off label, at least at the beginning of this time frame.

Using this approach to estimate potential budget impact, we then compared our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation, this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA each year, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 10.

For 2015-16, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage affordability is calculated to total approximately $904 million per year for new drugs.

Table 10. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2015-2016 (est.) +1%	3.75%	World Bank, 2015
2	Total health care spending ($)	$3.08 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	13.3%	CMS National Health Expenditures (NHE), Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$410 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.4 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	34	FDA, 2014
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$452 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$904 million	Calculation

Potential Budget Impact Model: Results

Table 11 below presents the potential budget impact of one year and five years of OCA in the candidate population, assuming the uptake patterns previously described. Results are presented for both one-year and five-year time horizons.

Results from the potential budget impact model showed that, with the uptake pattern assumptions mentioned above, an estimated 11,340 individuals would receive OCA in the first year. After one year of treatment, with net annual costs of approximately $65,200 per patient, one-year budget impact is estimated to be $739.3 million.

Over the entire five-year time horizon, we estimated that "unmanaged" uptake would lead to approximately 56,700 persons taking OCA. Across the full five-year time horizon, the weighted potential budgetary impact (i.e., adjusted for differing periods of drug utilization and associated cost-offsets) is approximately $89,300 per patient. Total potential budgetary impact over five years is approximately $5.1 billion, with an average budget impact per year of approximately $1.01 billion. This annualized potential budget impact is 112% of the budget impact threshold of $904 million for a new drug.

Table 11. Estimated Total Potential Budget Impact (BI) of OCA

		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
	Eligible Population	Number Treated	Annual BI per Patient*	Total BI (millions)	Number Treated	Weighted BI per Patient*	Average BI per year (millions)
OCA	567,000	11,340	$65,200	$739.3	56,700	$89,300	$1,012

*Weighted budget impact calculated by subtracting cost offsets from drug costs for one-year horizon. For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year. Those initiating in year 1 receive full drug costs and cost offsets, those initiating in year 2 receive 80% of drug costs and cost offsets, etc.

6.5 Value-based Benchmark Prices

Value-based price benchmarks will be provided as part of the full Evidence Report.

6.6 Summary and Comment

We conducted a cost-effectiveness analysis by developing a microsimulation model that simulated the long-term outcomes of NASH patients receiving OCA compared to placebo. We estimated that, in comparison with placebo, treatment with OCA would decrease the 15-year cumulative incidence of decompensated cirrhosis from 10% to 8.8%, hepatocellular carcinoma from 4.7% to 4.2%, liver transplant from 0.9% to 0.8%, and liver-related deaths from 12.9% to 11.3%, respectively. In

addition, treatment with OCA increased 15-year transplant-free survival from 68.6% to 69.9%. Assuming that the price of OCA is $65,000/year, the incremental cost-effectiveness of OCA was estimated to be approximately $2.57 million per QALY.

We also used the cost-effectiveness model to estimate the potential total budgetary impact of OCA for NASH patients over five years. Assuming that "unmanaged" uptake would lead to 10% of eligible patients (or approximately 56,700 persons) taking OCA, total potential budgetary impact over five years is approximately $5.1 billion, with an average budget impact per year of approximately $1.01 billion. This annualized potential budget impact is 112% of the budget impact threshold of $904 million for a new drug.

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This is the first ICER review of obeticholic acid for NASH.

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APPENDICES

Appendix A. Evidence Review Methods and PRISMA

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Search Strategies

Table A2: Search Strategy of Medline 1996 to Present with Daily Update, EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Cochrane Central Register of Controlled Trials

1	exp Fatty Liver/	15,607
2	((fatty and (liver* or hepat*)) or steatohepat* or NAFL* or NASH*).mp.	37,963
3	1 or 2	38,175
4	(obeticholic acid or OCA or INT-747).mp.	665
5	3 and 4	32
Date of Search: April 12, 2016		

Table A3: Search Strategy of Embase on April 12, 2016

#4	#3 AND [humans]/lim AND [english]/lim NOT [medline]/lim	73
#3	#1 AND #2	152
#2	'obeticholic acid' OR oca OR 'int 747'	2,774
#1	'fatty liver'/exp OR (fatty AND (liver* OR hepat*) OR steatohepat* OR nafl*or AND nash*)	49,819

Study Selection

We performed screening at both the abstract and full-text level. Two investigators screened abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. All exclusions were validated by a third reviewer. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text.

We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Two investigators reviewed full papers and provided justification for exclusion of each excluded study; a third investigator resolved any discrepancies in selection as necessary.

Data Extraction and Quality Assessment

Summary tables of extracted data are available in Appendix E. We abstracted data from conference abstracts and posters affiliated with publications included in the evidence review. We used criteria published by the U.S. Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor."[75]

Guidance for quality ratings using these criteria is presented below.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

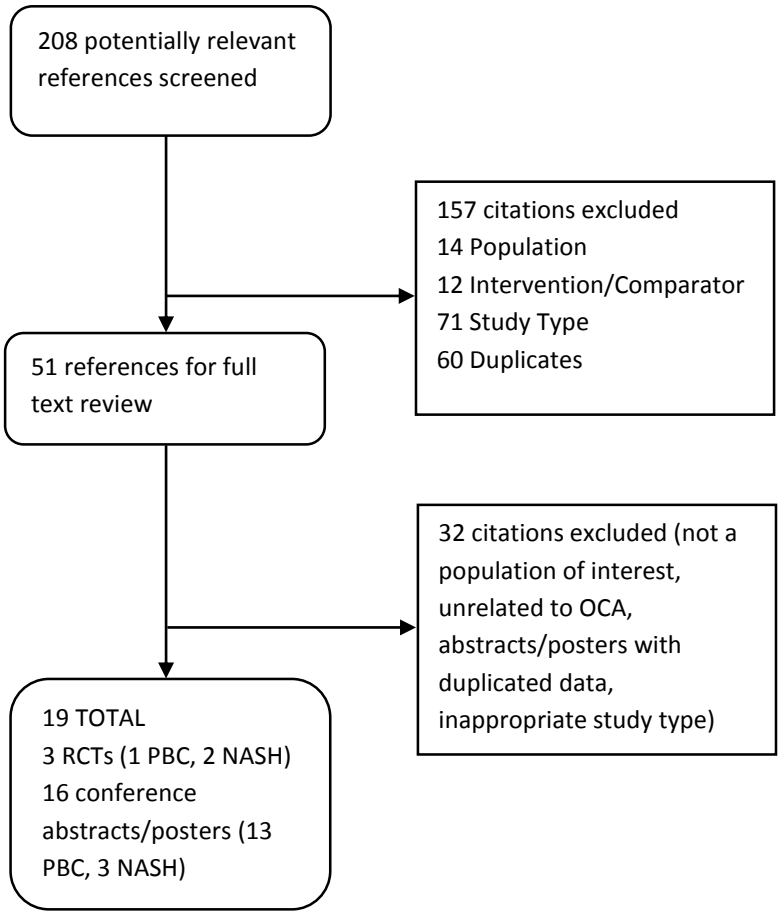
Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies identified provided qualitative evidence for use in ascertaining whether there was a biased representation of study results in the published literature. Although this process did not culminate in the suggestion of a publication bias, we are aware of one completed study in Japan on use of OCA among NASH patients that has not been published. Although this study was not listed in ClinicalTrials.Gov, the European manufacturer disseminated press releases about the trial, which was sponsored by a Japanese pharmaceutical company.

Data Synthesis and Statistical Analyses

Given the small numbers of relevant studies for OCA in NASH, we judged there to be no role for formal meta-analysis to generate pooled estimates of treatment effect.

Figure A1. PRISMA Flow Chart Showing Results of Literature Search for OCA in PBC and NASH



Appendix B. Clinical Guidelines

The American Gastroenterological Association, the American Association for the Study of Liver Diseases, the American College of Gastroenterology (2012)

http://www.gastrojournal.org/article/S0016-5085(12)00494-5/pdf

For treatment of biopsy-confirmed NASH, AASLD guidelines recommend Vitamin E as a first-line pharmacotherapy for non-diabetic patients. Vitamin E should be administered daily at a dose of 800 IU/day. It is not recommended for use by patients with diabetes, those with NAFLD who have not had a liver biopsy to confirm NASH, or those with NASH cirrhosis. Pioglitazone, a thiazolidnedione, may be used in the treatment of NASH, though its long-term safety and efficacy has not been well studied in non-diabetic patients. UDCA is not recommended for treatment of NASH. Bariatric surgery is not contraindicated for otherwise obese patients with NASH or NAFLD without established cirrhosis, but should not be considered a specific treatment option for NASH. Routinely repeated liver biopsies for patients with NASH are not recommended.

World Gastroenterology Organisation (2014)

http://journals.lww.com/jcge/Fulltext/2014/07000/World_Gastroenterology_Organisation_Global.4.aspx

The World Gastroenterology Organisation provides recommendations for lifestyle and pharmacologic interventions for management of NASH. The WGO recommends proper control of diabetes, hyperlipidemia, and cardiovascular risks for patients with NASH, noting that use of atorvastatin and pravastatin have shown improvements for patients with NASH. Weight loss of 5%-10% is recommended in addition to regular exercise. Vitamin E or pentoxifylline can be added, but are considered to be experimental. Bariatic surgery may be an option for patients with morbid obesity but should be considered early on, as surgery is often not an option for patients with cirrhosis. In cases of liver failure, liver transplantation is successful, but NASH may recur after transplant.

Appendix C. Previous Systematic Reviews and Technology Assessments

Because the approval for obeticholic acid is pending at the time of this report, we were not able to identify any previous health technology assessments of OCA for NASH. However, Singh et al. published a systematic review summarized in the following paragraph. No other systematic reviews were identified through the literature search.

- Sing S, Allen AM, Wang Z, et al. Fibrosis progression in nonalcoholic fatty liver vs. nonalcoholic steatohepatitis: A Systematic review and meta-analysis of paired biopsy results. *Clinical Gastroenterology and Hepatology.* 2015;13:643-654.[46]

Singh et al. conducted a systematic review of cohort studies and RCTs conducted among adult patients with histologic diagnosis of NAFLD with a repeat biopsy performed at least a year later. The primary outcome of intereste was estimating fibrosis progression rate (FPR) of patioents with NAFLD, nonalcoholic fatty liver (NAFL), and NASH with baseline 0 fibrosis. FPR was calculated by number of stages of change between biopsy time periods. From 1,994 unique studies, the authors ultimately included 11 observational studies (NAFLD n=411; NASH n=261). Although two RCTs were identified, these were excluded because FPR could not be obtained. Nearly half of the patients in the observational studies had diabetes. At baseline, the stages of fibrosis were distributed as follows: Stage 0 35.8%, Stage 1 32.5%, Stage 2 16.7%, Stage 3 9.3%, and Stage 4 5.7%. Upon follow-up examination 2145.5 person-years later, 33.6% had progressed by at least one stage of fibrosis since baseline, 43.1% remained stable, and 22.3% had improvement in fibrosis stage. Seven studies provided NASH-specific data for 116 patients: 34.5% had progressive fibrosis, 38.8% remained stable, and 26.7% had improvement in fibrosis. A meta-analysis of NASH patients with baseline F0 (n=21) revealed an annual FPR of 0.14 stages (95% CI 0.07-0.21), which calculates to ~7 years to progress to Stage 1. Among all patients, factors associated with progressive fibrosis included hypertension and a low AST:ALT ratio at the time of baseline biopsy.

Appendix D. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
REGENERATE (NCT02548351) Randomized Global Phase 3 Study to Evaluate the Impact on NASH with Fibrosis of Obeticholic Acid Treatment	Phase 3 Double-blinded Multicenter RCT	OCA 10mg vs. OCA 25g vs. Placebo	Adults with NASH	Histologic improvement Liver-related clinical outcomes	October 2021
CONTROL (NCT02633956) Combination OCA and Statins for Monitoring of Lipids	Phase 2 Double-blinded Multicenter RCT	OCA 5mg + Atorvastatin vs. OCA 10mg + Atorvastatin vs. OCA 25mg + Atorvastatin vs. Placebo	Adults with NASH	LDL	August 2016

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix E. Summary Evidence Tables

Author, Pub. Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics			Outcomes	Harms
Publication in Lancet Neuschwander-Tetri 2015 (FLINT) *good*	Phase II RCT Multicenter Double-blinded ITT analysis	1) OCA 25mg po qd (n=141; 110 in ITT analysis) 2) Placebo same size tablet daily (n=142; 109 in ITT analysis) Administered for 72 weeks with 24 weeks post-administration follow-up	Adults ≥ 18 years Histological e/o definite or borderline NASH based on liver bx ≤90d before randomization NAFLD activity score ≥4, with ≥1 in each component of the score Excluded cirrhosis, other causes of liver dz, substantial EtOH consumption, and other confounding conditions (listed in protocol)		1)	2)	<u>Primary outcome</u>: ≥2-point decrease in centrally scored NAFLD Activity Score w/o worsening fibrosis by treatment end (ITT results), n (%): 1) 50 (45%) 2) 23 (21%) RR 1.9 (95% CI 1.3-2.8); p=0.0002 No change in various subgroup analyses. <u>Secondary outcome</u>: Mean change in NAFLD score (SD): 1) -1.7 (1.8) 2) -0.7 (1.8) RR -0.9 (95% CI -1.3 to -0.5); p<0.0001 Resolution of NASH, n (%): 1) 22 (22%) 2) 13 (13%) RR 1.5 (95% CI 0.9-2.6); p=0.08 Patients w/ improved fibrosis, n (%): 1) 36 (35%) 2) 19 (19%) RR 1.8 (95% CI 1.1-2.7); p=0.004	Pruritus, n (%): 1) 33 (23%) 2) 9 (6%) p<0.0001 Nausea, vomiting, diarrhea, n: 1) 12 2) 12
				Mean age, yrs	52	51		
				Male, n (%)	43 (30)	53 (37)		
				Mean weight, kg (SD)	100 (23)	96 (18)		
				Hyperlipidemia, n (%)	87 (62)	86 (61)		
				Diabetes, n (%)	75 (53)	74 (52)		
				Mean ALT, U/L (SD)	83 (49)	82 (51)		
				Mean ALP, U/L (SD)	82 (29)	81 (25)		
				Mean tot chol, µmol/L (SD)	4.9 (1.2)	4.8 (1.2)		
				Mean HDL, µmol/L (SD)	1.1 (0.3)	1.1 (0.4)		
				Vitamin E in last 6 months, n (%)	29 (21)	32 (23)		
				Antilipidemic agent in last 6 months, n (%)	72 (51)	64 (45)		
				Definite steatohepatitis, n %)	114 (81)	111 (79)		

<table>
<tr><th>Author, Pub. Year (Trial) Quality rating</th><th>Study Design</th><th>Intervention (n) Dosing Schedule</th><th>Inclusion and Exclusion Criteria</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr><td></td><td></td><td></td><td></td><td><table><tr><td>Mean NAFLD score (SD)</td><td>5.3 (1.3)</td><td>5.1 (1.3)</td></tr></table></td><td>Mean change in values from baseline to 72 weeks (SD):<table><tr><th></th><th>1)</th><th>2)</th><th>p-value</th></tr><tr><td>ALT (U/L)</td><td>-38 (47)</td><td>-18 (44)</td><td><0.001</td></tr><tr><td>AST (U/L)</td><td>-27 (37)</td><td>-10 (31)</td><td>0.0001</td></tr><tr><td>ALP (U/L)</td><td>12 (26)</td><td>-6 (20)</td><td><0.0001</td></tr><tr><td>GGT (U/L)</td><td>-37 (70)</td><td>-6 (48)</td><td><0.0001</td></tr><tr><td>Tot chol (mmol/L)</td><td>0.16 (1.07)</td><td>-0.19 (0.96)</td><td>0.0009</td></tr><tr><td>HDL (mmol/L)</td><td>-0.02 (0.20)</td><td>0.03 (0.19)</td><td>0.01</td></tr><tr><td>HOMA-IR</td><td>15 (50)</td><td>4 (29)</td><td>0.01</td></tr><tr><td>Weight (kg)</td><td>-2.3 (6.7)</td><td>0.0 (6.1)</td><td>0.008</td></tr><tr><td>SF-36 physical</td><td>0 (7)</td><td>-1 (7)</td><td>0.22</td></tr><tr><td>SF-36 mental</td><td>0 (9)</td><td>1 (9)</td><td>0.65</td></tr></table></td><td></td></tr>
<tr><td>Abstract in Hepatology

Hameed, 2015

(FLINT)</td><td>See FLINT</td><td>See FLINT

Secondary analysis of 200 patients with baseline and end of treatment liver biopsy</td><td>See FLINT</td><td>See FLINT</td><td>Weight loss, n (%):
1) 43 (42)
2) 29 (30)
p=0.08

<u>Subanalysis</u>:
Change in NALFD Activity Score by weight loss status<table><tr><th></th><th>1)</th><th>2)</th></tr><tr><td>W/ wt loss</td><td>-2.4</td><td>-1.4</td></tr></table></td><td></td></tr>
</table>

<table>
<tr><th>Author, Pub. Year (Trial) Quality rating</th><th>Study Design</th><th>Intervention (n) Dosing Schedule</th><th>Inclusion and Exclusion Criteria</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>w/o wt loss</td><td>-1.2</td><td>-0.4</td></tr>
<tr><td>p-value</td><td><0.001</td><td>0.006</td></tr>
</table>
Change in ALT by weight loss status
<table>
<tr><th></th><th>1)</th><th>2)</th></tr>
<tr><td>W/ wt loss</td><td>-42</td><td>-27</td></tr>
<tr><td>w/o wt loss</td><td>-34</td><td>-11</td></tr>
<tr><td>p-value</td><td>0.15</td><td>0.01</td></tr>
</table>
Change in LDL by weight loss status
<table>
<tr><th></th><th>1)</th><th>2)</th><th>p-value</th></tr>
<tr><td>W/ wt loss</td><td>22</td><td>-17</td><td><0.001</td></tr>
</table>
</td><td></td></tr>
<tr><td>Poster in J of Hepatology

Hameed, 2015

(FLINT)</td><td>See FLINT</td><td>See FLINT

Secondary analysis of 200 patients with baseline and end of treatment liver biopsy</td><td>See FLINT</td><td>See FLINT</td><td>
Change in LDL (mg/dL) by weight loss status
<table>
<tr><th></th><th>1)</th><th>2)</th><th>p-value</th></tr>
<tr><td>W/ wt loss</td><td>23</td><td>-17</td><td><0.001</td></tr>
<tr><td>w/o wt loss</td><td>0</td><td>-2</td><td>NR</td></tr>
</table>
Change in HDL by weight loss status
<table>
<tr><th></th><th>1)</th><th>2)</th><th>p-value</th></tr>
<tr><td>W/ wt loss</td><td>-0.6</td><td>3.6</td><td>NR</td></tr>
</table>
</td><td></td></tr>
<tr><td>Poster in J of Hepatology

Neuschwander-Tetri, 2015

(FLINT)</td><td>See FLINT</td><td>See FLINT

Subanalysis of pts w/ more severe NASH (stage 2-3 fibrosis or stage 1 fibrosis w/ DM, obesity, or ALT≥60
1) n=85
2) n=77</td><td>See FLINT</td><td>See FLINT</td><td>
<u>Subanalysis</u>:
≥2 point improvement in NAFLD activity score:
1) 50%
2) 31%
p=0.001

NASH resolution:
1) 18%
2) 6.5%
p=0.03

Fibrosis regression ≥1 stage:
1) 39%
</td><td></td></tr>
</table>

<table>
<tr><th>Author, Pub. Year (Trial) Quality rating</th><th>Study Design</th><th>Intervention (n) Dosing Schedule</th><th>Inclusion and Exclusion Criteria</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>2) 22%
p=0.012

Fibrosis progression:
1) 16%
2) 29%
p=0.047

Statin therapy initiated on OCA reduced LDL levels to levels seen among pts treated w/ statins at baseline.</td><td></td></tr>
<tr><td>Publication in Gastroenterology

Mudaliar, 2013

(NCT00501592)

fair (not randomized evenly, poor labeling, does not disclose ITT)</td><td>Phase II
RCT
Multicenter
Double-blinded</td><td>1) 25mg OCA qd for 6 wks (n=20)

2) 50mg OCA qd for 6 wks (n=21)

3) Placebo qd for 6 wks (n=23)</td><td>Patients w/ Type 2 DM and NAFLD

Excluded high AST, ALT, bili, DM agents other than metformin or sulfonylureas, EtOH/substance abuse in prior 2 yrs, heart/renal disease</td><td>Male, n (%):
1) 14 (70)
2) 9 (43)
3)10 (43)

Mean age, years:
1) 52.7
2) 50.5
3) 53.1

Mean body weight, kg (SD):
1) 108.6 (23.0)
2) 106.4 (25.1)
3) 104.2 (25.6)

Glucose, mg/dL
1) 149
2) 132
3) 159</td><td><u>Primary outcomes</u>:
Percent change in low-dose glucose infusion rate (SD):
1) 28.0 (40.2); p=0.019
2) 20.1 (32.6); p=0.60
1+2) 24.5 (36.6); p=0.011
3) -5.5 (35.9)

Percent change in high-dose glucose infusion rate (SD):
1) 18.3 (36.3); p=0.036
2) 10.8 (21.8); p=0.076
1+2) 15.0 (30.4); p=0.025
3) -5.4 (24.3)

<u>Secondary outcomes</u>:
Change in mean LFTs (U/L) and lipids (mg/dL):
<table><tr><th></th><th>1)</th><th>2)</th><th>3)</th></tr><tr><td>AST</td><td>-2 (p=0.12)</td><td>5 (p=0.73)</td><td>5</td></tr><tr><td>ALT</td><td>-10 (p=0.003)</td><td>10 (p=0.84)</td><td>11</td></tr><tr><td>ALP</td><td>14 (p=0.003)</td><td>27 (p<0.001)</td><td>0</td></tr></table></td><td>Pt w/ any AEs, n (%):
1) 9 (45)
2) 16 (76)
3) 14 (61)

Pt w/ tx-related AEs, n (%):
1) 1 (5)
2) 8 (38)
3) 6 (26)

Pruritus, n (%):
1) 0 (0)
2) 1 (5)
3) 2 (9)

Infections, n (%):
1) 5 (22)
2) 2 (10)
3) 2 (10)

GI disorder, n (%):
1) 1 (5)</td></tr>
</table>

Author, Pub. Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					GGT -37 (p<0.001) -22 (p<0.001) 5 **tchol** 18 (p=0.08) 13 (p=0.15) 8 **HDL** -2 (p=0.42) -6 (p=0.01) 0 Change in FGF19 (ng/L): 1) 85; p=0.006 2) 176; p<0.0001 3) 7 Percent change in mean body weight: 1) 1; p=0.096 2) 1.9; p=0.008 3) ~0 Mean change in ELF score (SD): 1) -0.2 (0.4); p=0.004 2) 0.03 (0.8); p=0.21 3) 0.3 (0.5)	2) 6 (29) 3) 4 (17)

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