Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis with Fibrosis

Draft Evidence Report

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Prepared for

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals 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.

For a complete list of stakeholders from whom we requested input, please visit:
https://icer-review.org/material/nash-stakeholder-list/

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List of Acronyms Used in this Report

AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine transaminase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
CVD	Cardiovascular disease
FDA	Food and Drug Administration
HCC	Hepatocellular Carcinoma
HS	Hepatic Steatosis
ITT	Intention-to-treat
GGT	Gamma-Glutamyl Transpeptidase
LS	Least squares
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NICE	National Institute for Health and Care Excellence
No.	Number
NS	Not significant
NR	Not reported
OCA	Obeticholic acid
PICOTS	Population, Interventions, Comparisons, Outcomes, Timing, Setting, and Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
QOL	Quality of life
RCT	Randomized controlled trial
SAE	Serious adverse event
T2DM	Type 2 Diabetes Mellitus
WAC	Wholesale acquisition cost

1. Introduction

1.1 Background

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

The exact prevalence of NASH is uncertain since definitive diagnosis requires liver biopsy, and many patients with NAFLD do not undergo biopsy. It is estimated that the prevalence of NASH in the adult population is between 1.5% and 6.5%.[1] Patients with NASH may have liver fibrosis, and liver fibrosis can progress to cirrhosis. Patients with cirrhosis are at high risk of death from liver failure and liver cancer (hepatocellular carcinoma [HCC]), and may require liver transplantation.[2] NAFLD is highly associated with the metabolic syndrome with or without type 2 diabetes mellitus (T2DM) and NAFLD and metabolic syndrome have the common risk factor of obesity.[2] Metabolic syndrome has a number of different definitions, but a commonly used one is at least three of: increased waist circumference; elevated triglyceride level; reduced high density lipoprotein (HDL) cholesterol level; elevated blood pressure; and elevated blood glucose (blood sugar).[3] Metabolic syndrome is a major risk factor for cardiovascular disease (CVD), and despite an increased risk of death from liver-related causes, CVD is the most common cause of death in patients with NAFLD.[1] Statins appear to improve CV outcomes in patients with NASH.[4] NASH has become a major cause of cirrhosis and, as effective treatment of hepatitis C is now available, it is expected to become the leading reason for liver transplantation in the US.[2]

The prognosis of NAFLD is variable. Most patients with NAFL and with NASH without fibrosis do not progress, and while some patients with NASH and fibrosis do progress to advanced liver disease, many stabilize or regress without pharmacotherapy. A meta-analysis of the placebo arms of clinical trials in patients with NASH found that 25% showed improvement on a common measure of disease activity.[5] In unpublished results from one trial, similar percentages of patients receiving placebo improved and worsened (23.2% vs 20.9%); presumably more than half of patients showed stability in their degree of fibrosis.[6]

The diagnosis and assessment of NAFLD can involve invasive or noninvasive testing. Routine screening for NAFLD even in high-risk populations is not generally recommended.[2] Patients can be found to have HS incidentally on liver imaging (such as during abdominal ultrasonography); in the absence of significant alcohol consumption, coexisting chronic liver disease (e.g., chronic viral hepatitis), or other causes of HS, they are generally assumed to have NAFLD. A meta-analysis found

that ultrasonography has a sensitivity of 85% and specificity of 94% for moderate to severe HS,[7] however ultrasonography appears to have much lower sensitivity and somewhat lower specificity in very obese patients.[8,9] Transient elastography, a noninvasive technique used to assess liver fibrosis, is being assessed for its ability to measure HS as well.[10]

When patients are found to have NAFLD, they may have various tests to assess for fibrosis or cirrhosis. These can involve laboratory tests such as aminotransferase (transaminase) levels, coagulation tests, and complete blood count, ratios of some of these tests such as the ratio of the aspartate aminotransferase (AST) elevation to platelet count,[11], more complex or proprietary calculations based on laboratory tests,[12], and many other tests being developed or assessed. As mentioned, transient elastography, which assesses vibration within the liver in response to sound waves, is a sensitive and specific technique for assessing fibrosis,[13,14] and a number of related techniques have been developed. Liver biopsy remains the gold standard for assessing HS, fibrosis, and cirrhosis.[2]

Lifestyle changes that result in improvement in the metabolic syndrome, including exercise and weight loss, can improve NASH, as can weight loss after bariatric surgery; bariatric surgery also improves T2DM and the metabolic syndrome.[2,15] There have been limited pharmacologic options for treating NASH, although many are now in development. Vitamin E may have efficacy for the histologic changes of NASH.[2] It is uncertain whether medications that enhance weight loss improve NASH beyond lifestyle changes alone, although some medications that are being studied for NASH treatment also promote weight loss.[16]

Pioglitazone is a thiazolidinedione approved for the treatment of type 2 diabetes. Thiazolidenediones bind and activate peroxisome proliferator-activated receptors (PPARs) and exert effects in many different tissues including the liver.[17] Although pioglitazone does not carry an indication for the treatment of NAFLD, trials have suggested that it may improve NASH and, perhaps, have some effect on reducing liver fibrosis.[18] Pioglitazone increases the risk of heart failure, bone fractures and bladder tumors, and promotes weight gain.[19-22]

Obeticholic acid (OCA; Ocaliva™; Intercept Pharmaceuticals) is a bile acid analog that was approved for the treatment of patients with primary biliary cholangitis in 2016. OCA is a farnesoid X receptor agonist; the farnesoid X receptor is important in regulation of bile acids, and activation of the receptor may reduce hepatic inflammation and fibrosis.[6] OCA is under review as a treatment for NASH with fibrosis, with a Food and Drug Administration (FDA) decision expected in 2020. ICER had previously reviewed OCA as a treatment for NASH in 2016 and found the evidence insufficient at that time. That report can be accessed, here: https://icer-review.org/material/final-report-oca-nash/. Additional evidence has since become available for OCA as well as for other therapies for NASH.

1.2 Scope of the Assessment

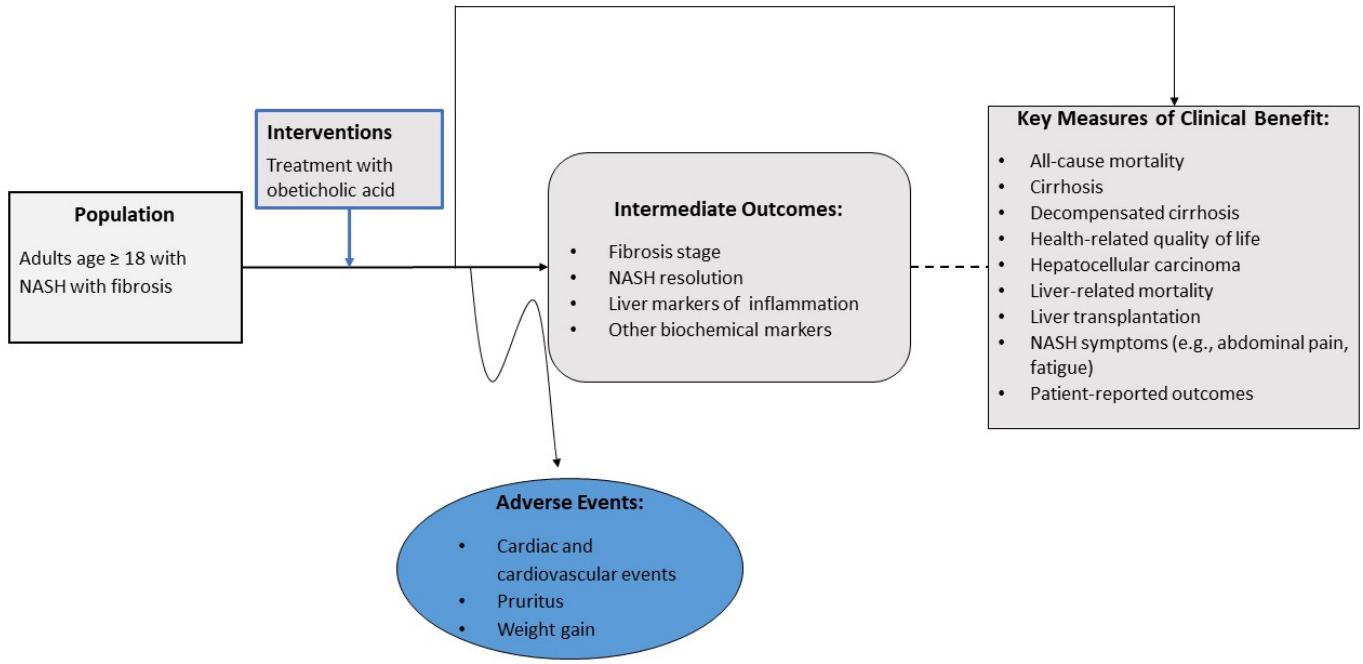
The scope for this assessment is described on the following pages using the Population, Intervention, Comparators, Outcomes, Timing, and Settings (PICOTS) framework. Evidence was abstracted from randomized controlled trials (RCTs) and nonrandomized studies as well as high quality systematic reviews; high-quality comparative cohort studies were considered, particularly for long-term outcomes and uncommon AEs. Our evidence review includes input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessmentframework/grey-literature-policy/).

All relevant evidence was summarized qualitatively. We sought head-to-head studies of the interventions and comparators of interest. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis were provided in a research protocol published on the Open Science Framework website https://osf.io/7awvd/ (Appendix Tables A2.1, A2.2, Figure 1).

Analytic Framework

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

Figure 1.1 Analytic Framework



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

Populations

The population of focus for the review is adults age ≥ 18 with NASH with fibrosis. As data allowed, we reviewed evidence of effectiveness across subgroups of patients with more or less advanced fibrosis and with or without diabetes.

Interventions

The intervention of interest is Obeticholic acid administered as oral tablets in addition to usual care. Usual care includes lifestyle interventions as well as usual care for associated metabolic comorbidities, and may include vitamin E.

Comparators

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

Outcomes

The outcomes of interest are described in Table 1.1 below.

Table 1.1. Key Outcomes and Harms

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

Additional intermediate and surrogate outcomes of interest include:

- Alterations in lipids
- Fibrosis stage
- Liver markers of inflammation
- Other biochemical markers
- NASH resolution

Timing

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

Settings

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

1.3 Definitions

Nonalcoholic fatty liver disease (NAFLD): Hepatic steatosis without another explanation such as alcohol consumption or use of medications that cause hepatic steatosis.

Hepatic steatosis (HS): Fat in the liver

Nonalcoholic fatty liver (NAFL): Hepatic steatosis without injury to liver cells

Nonalcoholic steatohepatitis (NASH): Hepatic steatosis with injury to liver cells

Cirrhosis: A late stage of liver fibrosis that in advanced stages is irreversible. Cirrhosis often has multiple signs and symptoms including fatigue, loss of appetite, jaundice, abdominal distension, bleeding and bruising, and many others.

Compensated cirrhosis: Cirrhosis without evidence of decompensation. Some patients with compensated cirrhosis may be asymptomatic.

Decompensated cirrhosis: Cirrhosis with signs and symptoms such as confusion (hepatic encephalopathy), fluid in the abdomen (ascites), yellowing of the skin and mucous membranes (jaundice), or kidney failure.

NAFLD Activity Score (NAS): A histologic scoring system for NAFLD that represents the sum of scores for steatosis, hepatocellular ballooning, and lobular inflammation.

Liver enzymes: Certain common laboratory tests that tend to increase in the setting of liver injury. These include alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

1.5. Potential Cost-Saving Measures in NASH

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by OCA (e.g., hospitalization for decompensated cirrhosis), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of NASH beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

2. Patient and Caregiver Perspectives

This report was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during calls with stakeholders and open input submissions from the public. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

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

Patients described the fatigue and brain fog of cirrhosis, the loss of the ability to work, drive, or productively contribute to the home, and the depression and fear caused by suddenly learning of a devastating disease. Patients with decompensated cirrhosis described abdominal pain and hospital admissions for ascites requiring paracentesis (removal of fluid from the abdomen) and for delirium from hepatic encephalopathy. A common experience was of having been told years earlier that they had fat in the liver but that it was nothing to worry about, only to next have the issue raised when diagnosed with cirrhosis.

Patients and patient groups described the strain on caregivers of having a family member become disabled and confused, as well as the potentially extreme financial strain of having medical bills for advanced liver disease mount at the same time that the patient became unable to contribute to the household income. The financial strain can be exacerbated if the caregiver needs to also give up working in order to provide care to the patient.

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

We received additional input from patient groups highlighting the broad impacts on health from liver dysfunction, concerns about lack of insurance coverage for pioglitazone given its lack of an FDA indication for NASH, and that NASH has very different implications for patients at different stages of

disease, including very different effects on quality of life. We also heard ongoing concerns about lack of knowledge of NASH both in the general public and among clinicians.

We heard that describing the difficult and ongoing reductions in weight that must be achieved and maintained to improve NASH are not adequately conveyed by describing these as "lifestyle interventions", and that need for weight loss may impact adherence to medications that tend to promote weight gain such as thiazolidinediones.

As noted in our Revised Scope, based on feedback we received from stakeholders we added decompensated cirrhosis as an outcome of interest, added subgroups of patients with more and less advanced fibrosis, and revised the descriptions of the comparators, the key outcomes, and the population of interest to improve clarity.

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

To understand the insurance landscape for treatments for NASH relevant to this review, we reviewed National and Local Coverage Determinations (NCDs and LCDs) from the Centers for Medicare and Medicaid Services (CMS), and publicly available coverage policies from representative national plans (Aetna and Cigna), national and regional private payers (HealthPartners and Blue Cross Blue Shield of Kansas City) and state Medicaid plans (MO Healthnet and IL Health and Family Services).

No coverage policies, nor any NCDs or LCDs, were available for OCA as treatment for NASH at the time of the publishing of this report. OCA is currently only indicated for the treatment of primary biliary cholangitis (PBC), and it is unlikely that the current coverage policies for PBC will mirror those for NASH. No NCDs or LCDs were available for pioglitazone, as NASH is not an approved indication for the medication.

3.2 Clinical Guidelines

American Association for the Study of Liver Diseases (AASLD)[2]

The AASLD's 2018 practice guidance indicate that any pharmacological treatments should be aimed at patients with biopsy-proven NASH with fibrosis.[2] Lifestyle interventions (increased physical activity, hypocaloric diet) that promote weight loss are recommended to improve hepatic steatosis. Sustained weight loss of at least 3%-5% of body weight is necessary to reduce steatosis; however, at least 7%-10% weight loss would be necessary for patients with biopsy-proven NASH[2]. Bariatric surgery may also be considered for eligible obese individuals on a case-by-case basis; however, it's safety and efficacy in NASH with cirrhosis patients has not been established.[2]

The AASLD's guidance indicated pioglitazone, a peroxisome proliferator-activated receptor agonist used for diabetes treatment, could be used to treat NASH patients with or without Type 2 Diabetes Mellitus. It was recommended that clinicians should weigh the risks and benefits with each patient before taking pioglitazone due to common side effects of weight gain, potential bone loss in women, and potential increased risk for bladder cancer. Vitamin E (800 IU/day) may benefit biopsy-proven NASH patients who do not have diabetes, but it is not recommended at this time for diabetic NASH patients until further studies assess its effectiveness in this population. The guidance also recommends modifications of cardiovascular (CVD) risk factors, including use of statins for

treatment of dyslipidemia in NASH patients. Statins should be avoided in patients with decompensated cirrhosis. At the time of the publishing of this guidance, the AASLD did not recommend the off-label use of OCA to treat NASH until further safety and efficacy data becomes available.[2]

European Association for the Study of the Liver; European Association for the Study of Diabetes; European Association for the Study of Obesity (EASL-EASD-EASO)[23]

The EASL-EASD-EASO 2016 guidelines for NASH Treatment included diet and lifestyle interventions such as 500-1000 kcal energy restriction, exclusion of processed foods and beverages high in added fructose, adherence to the Mediterranean diet, and exercise that incorporates aerobics and resistance training.[23] Due to lack of FDA approved treatments indicated for NASH, the guidelines state no firm recommendations can be made on pharmacotherapies for NASH, but agreed that pioglitazone and vitamin E or a combination of both could be used for NASH. Statins may also be used to reduce LDL-cholesterol (LDL-C) and cardiovascular risk without harming or benefiting the liver. In addition, bariatric surgery could be considered when patients are unresponsive to lifestyle changes and pharmacotherapies.

World Gastroenterology Association (WGO)[24]

The WGO 2014 guidelines also recommend first-line diet and lifestyle changes for treatment of NAFLD/NASH, including aiming for 5%-10% weight reduction, exercise (3-4 times/week).[24] If interventions are ineffective for patients after a 6-month period, pharmacotherapies can then be considered. Bariatric surgery can also be considered for patients who are morbidly obese but are not recommended in cirrhosis patients. Thiazolidinediones and metformin targeting insulin resistance and Vitamin E could be considered but are experimental only as they are not approved for NASH.[24] At the time of the publishing of these guidelines, the WGO indicated there was insufficient safety and efficacy data for the use of Vitamin E and thiazolidinediones in NASH patients.

National Institute for Health and Care Excellence (NICE)[25]

NICE's 2016 guidelines recommend pioglitazone or vitamin E for adults with advanced liver fibrosis with or without diabetes. Precautions should be taken with these treatments in patients who have other comorbidities, as pioglitazone is contraindicated in patients with a history of heart failure, previous or active bladder cancer, and macroscopic hematuria.[25] NICE also recommends lifestyle interventions as described by previous clinical societies above.

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the clinical effectiveness of OCA and pioglitazone for NASH, we sought evidence related to each in comparison with optimal usual care as head-to-head trials have not been performed. Our review focused on clinical benefits (i.e., cirrhosis, hepatocellular carcinoma, liver transplantation, mortality, and quality of life), as well as potential harms (drug-related AEs). The studies of OCA and pioglitazone were sufficiently different that we felt that quantitative indirect comparisons of outcomes could not be performed, and so our assessments comparing these two therapies are qualitative. Methods and findings of our review of the clinical evidence are described in the sections that follow.

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for NASH followed established best research methods.[26,27] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[28] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms (see Appendix Tables A2.1 and A2.2). The date of our most recent search was November 18, 2019.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also 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/).

Study Selection

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection was accomplished through two levels of screening at the abstract and full-text level. Two reviewers independently screened the titles and abstracts of all identified publications using DistillerSR (Evidence Partners, Ottawa, Canada); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. Citations accepted during abstract-level screening were retrieved in full text for review. Reasons for exclusion were categorized according to the PICOTS elements during full-text review.

Data Extraction and Quality Assessment

Two reviewers extracted key information from the full set of accepted studies (See Appendix Tables D1-D13). Elements included a description of patient populations, sample size, duration of follow-up, study design features, interventions (agent, dosage, dosing frequency, method of administration), results, and quality assessment for each study. Extracted data were reviewed for logic and were validated by a third investigator for additional quality assurance.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[29]

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).

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 these newer treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms included nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, obeticholic acid, INT 727, and OCA. We searched for studies which would have met our inclusion criteria, and for which no findings have been published.

Data Synthesis and Statistical Analyses

The results of included studies are described narratively in the sections that follow. Analyses are descriptive in nature only, as we did not intend to compare obeticholic acid and pioglitazone to each other through indirect quantitative analysis. Insufficient data were identified to allow for pairwise meta-analyses of individual agents. However, sufficient data were identified to perform a meta-analysis of studies comparing pioglitazone to placebo on the fibrosis improvement outcome. This analysis was performed using a random effects model using R.

4.3 Results

Study Selection

Studies meeting the PICOTS criteria described in Section 1.2 were eligible for our review. To be included, studies were required to assess obeticholic acid or pioglitazone (any dose or regimen) in adults with NASH with fibrosis. Case-control studies and single-arm studies were excluded.

Key Studies of Obeticholic Acid

Our literature search identified four individual studies of obeticholic acid (OCA) that met our inclusion criteria (see Table 4.1 for characteristics of the studies and Appendix Table D1). Evidence of the clinical effectiveness of OCA was derived primarily from interim (18 month) results from the REGENERATE trial, a phase 3, multi-center trial that randomized 931 adults (in the primary, intention-to-treat analysis) with fibrosis stages F2-F3 to receive oral placebo (n=311), OCA 10mg (n=312), or OCA 25mg daily (n=308).[6]

In the REGENERATE trial, biopsies were done at baseline and 18 months and liver biochemistries (ALT, AST, GGT, ALP) and other measures such as glucose, lipids, and bodyweight were obtained every three months.[6]

The other key trial of OCA was the Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment (FLINT) Trial.[30] This phase 2 trial randomized 283 adults with biopsy evidence of NASH to receive

either 25 mg of OCA daily (n=141) or placebo (n=142). Biopsies, liver enzymes, and other metabolic factors at 72 weeks (18 months), were compared to baseline.

Two additional phase 2 trials, CONTROL (Pockros 2019) and NCT00501592 (Mudaliar 2013), were identified.[31,32] CONTROL focused primarily on the effect of OCA on lipid profiles and NCT00501592 on insulin sensitivity, liver enzymes, and lipids.

Table 4.1 Key Studies of Obeticholic Acid

Trial	Interventions	Inclusion Criteria	Exclusion Criteria	Outcomes
REGENERATE[6] **Phase 3 randomized, double blind, multi-center** **Follow-up: 18 months** **N=931 (ITT)**	- OCA 25mg - OCA 10mg - Placebo	Patients ages 18-65 years with biopsy confirmed NASH with fibrosis stages F2-F3, or F1 with at least one comorbidity	- MELD score >12 - ALT ≥10× ULN - HbA1c >9.5 - Total bilirubin >1.5 mg/dL - BMI >45 kg/m2 - Other chronic liver disease, hepatocellular carcinoma (HCC), or cirrhosis - History of liver transplant, or placement on a liver transplant list - Current or history of significant alcohol consumption - Prior or planned ileal resection, or bariatric surgery - HIV infection; acute cholecystitis or acute biliary obstruction	<u>Primary:</u> - Improvement of fibrosis (≥1 stage) with no worsening of NASH - NASH resolution with no worsening of fibrosis <u>Secondary:</u> - Improvement in fibrosis (≥1 stage) or resolution of NASH, or both, without worsening of either - Histological improvement of features of NASH as well as NAS, and liver biochemistry
FLINT[30] **Phase 2 randomized, double blind, multi-center** **Follow-up: 18 months** **N=283**	- OCA 25mg - Placebo	Patients ≥ 18 years with biopsy confirmed NASH and NAS of 4 or more with a score of 1 or more in each component of the score	- Current or history of significant alcohol consumption - Prior or planned bariatric surgery - Uncontrolled diabetes - Presence of cirrhosis or hepatic decompensation - Other forms of chronic liver disease: Hepatitis B, Hepatitis C, evidence of ongoing autoimmune liver disease, Primary biliary cirrhosis, Primary sclerosing cholangitis, etc.	- Decrease in NAS by ≥ 2 points without worsening of fibrosis - NASH resolution - Fibrosis improvement - Improvement in liver biochemistry
CONTROL[31] **Phase 2 randomized, double blind, multi-center** **Follow-up: 16 weeks**	- OCA 5mg - OCA 10mg - OCA 25mg - Placebo	- Patients ≥ 18 years with biopsy confirmed NASH with fibrosis of any stage	- Current or history of significant alcohol consumption - Uncontrolled diabetes	Changes in lipid profile: LDLc, HDL, VLDLc, triglycerides, total cholesterol, apolipoprotein, PCSK9

Trial	Interventions	Inclusion Criteria	Exclusion Criteria	Outcomes
N=84	**All groups were on background atorvastatin*	- On stable anti-diabetic medication if subject has T2DM	- LDLc >200 mg/dL or LDLc ≥190 mg/dL and on statin	
NCT00501592[32] **Phase 2 randomized, double blind, multi-center** **Follow-up: 6 weeks** **N=101**	- OCA 50mg - OCA 25mg - Placebo	- Patients age 18-75 with NAFLD* and type 2 diabetes	- Bilirubin >2 × ULN - ALT >155 U/L for females and >185 U/L for males - AST >155 U/L for females and >200 U/L for males - Patients taking any antidiabetic medications other than metformin and sulfonylureas	- Changes in glucose and lipid profiles - Improvement in liver biochemistry

ALT: alanine aminotransferase, AST: aspartate aminotransferase, HDLc: high-density lipoprotein cholesterol, LDLc: low-density lipoprotein cholesterol, mg: milligram, mg/DL: milligram per deciliter, N: total number, NAFLD: non-alcoholic fatty liver disease, OCA: obeticholic acid, T2DM: type 2 diabetes mellitus

* NAFLD was defined by liver biomarkers, enlarged liver on imaging, or biopsy

At baseline, characteristics of the study participants were balanced across intervention groups in the REGENERATE and FLINT trials (see Table 4.2).

Table 4.2 Baseline Characteristics of REGENERATE and FLINT

	REGNERATE (ITT Analysis)[6]			FLINT[30]	
	Placebo (n=311)	OCA 10mg (n=312)	OCA 25mg (n=308)	Placebo (n=142)	OCA 25 mg (n=141)
Age, mean (SD)	56 (12)	55 (11)	55 (11)	51 (12)	52 (11)
Male, n (%)	124 (39.9%)	135 (43.3%)	133 (43.2%)	53 (37.3%)	43 (30.5%)
T2DM, n (%)	171 (56.3%)	171 (54.8%)	171 (55.5%)	74 (52.0%)	75 (53.0%)
Weight, mean kg (SD)	95.3 (19)	95.2 (19)	95.4 (20)	96.0 (18)	100.0 (23)
Lipid Lowering/ Statin use, n (%)	175 (56.7%)	170 (54.5%)	160 (51.9%)	64 (45.1%)	72 (51.1%)
Anti-diabetic medication use, n (%)	167 (54.2%)	171 (54.8%)	159 (51.1%)	73 (51.4%)	67 (47.5%)
Vitamin E use, n (%)	42 (13.5%)	34 (10.9%)	32 (10.4%)	32 (22.5%)	29 (20.6%)

ITT: intention to treat, kg: kilogram, mg: milligram, N: total number, n: number, OCA: obeticholic acid, SD: standard deviation, T2DM: type 2 diabetes mellitus, SD: standard deviation

Quality of Individual Studies

We rated the key studies of obeticholic acid (REGENERATE and FLINT) to be of good quality using the criteria from USPSTF (Appendix Table D13). The studies were well-designed and had balanced baseline characteristics between arms. The two additional phase 2 trials we identified (CONTROL and Mudaliar 2013) were rated to be fair quality. CONTROL was rated fair because of some baseline imbalances and short duration of follow up. Mudaliar 2013 was rated fair because of the inadequacy in their approach to missing data and short duration of follow up.

Clinical Benefits of Obeticholic Acid

Summary: *Patients treated with OCA 10 mg or 25 mg had higher rates of improvement in fibrosis (at least one stage) at 18 months than patients who received placebo. NASH resolution was not significantly better. Dose-dependent decreases in markers of liver injury (ALT and AST) were seen in both trials. Progression to cirrhosis, hepatocellular carcinoma, liver transplantation, and mortality were not assessed. The impact of Obeticholic acid on quality of life and other patient-reported outcome measures remains unclear. Harms of Obeticholic acid include pruritus (itching of the skin) and changes in lipid profiles, particularly increases in LDL.*

Fibrosis improvement and NASH resolution

More patients in REGENERATE treated with OCA 10 mg or 25 mg than those treated with placebo met the co-primary endpoint of fibrosis improvement of at least one stage with no worsening of NASH at 18 months (55/312 [18%] and 71/308 [23%] vs 37/311 [12%]; RR of response 1.5 [95% CI 1.0-2.2] and 1.9 [CI 1.4-2.8], respectively).[6] Similarly, in the FLINT trial, of 109 patients on placebo, 19 (19%) improved compared to 36/110 (35%) in the OCA 25mg group; RR of response 1.8 [95% CI 1.1-2.7].[30]

On the co-primary endpoint in REGENERATE of NASH resolution with no worsening of fibrosis at 18 months there were no statistically significant differences between the 10 mg OCA and 25 mg OCA arms compared with placebo (35/312 [11%] and 36/308 [12%] vs 25/311 [8%]; RR of response 1.4 [CI 0.9-2.3] and 1.5 [0.9-2.4], respectively).[6] In the FLINT trial, of 109 patients on placebo 13 (13%) had NASH resolution compared to 36/110 (22%) in the OCA 25mg group; RR of response 1.5 [95% CI 0.9-2.6].[30]

Table 4.2 Fibrosis Improvement and NASH Resolution in the REGENERATE and FLINT Trials

	REGENERATE (ITT analysis)[6]			FLINT[30]	
	Placebo (n=311)	OCA 10mg (n=312)	OCA 25mg (n=308)	Placebo (n=109)	OCA 25 mg (n=110)
Improvement in Fibrosis at 18 Months, n (%)	37 (12%)	55 (18%) RR=1.5 (1.0-2.2)	71 (23%) RR=1.9 (1.4-2.8)	19 (19%)	36 (35%) RR=1.8 (1.1-2.7)
Resolution of NASH at 18 Months, n (%)	25 (8%)	35 (11%) RR=1.4 (0.9-2.3)	36 (12%) RR=1.5 (0.9-2.4)	13 (13%)	22 (22%) RR=1.5 (0.9-2.6)

ITT: intention to treat, mg: milligram, n: number, OCA: obeticholic acid

Histologic features of NASH

More patients in the OCA 25 mg group had improvement in lobular inflammation and hepatocellular ballooning compared to placebo in both the REGENERATE and FLINT trials (see Table 4.3).[6,30] Statistically significant improvement in steatosis was not observed in the REGENERATE trial but was in FLINT.

Table 4.3 Histologic Features of NASH (Steatosis, Lobular Inflammation, Hepatocellular Ballooning) at 18 Months in the REGENERATE and FLINT Trials

	REGENERATE (ITT analysis)[6]			FLINT[30]	
	Placebo (n=311)	OCA 10mg (n=312)	OCA 25mg (n=308)	Placebo (n=109)	OCA 25 mg (n=110)
Improvement in Steatosis, n (%); RR (95%CI)	118 (38%)	127 (41%); 1.1 (0.9-1.3)	127 (41%); 1.1 (0.9-1.3)	37 (38%)	62 (61%); 1.7 (1.2-2.3)
Improvement in Lobular Inflammation, n (%); RR (95%CI)	111 (36%)	123 (39%); 1.1 (0.9-1.4)	136 (44%); 1.2 (1.0-1.5)	34 (35%)	54 (53%); 1.6 (1.1-2.2)
Improvement in Hepatocellular Ballooning, n (%); RR (95%CI)	72 (23%)	85 (27%); 1.2 (0.9-1.5)	108 (35%); 1.5 (1.5-2.0)	30 (31%)	47 (46%); 1.5 (1.0-2.1)

ITT: intention to treat, mg: milligram, n: number, OCA: obeticholic acid, RR: risk ratio

Liver biomarkers

Dose-dependent improvement in markers of liver injury (ALT and AST) at 18 months were observed in the OCA arms for both REGENERATE and FLINT.[6,30] The statistical significance of this improvement was reported in the FLINT trial, but not REGENERATE (Table 4.4).

Table 4.4 Change in liver biomarkers at 18 months in REGENERATE and FLINT trials

	REGENERATE (ITT analysis)[6]			FLINT[30]	
	Placebo (n=311)	OCA 10 mg (n=312)	OCA 25 mg (n=308)	Placebo (n=109)	OCA 25 mg (n=110)
ALT, Mean Change From Baseline U/L (SE/SD)	-15.6 (SE: 3.6)	-23.8 (SE: 2.6)	-36.0 (SE: 3.6)	-18 (SD: 44)	-38 (SD:47), p<0.0001
AST, Mean Change From Baseline U/L (SE/SD)	-9.8 (SE: 2.4)	-14.1 (SE: 2.1)	-20.4 (SE: 2.4)	-10 (SD: 31)	-27 (SD:37), p<0.0001

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ITT: intention to treat, mg: milligram, n: number, OCA: obeticholic acid, SD: standard deviation, SE: standard error, U/L: units per liter

Patient-reported outcomes and quality of life

Patient-reported outcomes, as measured by the Chronic Liver Disease Questionnaire-NASH (CLDQ-NASH) and the EuroQOL (EQ-5D), were collected in the REGENERATE trial at baseline and at 18 months.[33] In the safety population (n=1218), the baseline mean CLDQ-NASH total score was 5.15 (SD: 1.13) and EQ-5D utility score was 0.814 (SD: 0.173). There was no difference across treatment groups at baseline. By month 18, CLDQ-NASH total scores increased 18% (SE: 10-26%) from baseline in the placebo group, 16% (SE: 6-26%) in the OCA 10mg group and 30% (SE: 20-40%) in the OCA 25mg group [data digitized from figure in the poster]. EQ-5D scores at 18 months were not reported but were described as being not different between the two treatment groups and placebo.

Quality of life, as measured by the 36-item short-form survey (SF-36) instrument, was collected in the FLINT trial at baseline and 72 and 96 weeks.[30] Physical and mental component summary scores of the SF-36 were unchanged from baseline in the obeticholic acid arm at 72 and 96 weeks (see Table 4.5).

Table 4.5 SF-36, Physical and Mental Components in FLINT Trial[30]

Trial	Follow-Up	Arms	Change From Baseline, SF-36 Physical Component Summary, Mean (SD); p-value	Change From Baseline, SF-36 Mental Component Summary, Mean (SD); p-value
FLINT	72 weeks	OCA 25 mg (n=102)	0 (7), p=0.22	0 (9), p=0.65
		Placebo (n=98)	-1 (7)	1 (9)
	96 weeks	OCA 25 mg (n=122)	0 (8), p=0.19	0 (9), p=0.14
		Placebo (n=120)	-1 (7)	-1 (10)

OCA: obeticholic acid, SF-36: 36-item short form survey, SD: standard deviation

Harms

One death occurred in the OCA 25mg arm and 2 deaths in the placebo arm of the REGENERATE trial.[6] None of these were deemed to be related to study treatment. Discontinuation of the study drug due to adverse events (AEs) was 6% in the placebo arm, 6% in the OCA 10 mg arm, and 13% in the OCA 25 mg arm of the REGENERATE trial. Rates of serious AEs were similar between groups (11%, 11%, and 14% in the placebo, OCA 10 mg, and OCA 25 mg arms respectively).

Pruritus

The most common adverse event in both the REGENERATE and FLINT trials was pruritus (itching of the skin).[6,30] About half (51%) of patients in the OCA 25 mg group of the REGENERATE trial experienced pruritus of any grade, while 30% of patients in the OCA group of the FLINT trial experienced pruritus. The pruritus was most commonly grade 2 (intense or widespread) (see Table 4.6).

Table 4.6 Pruritus in the REGNERATE and FLINT Trials

Pruritus	REGENERATE (Safety Population)[6]			FLINT[30]	
	Placebo (n=657)	OCA 10mg (n=635)	OCA 25mg (n=658)	Placebo (n=109)	OCA 25 mg (n=110)
Any, n (%)	123 (19%)	183 (28%)	336 (51%)	9 (8%)	33 (30%)
Grade 1	90 (14%)	113 (17%)	148 (22%)	6 (8%)	9 (8%)
Grade 2	30 (5%)	67 (10%)	152 (23%)	3 (2%)	21 (19%)
Grade 3	3 (<1%)	3 (<1%)	36 (5%)	0 (0%)	3 (3%)

mg: milligram, n: number, OCA: obeticholic acid

Lipid levels

OCA appears to have unfavorable effects on lipid levels. Because this is a particularly important issue to assessing the net benefits of OCA, it is discussed in detail in a separate section below.

Fatigue

Fatigue was commonly cited by patients and stakeholders as a major side effect of NASH; however, this outcome was only reported in the REGENERATE trial. In the safety population, 88/657 (13%) of patients in the placebo group reported fatigue at 18 months compared with 78/653 (12%) in the OCA 10mg and 71/658 (11%) in the OCA 25mg group.[6] These rates appear similar and no comparative statistical test was reported.

Subgroup Analyses

Fibrosis Stage

It is uncertain if the effects of OCA are different at different stages of fibrosis. In REGENERATE, rates of improvement in fibrosis with OCA 25 mg compared with placebo were similar in patients with F2 and F3 fibrosis (RR 2.0 and 1.8, respectively); the magnitude of this increase did not vary across fibrosis subgroups.[6] Results from patients with F1 disease were not reported. In FLINT, rates of improvement compared with placebo was similar in patients with F0-F1 fibrosis and F2-F4 fibrosis (RR 3.0 and 3.3, respectively).[30] Results from the REVERSE study, a phase 3 trial of obeticholic acid in patients with NASH with compensated cirrhosis (stage 4) are not expected until late 2021 (clinicaltrials.gov) (see Appendix C for ongoing trials).

Diabetes

Type-2 diabetes is a common comorbidity with NASH.[2] There is some evidence to suggest that the presence of T2DM is associated with faster progression of NASH (Bugianesi 2007)[34]. It is uncertain if the effects of OCA are different for diabetics compared to non-diabetics. More than half of the patients in REGENERATE (55-56%) and FLINT (53%) had diabetes at enrollment.[6,30] Improvement in fibrosis was observed in patients with and without diabetes in both the REGENERATE and FLINT trials. Histologic features of NASH also improved in both diabetics and non-diabetics in the FLINT trial; the magnitude of the improvement did not vary across diabetes subgroups.

OCA Effects on Lipids

OCA raises levels of LDL-C and lowers levels of HDL-C.[31] This is of particular importance in a population with NASH since many of these patients are at very high CV risk because of their comorbidities including T2DM, hypertension, and the metabolic syndrome.[1] Additionally, there is some evidence that NAFLD and NASH may be independent risk factors for CV disease even after controlling for the high rates of baseline risk.[35]

In the key trials of OCA, REGENERATE and FLINT, statin treatment was not held steady over the trial or required at baseline.[6,30] As a result, the lipid outcomes in those trials reflect changes in statin therapy that occurred differentially in patients treated with OCA and placebo.

In REGENERATE, more than half (52-56% across study arms) of participants were on lipid lowering medications (primarily statins of unreported dose) at enrollment and were differentially given new statins of unreported dose during the trial (24% both OCA groups vs 10 % in the placebo arm) were given new statins of indeterminant dose during the trial.[6] One month after starting OCA, LDL-C levels increased in the 10 mg and 25 mg arms by 17.8 mg/dL and 23.8 mg/dL and decreased in the placebo arm by -3.0 mg/dL). At 18 months with differential use of statins, these numbers were 1.4 mg/dL and 2.7 mg/dL in the OCA arms and -7.1 mg/dL in the placebo arm.

In FLINT, rates of new statin use were not reported, but the overall effects on LDL-C were similar to what was seen in REGENERATE.[30] At 72 weeks patients who received OCA 25 mg had an increase in LDL-C of 8.5 mg/dL compared with a decrease of 8.5 mg/dL in the placebo arm.

In a small phase 2 trial with 43 days of follow-up, mean LDL increased 9 mg/dL from baseline in the placebo group and 22mg/dL in the obeticholic acid 25mg group (p=0.01).[32]

Given the high baseline CV risk and high rates of T2DM in patients with NAFLD, nearly all these patients would be recommended for treatment with moderate or high intensity statin therapy. [4,36] Thus a fairer assessment of the effects of OCA on lipids and CV risk would be one that was conducted on a background of statin therapy and, ideally, of sufficient duration to achieve steady state.

In the CONTROL study, 84 patients with NASH were randomized to receive placebo or OCA at doses of 5 mg, 10 mg, or 25 mg.[31] All patients were started on atorvastatin 10 mg at baseline, and this dose was increased to 20 mg as tolerated at week 8. At week 12, statin use was determined per US guidelines. Thus, the changes in lipids in CONTROL at week 12 reflect a reasonably steady-state situation in patients on a background of a moderate intensity (atorvastatin 20 mg) lipid regimen.

At week 12, the LS mean difference in LDL-C from baseline was -56.6 mg/dL in the placebo group and -39.4 mg/dL in the obeticholic acid 25mg group, a difference of 17.2 mg/dL (see Table 4.7). We believe this increase of 17.2 mg/dL in patients receiving OCA rather than placebo on a background of statin therapy is currently our best estimate of the effects of OCA on LDL-C in appropriately managed patients with NASH.

Table 4.7 Changes in LDL Levels at 12 Weeks in the CONTROL Study[37]

Arm	LS Mean Δ From Baseline mg/dL (SE), Week 12*	Δ From Placebo
Placebo + Atorvastatin (n=19)	-56.6 (4.2)	---
OCA 10mg + Atorvastatin (n=17)	-42.6 (5.1)	14.0
OCA 25mg + Atorvastatin (n=18)	-39.4 (4.3)	17.2

*Estimates of LS mean Δ from baseline LDLc at 12 weeks were derived from digitizing Figure 2B and should be interpreted with caution.

Small decreases in HDL were also observed in patients who received OCA in REGENERATE and FLINT.[6,30] In the 12-week results in CONTROL, HDL-C decreased 4.0mg/dL (SE: 1.6) from baseline (LS mean digitized from Figure 4B) with OCA 25 mg and 2.5mg/dL (SE: 1.5) with placebo.[31]

The LDL hypothesis (that the magnitude of benefit/harm from lipid therapy is proportional to the change in LDL-C) has become a generally accepted way of assessing how lipid changes with

medications result in changes in CV risk.[38] As such, increases in LDL-C with medications are considered concerning for resulting in increased CV risk.[39]

In contrast, although HDL-C is lowered by OCA, and patients with lower HDL-C levels at baseline have increased CV risk, there is no consistent evidence that medications that change HDL-C levels alter CV risk by this mechanism.[40] As such, the effects of OCA on HDL-C are less concerning than the effects on LDL-C.

Key Studies of Pioglitazone

We identified seven individual trials of pioglitazone that met our inclusion criteria (Appendix Table D1), of which five were determined to be of fair or good quality. The design of the key trials of pioglitazone is summarized below (Table 4.8).

Table 4.8 Key Studies of Pioglitazone

Trial	Interventions	Inclusion Criteria	Exclusion Criteria	Outcomes
NCT00994682 **Cusi 2016[41]** **Phase 4 randomized, double blind, single-center** **Follow-up: 18 months; 18 month OLE** **N=101**	Pioglitazone 45mg Placebo	Patients age 18-70 with biopsy confirmed NASH and prediabetes or T2DM	Any cause of chronic liver disease other than NASH Current history of alcohol abuse Change in use of chronic medications with known adverse effects on glucose levels 4 weeks prior to study entry History of clinically significant heart disease, peripheral vascular disease, or pulmonary disease Severe osteoporosis	Primary: Reduction in NAS of ≥ 2 points without worsening of fibrosis Secondary: Resolution of NASH Improvement in histologic scores or outcomes
PIVENS **Sanyal 2010[37]** **Phase 3 randomized, double blind, multi-center** **Follow-up: 24 months** **N=247**	Pioglitazone 30mg Vitamin E Placebo	Patients ≥18 with biopsy confirmed NASH	History of diabetes Current or history of significant alcohol consumption Presence of cirrhosis or other chronic liver disease Use of drugs for NAFLD/NASH or T2DM prior to entry, non-stable dose of statins or fibrates	Primary: Improvement in histologic features of NASH NAS improvement of at least 2 points Secondary: Improvement in fibrosis; liver biomarkers; insulin resistance; lipid profile; SF-36
NCT01002547 **Bril 2019[42]**	Pioglitazone 45mg + vitamin E	Patients 18-70 with biopsy	Current or history of significant alcohol consumption	Primary:

Trial	Interventions	Inclusion Criteria	Exclusion Criteria	Outcomes
Phase 4 randomized, double blind, multi-center **Follow-up: 18 months** **N=105**	Placebo	confirmed NASH with T2DM	Presence of any chronic liver disease other than NASH Type-1 diabetes History of clinically significant renal, pulmonary, or heart disease	NAS improvement of at least 2 points without worsening of fibrosis Secondary: NASH resolution; improvements in histologic features of NASH; liver biomarkers; insulin sensitivity fibrosis
NCT00227110 Belfort 2006[43] **Phase 4 randomized, double blind, single-center** **Follow-up: 6 months** **N=55**	Pioglitazone 45mg + hypocaloric diet Placebo + hypocaloric diet	Patients ≥18 with biopsy confirmed NASH and pre-diabetes or T2DM On stable anti-diabetic medication if subject has T2DM	Current or history of significant alcohol consumption Presence of cirrhosis or other chronic liver disease Type-1 diabetes	Improvements in hepatic fat; insulin sensitivity; histologic features of NASH; fibrosis
N0192119052 Aithal 2008[44] **Phase 2 randomized, double blind, multi-center** **Follow-up: 12 months** **N=74**	Pioglitazone 30mg + diet and exercise Placebo + diet and exercise	Patients ≥18 with biopsy confirmed NASH	History of diabetes Current or history of significant alcohol consumption Presence of cirrhosis or other chronic liver disease Use of drugs for NAFLD/NASH or T2DM prior to entry, non-stable dose of statins or fibrates	Improvements in histologic features of NASH; fibrosis; insulin and lipid profiles; liver biomarkers

mg: milligram, N: total number, NAFLD: non-alcoholic fatty liver disease, NAS: NAFLD activity score, NASH: non-alcoholic steatohepatitis, T2DM: type 2 diabetes mellitus

Quality of Individual Studies

We rated the key studies of pioglitazone to be of good or fair quality using the criteria from USPSTF (Appendix Table D13).

Clinical benefits of pioglitazone

Summary: *Trials of pioglitazone for NASH vary in their size, quality, choice of comparator, dose of pioglitazone, duration of follow-up and outcomes assessed. In general, pioglitazone was not proven to improve fibrosis in patients with NASH in the individual trials, however when these results were pooled together, the data suggest a net benefit. Pioglitazone appears to have a benefit relative to placebo on histologic features of NASH (steatosis, hepatocellular ballooning, and lobular inflammation), NASH resolution, and markers of liver injury (ALT and AST). Harms of pioglitazone include weight gain, potential increased risk of bladder cancer and heart failure, and small decreases in bone mineral density.*

Fibrosis

Improvement in fibrosis (by at least one stage) was not demonstrated in any of the five trials of pioglitazone.[34,37,41,43,44] Improvement in fibrosis was observed in 29-51% of patients in the pioglitazone arms and in 20-31% of patients in the placebo arms of the five trials. These differences did not rise to the level of statistical significance in any of the individual trials (Table 4.9).

Table 4.9 Improvements in Fibrosis in Pioglitazone Trials

Trial (Follow-up)	Arms (n)	Improvement in Fibrosis, N (%)	p-Value
Cusi 2016[41] (18 Months)	PIO 45mg (n=50)	20 (40%)	p=0.13
	Placebo (n=51)	13 (25.5%)	
PIVENS[37] (24 Months)	Pio 30mg (n=80)	35 (44%)	p=0.12
	Placebo (n=83)	26 (31%)	
Belfort 2006[43] (6 Months)	Pio 45mg (n=26)	12 (46%)	p=0.08
	Placebo (n=21)	7 (33%)	
Aithal 2008[44] (12 Months)	Pio 30mg (n=31)	9 (29%)	p=0.05
	Placebo (n=30)	6 (20%)	
Bril 2019[42] (18 Months)	Pio 45mg + Vitamin E (n=37)	19 (51%)	NR
	Vitamin E (n=36)	19 (52%)	

The pooled results on improvement in fibrosis from the meta-analysis of the four placebo-controlled pioglitazone trials and one trial comparing pioglitazone plus vitamin E to vitamin E alone [42] are summarized in Figure 4.1. Although fibrosis was not shown to improve in any single trial,

when pooled together the data suggest an improvement (RR=1.32, 95% CI 1.04-1.68, test of heterogeneity Q[df=4]=2.07; I^2=0%). Because one study assessed pioglitazone in patients receiving vitamin E, we also performed a meta-analysis excluding this trial (Figure 4.2). The combined for these four placebo-controlled trials of pioglitazone also suggest an improvement (RR=1.47 CI 1.10-1.95, test of heterogeneity Q[df=3]=0.311; I^2=0%). Of note, the trials included in the meta-analysis varied in dose of pioglitazone (30-45mg), duration of follow-up (6-24 months), use of concomitant vitamin E, and prevalence of T2DM. In all five studies, fibrosis was assessed and reported in similar ways (either at baseline or using existing biopsies within 6 months of the start of the study and again at study completion). Fibrosis improvement was also defined as improvement in fibrosis of at least one stage per biopsy at study conclusion. The distribution of fibrosis stage at baseline did vary between the studies (see Appendix Table D3).

Figure 4.1 Meta-Analysis Results for Fibrosis Improvement Comparing Pioglitazone to Placebo or Vitamin E

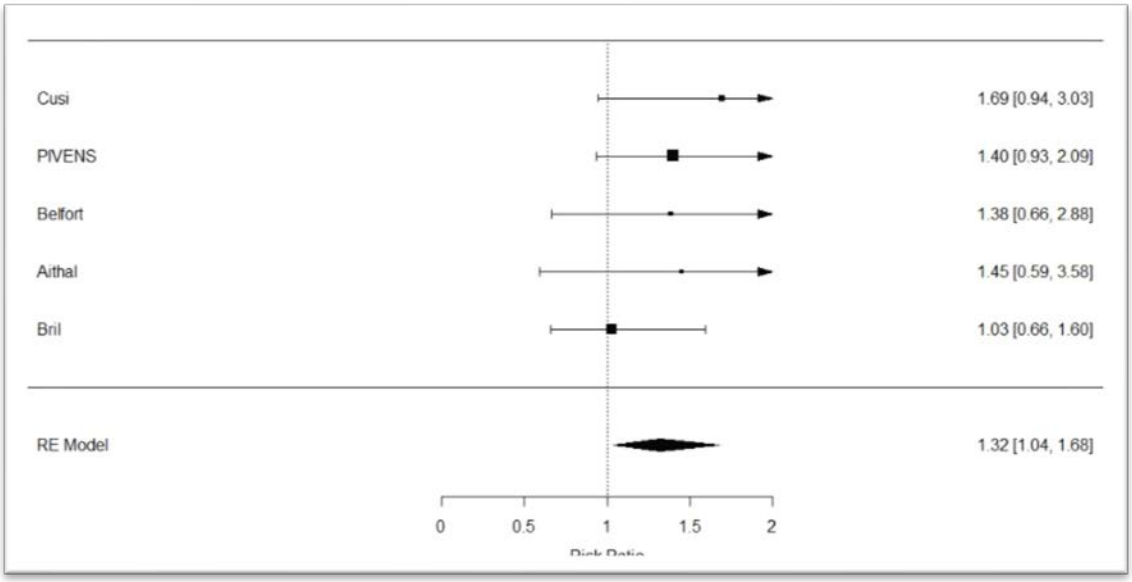
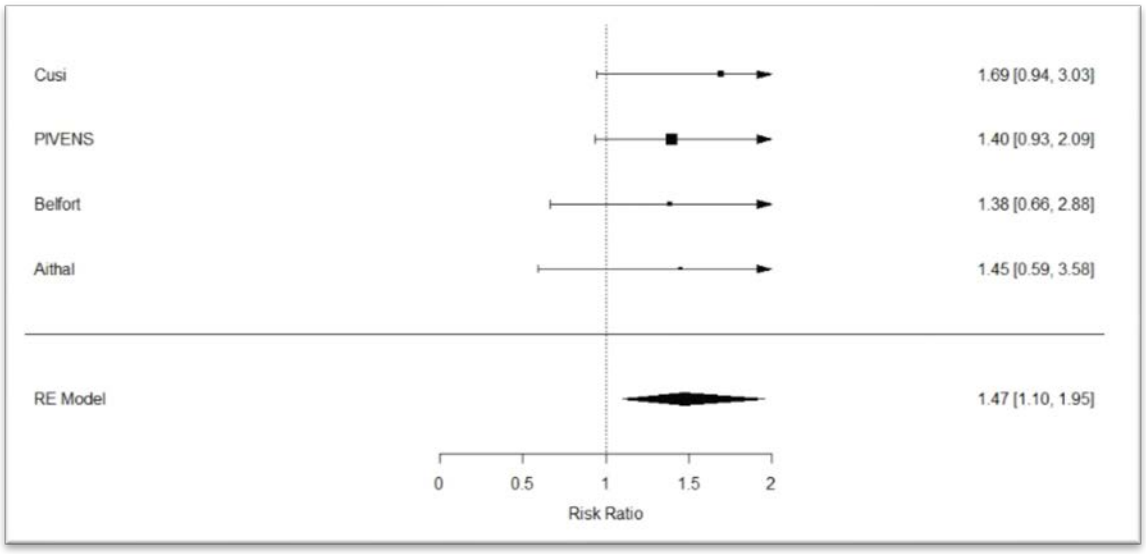


Figure 4.2 Meta-analysis results for fibrosis improvement comparing pioglitazone to placebo, excluding Bril 2019



NASH resolution

Resolution of NASH at 18 or 24 months was reported in three trials. NASH resolved in 43-52% of patients in the pioglitazone arms compared to 12-21% of patients in the placebo arms, a statistically significant difference in all three trials (see Table 4.10).

Table 4.10 NASH Resolution in Pioglitazone Trials

Trial (Follow-up)	Arms (n)	NASH Resolution, n (%)	p-Value
Cusi 2016[41] (18 Months)	Pio 45mg (n=50)	26 (52.0%)	p<0.001
	Placebo (n=51)	10 (17.6)	
PIVENS[37] (24 Months)	Pio 30mg (n=80)	38 (47%)	p=0.05
	Placebo (n=83)	17 (21%)	
Bril 2019[42] (18 Months)	Pio 45mg + Vitamin E (n=37)	16 (43.2%)	NR
	Vitamin E (n=36	12 (33%)	

n: number, NASH: non-alcoholic steatohepatitis

Histologic features of NASH

Improvements in histologic features of NASH (steatosis, hepatocellular ballooning, and lobular inflammation) varied across studies of pioglitazone in which these outcomes were reported (see Table 4.11). Steatosis improved in 48-70% of patients in the pioglitazone 30mg or 45mg arms compared with 25.5-50% in the placebo or vitamin E arms. Significantly more patients in the pioglitazone arms of one trial [41] had improvement in hepatocellular ballooning at 18 months compared to placebo, however this was not observed in the PIVENS trial[37] at 24 months. This could

be because the PIVENS trial excluded patients with diabetes and the placebo arm of this trial experienced more histologic improvement than the other two trials in patients with diabetes. Lobular inflammation improved in 45-65% of patients in the pioglitazone arms compared to 21-35% in the placebo or vitamin E arms. This difference rose to the level of statistical significance in three trials.[37,41,43]

Table 4.11 Histologic Features of NASH in Pioglitazone Trials

Trial (Follow Up)	Arms (n)	Improvement in Steatosis	Improvement in Hepatocellular Ballooning	Improvement in Lobular Inflammation
Cusi 2016[41] (18 Months)	PIO 45mg (n=50)	35 (70%)*	25 (50%)*	25 (49%)*
	Placebo (n=51)	13 (25.5%)	12 (23.5%)	11 (22%)
PIVENS[37] (24 Months)	Pio 30mg (n=80)	55 (69%)*	35 (44%)	48 (60%)*
	Placebo (n=83)	26 (31%)	24 (29%)	29 (35%)
Belfort 2006[43] (6 Months)	Pio 45mg (n=26)	17 (65%)*	NR	17 (65%)*
	Placebo (n=21)	8 (38%)	NR	6 (21%)
Aithal 2008[44] (12 Months)	Pio 30mg (n=31)	15 (48%)	NR	14 (45%)
	Placebo (n=30)	11 (37%)	NR	8 (27%)
Bril 2019[42] (18 Months)	Pio 45mg + Vitamin E (n=37)	32 (87%)†	23 (62.1%)†	25 (66%)†
	Vitamin E (n=36)	24 (68%)	18 (50%)	13 (36%)

mg: milligram, n: number, PIO: pioglitazone

*p<0.05 †statistical significance not reported

Liver biomarkers

Improvements in markers of liver injury (ALT and AST) varied across the five studies of pioglitazone where this outcome was reported (see Table 4.12).[37,41-44]. ALT decreased between 20.8 and 54 U/L on average from baseline in the pioglitazone arms, while ALT decreased between 6.9 and 21 U/L on average from baseline in the placebo or vitamin E arms. This difference was significant in three of the trials[37,43,44] and was not reported in the other two.[41,42] AST decreased between 13 and 20.4 U/L on average from baseline in the pioglitazone arms, while AST decreased between 3.8 and 9 U/L from baseline in the vitamin E or placebo arms. This difference was significant in two trials[37,43] and not reported or not calculated in three trials.[41,42,44] Calculations of variance (SD/SE) in mean change in ALT/AST was not reported in any of the trials listed below.

Table 4.12 Liver Biomarkers in Pioglitazone Trials

Trial (Follow Up)	Arms (n)	ALT, Mean Change From Baseline U/L	AST, Mean Change From Baseline U/L
Cusi 2016[41] (18 Months)	PIO 45mg (n=50)	-25*	-18*
	Placebo (n=51)	-13	-5
PIVENS[37] (24 Months)	Pio 30mg (n=80)	-54†	-20.4†
	Placebo (n=83)	-20.1	-3.8
Belfort 2006[43] (6 Months)	Pio 45mg (n=26)	-39†	-19†
	Placebo (n=21)	-21	-9
Aithal 2008[44] (12 Months)	Pio 30mg (n=31)	-37.7†	NR
	Placebo (n=30)	-6.9	NR
Bril 2019[42] (18 Months)	Pio 45mg + Vitamin E (n=37)	-20.8*	-13*
	Vitamin E (n=32)	-7.2	-8.5

ALT: alanine Aminotransferase, AST: aspartate aminotransferase, mg: milligram, n: number, NR: not reported, PIO: pioglitazone

*p-value not reported; †p<0.05

Harms

BMI and body weight

BMI increased between 0 and 1.8 kg/m2 from baseline in the pioglitazone arms in the five trials that reported BMI compared to between 0 and 0.7 kg/m2 in the placebo or vitamin E arms (see Table 4.13).[37,41-44] Body weight increased between 1.2 and 5.7 kg from baseline in the pioglitazone trials compared to between -0.2 and 0.7 kg in the placebo or vitamin E arms in four trials that reported weight.[37,41-43]. This is significant considering that the incidence of metabolic syndrome and obesity is high in the NASH population. Furthermore, the mean BMI of participants in the trials were between 30 and 35kg/m2 at baseline.

Table 4.13 BMI and Body Weight Changes in Pioglitazone Trials

Trial (Follow up)	Arms (n)	BMI, Change From Baseline, kg/m2, Mean	Weight Change From Baseline, kg, Mean
Cusi 2016[41] (18 Months)	PIO 45mg (n=50)	0.3*	1.2*
	Placebo (n=51)	0.1	0.3
PIVENS[37] (24 Months)	Pio 30mg (n=80)	1.8†	4.7†
	Placebo (n=83)	0.4	0.7
Belfort 2006[43] (6 Months)	Pio 45mg (n=26)	1.1*	2.5†
	Placebo (n=21)	-0.2	-0.5
Aithal 2008[44] (12 Months)	Pio 30mg (n=31)	0	NR
	Placebo (n=30)	0.7	NR
Bril 2019[42] (18 Months)	Pio 45mg + Vitamin E (n=29)	1.4*	5.7*
	Vitamin E (n=33)	0.1	0.5

BMI: body mass index, kg: kilogram, kg/m2: kilogram per meters squared, n: number
*p-value not reported; †p<0.05

Bladder Cancer

In 2016, the FDA issued a warning that pioglitazone use may be associated with an increased risk of bladder cancer[45] after results from a 10-year observational study found weak dose and exposure-related associated increases in risk of bladder cancer in patients with type 2 diabetes [46]. Of the trials we reviewed of pioglitazone for NASH, none addressed bladder cancer. One study[44] reported 1 case of hematuria and another reported 1 case of prostate cancer in the pioglitazone groups[34].

Bone mineral density

The impact of thiazolidinediones on bone mineral density is controversial. This is important because patients with T2DM are at an increased risk of fractures [47]. In a systematic review with meta-analysis of RCTs of pioglitazone for diabetes, risk of bone fractures was increased (RR 1.52, 95% CI 1.17 to 1.99)[22]. None of the trials of pioglitazone for NASH outcomes we summarized previously addressed bone mineral density. In a randomized trial of pioglitazone 30 mg uptitrated to 45mg after 8 weeks (n=46) vs placebo (n=46) in patients with NASH, pioglitazone use was associated with a small (-3.5%, p=0.002) decrease in bone mineral density at the level of the spine at 18 months, but no change was seen at the femoral hip, total hip, or one third radius.[48] This decrease appeared to stabilize between 18 and 36 months follow-up.

Heart failure

In a systematic review with meta-analysis of RCTs of pioglitazone for diabetes, risk of heart failure was increased (RR 1.32; CI 1.14 to 1.54)[22]. The FDA label for pioglitazone (Actos) contains a warning about heart failure and cardiac events in patients with pre-existing heart disease. Patients should be monitored for signs and symptoms of heart failure (weight gain, edema) and the drug should be discontinued if these signs develop.[49]

Subgroups

Diabetes

As previously described, the presence of type 2 diabetes appears to alter the progression of NASH. Trial results suggest there may be a differential benefit of pioglitazone in patients with and without diabetes; improvements in all histologic features of NASH were observed in trials of pioglitazone in patients with diabetes[41,42], but not in patients without diabetes (see Table 4.11).[44] In a randomized trial of pioglitazone 45 mg vs placebo in patients with NASH with type 2 diabetes (n=52) and pre-diabetes (n=49), the primary outcome of a 2 point decrease in NAFLD score without worsening of fibrosis at 18 months was met by 48% of patients with diabetes and 46% of patients without diabetes.[34] Resolution of NASH was achieved in 44% of patients with diabetes vs 26% of patients without diabetes. Fibrosis improvement from baseline was observed only in patients with type 2 diabetes.

Controversies and Uncertainties

NASH is typically asymptomatic for most of its clinical course, and that course can be long. As such, therapies that are intended to alter the outcomes of liver fibrosis over many years but have only been studied in short-term trials necessarily present many uncertainties about their actual benefits.

Similarly, a treatment for a condition that may never become symptomatic must necessarily be quite safe if it is to be used for many years. As discussed in detail above, we have reasons for concern around the safety of both OCA and pioglitazone and lack long-term trials demonstrating that the benefits exceed the harms. Pioglitazone carries FDA warnings for heart failure and bladder tumors among other issues. OCA raises LDL-C levels in patients who are already at high risk for CV disease and, when used for primary biliary cirrhosis at doses lower than will be likely used for NASH, has had reports of hepatic decompensation and death.

Trials of pioglitazone and OCA in NASH have examined different populations, used different outcome measures, and been studied for varying durations. These trials were sufficiently different that we felt indirect quantitative comparisons for pioglitazone and OCA via NMA were not possible.

There is very limited evidence on the effects of OCA when used on patients with earlier stage NASH.

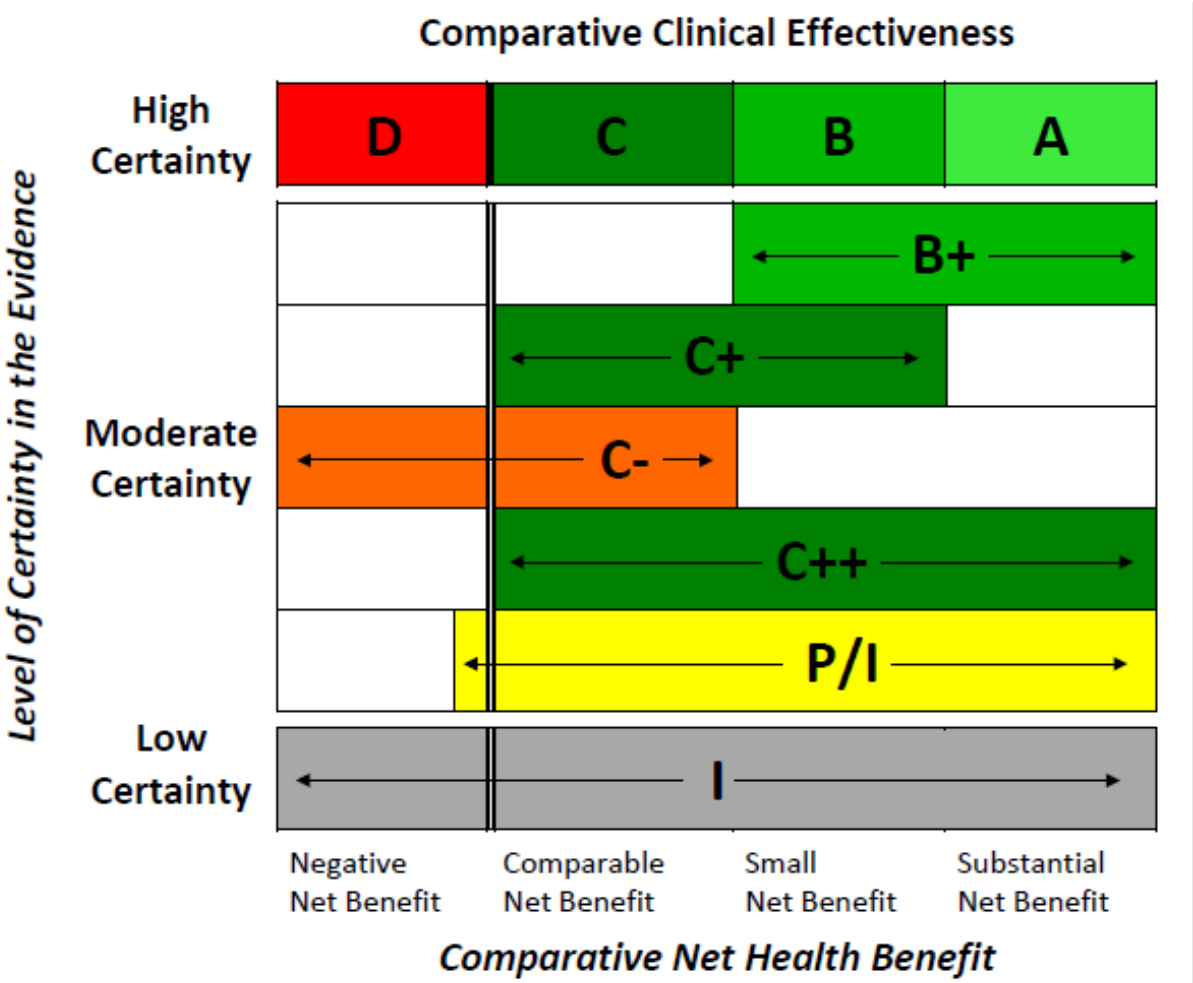
It is uncertain whether NASH with F3 fibrosis is typically symptomatic. We heard from some patients that there was substantial fatigue associated with F3 fibrosis, but this is potentially difficult to interpret since many patients with NASH have other comorbid conditions that could cause fatigue, and these comorbidities are more common in more advanced disease. Additionally, even if F3 fibrosis is symptomatic, we do not have evidence demonstrating improvement in symptoms with OCA or pioglitazone.

The results of the lipid effects of OCA are uncertain in the absence of long-term trials. It is likely, but not certain, that the LDL-C increases from OCA will increase the risk of CV events. Statin therapy could be expected to blunt this effect as discussed above, but many patients are non-adherent to lipid lowering therapies. Other lipid-lowering therapies such as PCSK9 inhibitors could also potentially be used to offset the LDL-C effects of OCA. The HDL-C lowering effects of OCA are less likely to be harmful given the general lack of evidence that drugs that affect HDL levels predictably affect CV risk.

Although concerns had been raised in the past about the effects of thiazolidinediones on CV risk, the preponderance of evidence suggests that pioglitazone either reduces CV events in patients with T2DM or, at least, does not increase this risk.[50,51] It is further uncertain what effect pioglitazone would have on CV outcomes in patients with NASH in the absence of T2DM.

4.4 Summary and Comment

Figure 4.3. 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 or substantial net health benefit, with high certainty of at least a small net health benefit*
***C+ = "Comparable or Incremental"** - Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
***C- = "Comparable or Inferior"** – Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
***C++ = "Comparable or Better"** - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a 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"** – Any situation in which the level of certainty in the evidence is low*

In patients with NASH and fibrosis, OCA appears to reduce progression and promote regression of liver disease compared with placebo. There is uncertainty about the long-term importance and benefit of these changes, but we assess that it is likely that OCA will reduce progression to cirrhosis, and thus improve certain patient-important outcomes, over the long-term. The magnitude of this benefit, however, is uncertain.

OCA commonly causes pruritus, so it can worsen quality of life in previously asymptomatic patients. OCA when used for primary biliary cirrhosis has had reports of severe harms with liver decompensation and death. It is uncertain whether this is a concern in patients with NASH, particularly if F3 disease were to progress to cirrhosis in a patient who remains on OCA. The lipid effects of OCA are particularly concerning as discussed above. In the absence of long-term trials and given that CV death is the primary cause of death in patient with NASH, it is difficult to be certain whether OCA will improve outcomes overall.

Viewing the evidence as a whole, we feel the long-term net effects of OCA on quality of life and health of patients with NASH and F2/F3 fibrosis are uncertain. We are more uncertain in patients with less severe fibrosis (F2) where the balance against harms is more concerning, but even in patients with F3 fibrosis it is hard to be certain that the benefits outweigh the harms. We judge the evidence for OCA in NASH with F2 fibrosis to be insufficient ("I") and with F3 fibrosis to be promising but inconclusive ("P/I").

Pioglitazone has somewhat less convincing evidence of improving fibrosis than OCA given the smaller trials with varying designs, however the magnitude of effect seen when we meta-analyzed those results appears similar to that of OCA. Pioglitazone has more evidence on long-term use because it has been available for treatment of T2DM. In patients with T2DM, pioglitazone may reduce CV events, however given the risks of heart failure and weight gain, the balance between long-term benefits and harms in treating NASH remains uncertain. We judge the evidence for pioglitazone in NASH to be promising but inconclusive ("P/I").

Given the above, we clearly have inadequate evidence to compare OCA with pioglitazone. We note, however, that it is a standard narrative that OCA, unlike pioglitazone, improves fibrosis, while pioglitazone only improves liver inflammation. We do not think the reviewed evidence necessarily supports this conclusion, as pioglitazone appears likely to have effects on fibrosis as well. We judge the evidence comparing OCA and pioglitazone for patients with NASH and F2 or F3 fibrosis to be insufficient ("I").

5. Long-Term Cost Effectiveness

5.1 Overview

We sought to estimate the lifetime cost-effectiveness of obeticholic acid (OCA), compared to current standard care, for adults with NASH with fibrosis. We developed a *de novo* decision analytic model for this evaluation in Microsoft Excel, informed by key clinical trials including REGENERATE[6] and prior relevant economic models.[52-55] The model estimated outcomes that included life years (LYs), equal value life years gained (evLYG), quality adjusted life years (QALYs), cardiovascular (CV) events (myocardial infarctions [MIs] and strokes), hepatic complications (decompensated cirrhosis, hepatocellular carcinoma [HCC], and liver transplants), and total costs for OCA and standard care over a lifetime time horizon. For the comparison, the model also calculated incremental cost-effectiveness ratios for each outcome (i.e., cost per LY gained, cost per evLYG, cost per QALY gained, and cost per clinical event avoided). The base case analysis took a health care sector perspective, focused on direct medical care costs only, while a scenario analysis also evaluated the modified societal perspective. We modeled additional scenarios that varied the severity of fibrosis of patients at treatment initiation, varied the distribution of patients with a history of CV events, and explored the differences of two fibrosis diagnostic strategies.

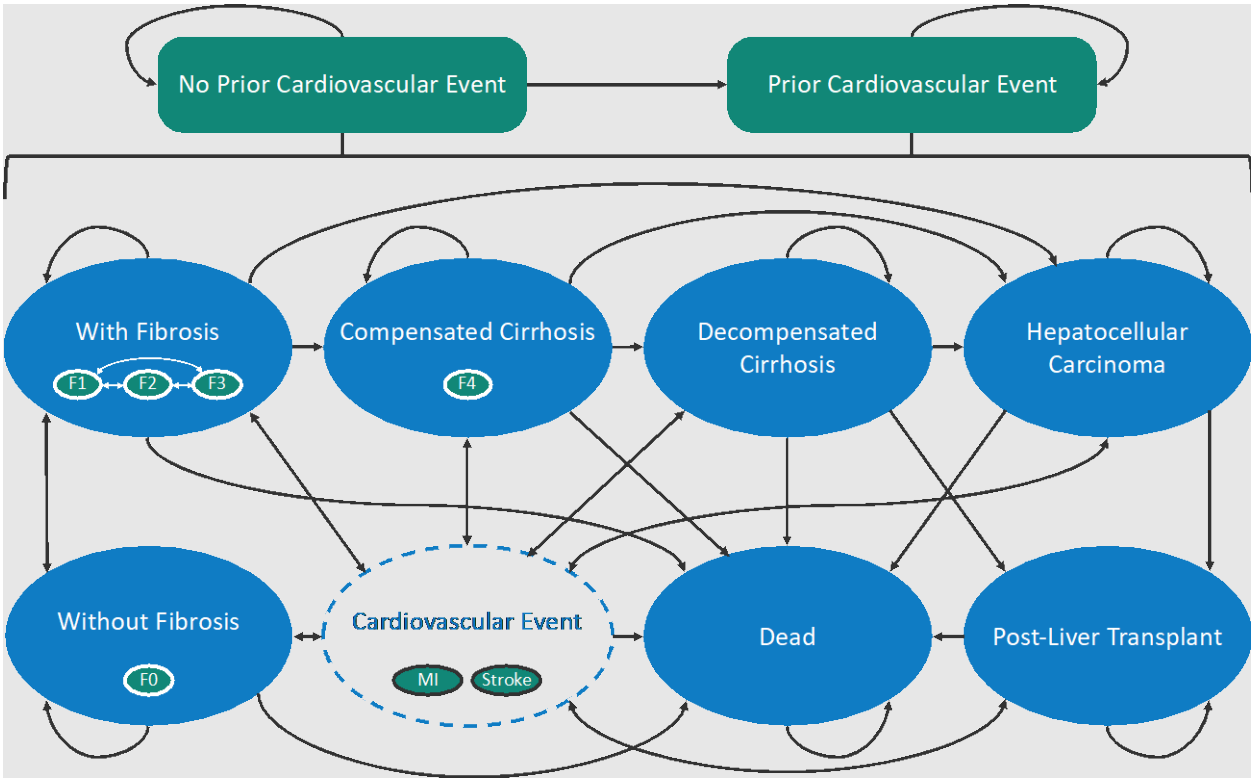
5.2 Methods

Model Structure

We used a Markov model structure composed of two cardiovascular (CV) event history submodels with equivalent liver disease-specific state transition probabilities (Figure 5.1). Each submodel allowed for transitions among no fibrosis (F0) and discrete fibrosis (F1-F3) stages, compensated cirrhosis (F4), decompensated cirrhosis, hepatocellular carcinoma (HCC), post-liver transplant, and death; the costs and health impacts of undergoing liver transplant were assessed within the transition to post-liver transplant. Patients were able to transition from any of the alive health states to death from all causes including compensated cirrhosis, decompensated cirrhosis, HCC, liver transplant, CV events, or background mortality.

The transition from the first submodel (no prior CV event) to the second submodel (prior CV event) was driven by the first occurrence of a nonfatal CV event; the costs, quality of life, and survival of first CV events were assessed with the transition between submodels. NASH patients who entered the prior CV event submodel were assumed to be at increased risk for recurrent CV events and mortality.

Figure 5.1. Model Framework



Key Model Choices and Assumptions

Below is a list of key model choices:

- The intervention of interest was treatment with OCA administered as oral tablets in a dose of 25 mg once daily.
- We utilized a health care sector perspective (i.e., focused on direct medical care costs only) and a lifetime horizon, modeling patients from treatment initiation until death.
- The first 24 model cycles were one month each (=2 years) to align with the REGENERATE trial (18-month follow-up) and to facilitate tracking of treatment discontinuation and changes in LDL-C, a CV event risk factor; all subsequent (long-term) cycles were annual in length, similar to prior published economic models of NASH.[52-55]
- We employed a half-cycle correction for all annual model cycles.
- OCA efficacy versus standard care (change in fibrosis stage) was based on the REGENERATE trial.[6] Fibrosis worsening was calculated as the remainder of improvement and no change.
- Specific fibrosis stage transitions (e.g., F2 to F0, F1, F3, or F4) were calculated using a recent meta-analysis of fibrosis progression in NAFLD and NASH patients[56] to derive conditional probabilities applied to improvement/worsening/no change transitions from REGENERATE.[6]

- NASH worsening to cirrhosis, HCC, and liver-related death were based on data from published sources and a previous ICER assessment of OCA for NASH.[54,57-59]
- Adverse events related to OCA, including pruritus and dyslipidemia, were included in the model.[6]
- CV events (nonfatal or fatal MI or stroke) were modeled using a combination of patient characteristics (Table 5.2), Framingham Heart Study calculators,[60] American Heart Association statistics for heart disease and stroke,[61] and risk ratio adjustments based on LDL-C level.[62]
- Costs included current and subsequent treatment, management of adverse events, ongoing NASH-related care, and management of advanced disease outcomes such as HCC.[63-65]
- Unadjusted survival (life years) was calculated. In addition, all health states were weighted by health state utilities obtained from the published literature to derive quality-adjusted life years (QALYs) and evLYG.[66]
- A 3% annual discount rate for costs, QALYs, evLYG, and life years was used.[66]
- Primary results were expressed as the incremental cost per QALY gained, per equal value life-year gained (evLYG), per life year, and per liver-related and cardiovascular-related event avoided for OCA versus the standard care treatment strategy; evLYG methodology may be found in Appendix E.

Key Model Characteristics and Assumptions

Key model assumptions are listed in Table 5.1, along with the rationale for each.

Table 5.1. Key Model Assumptions

Assumption	Rationale
REGENERATE trial-reported secondary outcomes for "improvement" and "no change", used as the basis for deriving transition probabilities among fibrosis stages, were applied uniformly regardless of starting stage.	Stage-level outcome achievement is not reported in the REGENERATE trial results. Specific stage transitions were weighted (after REGENERATE outcomes were calculated) by results of a meta-analysis of fibrosis progression in NAFLD vs. NASH.[56]
In each model cycle, 50% of patients in the fibrosis stage F4 (compensated cirrhosis) health state could improve to lower fibrosis stages but 50% could not improve.	A clinical expert advised that compensated cirrhosis demonstrates a spectrum of liver functionality, and that early stage cirrhosis is potentially reversible.
Patients among the 50% with F4 who could not improve were assumed to discontinue OCA treatment.	While there is still a possibility of slowing further deterioration by treating patients with compensated cirrhosis, a clinical expert advised that this would be an acceptable assumption for the model.
Patients continued OCA treatment for life as long as they continued to respond to treatment.	A clinical expert advised that clinicians would not be inclined to discontinue treatment in patients who are benefitting from it.
Patients who entered the "Prior CV Event" submodel had the same per-event costs, quality of life, and mortality regardless of the number of subsequent CV events they accrued over time.	Markov models are limited by the inability to track individual patient history without employing a large number of health states. The "Prior CV Event" cohort represented the average of people who had experienced a prior CV event.
Patients were at increased risk of CV events based on increased LDL-C from baseline. Patients on a statin had a relative risk of 1.30 per 1 mmol/L increase in LDL-C; patients not on a statin had a relative risk of 1.33 per 1 mmol/L increase in LDL-C.[62]	Input from clinical experts indicated that increased LDL-C puts patients at an increased risk of CV events.
All patients received treatment for systolic blood pressure and no patients were smokers. Patient systolic blood pressure (132 mm Hg) was based on the FLINT trial.[67]	These demographic characteristics are not reported in the REGENERATE trial,.[6] but were required for the Framingham Heart Study calculations which were used to calculate CV event risk in the model.[60]

Target Population

The modeled base case analysis utilized a hypothetical cohort of patients with NASH fibrosis stages 2 and 3 in the U.S. being treated with either OCA 25mg or standard care, using demographic characteristics from the REGENERATE trial (Table 5.2).[6] We note that these demographic characteristics are similar to epidemiology estimates for NASH patients.[1]

Table 5.2. Base-Case Model Cohort Characteristics[6]

Baseline Characteristics	Obeticholic Acid 25 mg (n=308)	Standard Care (Placebo) (n=311)	Pooled Population Used in the Model
Mean Age, Years (SD)	55 (11)	55 (12)	55
Female, n (%)	175 (57)	187 (60)	58.5%
Fibrosis Stage F2, n (%)	139 (45)	142 (46)	45.4%
Fibrosis Stage F3, n (%)	169 (55)	169 (54)	54.6%
Mean LDL-C, mg/dL (SD)	113.3 (38.8)	114.8 (38.2)	114.1
Mean HDL-C, mg/dL (SD)	44.3 (11.0)	45.6 (11.1)	45
Mean Total Cholesterol, mg/dL (SD)	183.5 (44.7)	184.5 (42.7)	184
Type 2 Diabetes, n (%)	171 (56)	175 (56)	56%

HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol

Model Inputs

Clinical Inputs

Clinical Probabilities/Response to Treatment

We utilized interim results of the REGENERATE trial as the basis for modeling transitions among fibrosis health states. Specifically, the per-protocol placebo probabilities were utilized to calculate improvement/worsening/no change for the standard care comparator, and these same probabilities were multiplied by the per-protocol response ratio estimates for OCA to derive the OCA outcomes. Fibrosis worsening outcomes were calculated as the remainder of improvement and no change outcomes. We plan to update these probabilities and response ratio estimates with intention-to-treat estimates when they become available.

Table 5.3. Efficacy Endpoints for Improvement and No Change in Fibrosis[6]

Parameter	Base Case	Lower Value	Upper Value	Modeled SA Distribution
Obeticholic Acid Response Ratio vs. Standard Care*				
Improvement of fibrosis	1.65	1.29	2.12	Log Normal
No change of fibrosis	0.88	0.75	1.02	Log Normal
Standard Care Probabilities*				
Improvement of fibrosis	0.23	0.18	0.28	Beta
No change of fibrosis	0.56	0.50	0.62	Beta

SA: sensitivity analysis

*Per-protocol estimates. We plan to replace these with intention-to-treat estimates when available.

The REGENERATE trial interim results report improvement in fibrosis and no change in fibrosis at 18 months, but not specific fibrosis stage transitions, which will not be available until the final analysis.[6] Therefore, we used the distributions of transitions of NASH patients between fibrosis stages from Singh et al. to calculate transition weights (Table 5.4) that were applied to the REGENERATE improvement/worsening/no change outcomes to estimate specific stage transition probabilities.[56]

Table 5.4. Fibrosis Improvement/Worsening/No Change Conditional Probability Weights[56]

	Base case	Lower Value (-20%)	Upper Value (+20%)	Modeled SA Distribution
F0 to F1 (worsening)	0.64	0.51	0.76	Dirichlet
F0 to F2 (worsening)	0.18	0.15	0.22	Dirichlet
F0 to F3 (worsening)	0.09	0.07	0.11	Dirichlet
F0 to F4 (worsening)	0.09	0.07	0.11	Dirichlet
F1 to F2 (worsening)	0.60	0.48	0.72	Dirichlet
F1 to F3 (worsening)	0.33	0.27	0.40	Dirichlet
F1 to F4 (worsening)	0.07	0.05	0.08	Dirichlet
F2 to F1 (improvement)	0.77	0.62	0.92	Beta
F2 to F3 (worsening)	0.50	0.40	0.60	Beta
F3 to F0 (improvement)	0.00	0.00	0.00	Dirichlet
F3 to F1 (improvement)	0.50	0.40	0.60	Dirichlet
F3 to F2 (improvement)	0.50	0.40	0.60	Dirichlet
F4 to F0 (improvement)	0.00	0.00	0.00	Dirichlet
F4 to F1 (improvement)	0.00	0.00	0.00	Dirichlet
F4 to F2 (improvement)	0.00	0.00	0.00	Dirichlet
F4 to F3 (improvement)	1.00	0.80	1.00	Dirichlet

Nondisplayed transition weights are calculated as the remainders of the displayed transition weights; SA: sensitivity analysis

Advanced Liver Disease Events

Liver disease-related transition probabilities were based on data from published sources and a previous ICER assessment of OCA for NASH.[54,57-59] We assumed F0-F2 patients did not transition to decompensated cirrhosis or HCC. We derived annualized (converted to monthly for cycles 1-24)

transition probabilities from the 10-year cumulative incidences of decompensated cirrhosis and HCC for F3 and F4 patients.[58] The annual probability of transitioning to HCC from decompensated cirrhosis, obtained from Ascha et al.,[57] was the same each year. All year 10 transition probabilities were held constant for the remaining time horizon.

Table 5.5. Advanced Liver Disease Transitions

	Decompensated Cirrhosis (DCC) Transitions		Hepatocellular Carcinoma (HCC) Transitions			Modeled SA Distribution
Annual Probability:	F3 to DCC [58]	F4 to DCC [58]	F3 to HCC [58]	F4 to HCC [58]	DCC to HCC [57]	
Year 1	0.004	0.019	0.003	0.014	0.026	Beta (±20%)
Year 2	0.004	0.025	0.004	0.015	0.026	Beta (±20%)
Year 3	0.005	0.031	0.007	0.023	0.026	Beta (±20%)
Year 4	0.003	0.032	0.001	0.012	0.026	Beta (±20%)
Year 5	0.009	0.076	0.003	0.013	0.026	Beta (±20%)
Year 6	0.010	0.040	0.004	0.016	0.026	Beta (±20%)
Year 7	0.010	0.038	0.003	0.007	0.026	Beta (±20%)
Year 8	0.010	0.034	0.009	0.037	0.026	Beta (±20%)
Year 9	0.004	0.025	0.010	0.023	0.026	Beta (±20%)
Year 10+	0.006	0.009	0.011	0.020	0.026	Beta (±20%)

SA: sensitivity analysis

Liver Transplant and Liver-Related Mortality Events

Liver transplant and liver-related mortality event transition probabilities were based on data from published sources and a previous ICER assessment of OCA for NASH.[54,57,59] We derived annualized (converted to monthly for cycles 1-24) transition probabilities from the 5-year cumulative incidences of liver transplant and death from HCC.[59] The annual probabilities of transitioning to death from F4 and decompensated cirrhosis were the same each year.[54,57] All year five transition probabilities were held constant for the remaining time horizon. Mortality transitions due to complications following liver transplant were calculated at the time of the liver transplant, so that the remainder of patients who survived entered the post-liver transplant health state.[54,57]

Table 5.6 Liver Transplant and Liver-Related Mortality Transitions

	Liver Transplant Transitions		Liver-Related Mortality Transitions			Modeled SA Distribution
Annual Probability:	DCC to LT* [59]	HCC to LT‡ [59]	F4 to Death [54,57]	DCC to Death [54,57]	HCC to Death [59]	
Year 1	0.430	0.557	0.021	0.130	0.144	Beta (±20%)
Year 2	0.060	0.136	0.021	0.130	0.044	Beta (±20%)
Year 3	0.030	0.025	0.021	0.130	0.012	Beta (±20%)
Year 4	0.012	0.018	0.021	0.130	0.009	Beta (±20%)
Year 5+	0.008	0.017	0.021	0.130	0.008	Beta (±20%)

DCC: decompensated cirrhosis; HCC: hepatocellular carcinoma; SA: sensitivity analysis

*Conditional probability of death due to complications of liver transplant, from DCC: 0.094 (±20%)[54,57]

‡Conditional probability of death due to complications of liver transplant, from HCC: 0.101 (±20%)[54,57]

Cardiovascular Events and Non-Liver Mortality

We utilized a combination of pooled REGENERATE trial baseline patient characteristics (Table 5.2), Framingham Heart Study risk calculators,[60] American Heart Association statistics for heart disease and stroke,[61] and risk ratio adjustments[62] based on LDL-C level[6,31] to derive cycle-level estimates of CV event risk. In each model cycle, age-updated 10-year risk of CV events was converted to a sex-weighted, cycle-specific risk; we assumed that REGENERATE-reported total and HDL cholesterol at baseline (Table 5.2; used in the Framingham calculator) were held constant over the lifetime horizon. Each cycle's calculated risk was adjusted using a relative risk per change in LDL-C from baseline in the OCA treated cohort.[62] We assumed that the OCA treated cohort experienced an elevation in LDL-C of 17.2mg/dL (0.44 mmol/L) at 12 weeks, and held that difference constant for the remainder of the lifetime horizon;[31] baseline LDL-C was held constant in the standard care arm for all model cycles.

We utilized data from the American Heart Association to differentiate CV events, including nonfatal and fatal CV events.[61] Gender- and age-specific background mortality from the Centers for Disease Control and Prevention U.S.-specific tables was used for background mortality rates.[68] Additionally, once in the prior CV event submodel, the cohort experienced an additional relative risk of CV event recurrence of 1.44.[69]

Table 5.7. Cardiovascular and Non-Liver Mortality Parameters

	Base case	Lower Value (-20%)	Upper Value (+20%)	Modeled SA Distribution
OCA LDL-C Difference vs. Standard Care at 12 weeks[31]	17.2 mg/dL	13.8 mg/dL	20.6 mg/dL	Normal
Cardiovascular Risk by LDL-C				
On statins: RR per 1 mmol/L increase[62]	1.30	1.04	1.56	Log Normal
Not on statins: RR per 1 mmol/L increase[62]	1.33	1.07	1.60	Log Normal
Cardiovascular Event Parameters				
MI vs. Stroke: Proportion if CV Event [61]	0.79	0.63	0.94	Beta
Proportion of MIs that are fatal[61]	0.24	0.19	0.29	Beta
Proportion of strokes that are fatal[61]	0.21	0.17	0.25	Beta
Recurrent CV Event Relative Risk[69]	1.44	1.40	1.49	Log Normal

RR: relative risk; MI: myocardial infarction; CV: cardiovascular; SA: sensitivity analysis; LDL-C: low-density lipoprotein-cholesterol

Utilities

Health state utilities were derived from the Global Assessment of the Impact of NASH (GAIN) study, which quantified the impact of NASH on patients' quality of life (QOL) using the EQ-5D-5L for several European countries plus the U.S.[70] Cirrhosis, HCC, and liver transplantation utilities were obtained from a recently published cost-effectiveness analysis.[65] Additionally, we included disutilities for CV events as well as living with CV disease.[71]

Table 5.8. Utility Values for Health States

Parameter	Base Case	Lower Value*	Upper Value*	Modeled SA Distribution
NASH Fibrosis Stage 0-2[70]	0.76	0.61	0.91	Beta
NASH Fibrosis Stage 3[70]	0.73	0.64	0.82	Beta
Compensated Cirrhosis[65]	0.66	0.49	0.83	Beta
Decompensated Cirrhosis[65]	0.57	0.46	0.68	Beta
Hepatocellular Carcinoma[65]	0.50	0.40	0.60	Beta
Liver Transplantation (Year of)[65]	0.57	0.45	0.68	Beta
Post-Liver Transplantation[65]	0.58	0.46	0.69	Beta
Disutility: Myocardial Infarction Event[71]	-0.041	-0.041	-0.041	Beta
Disutility: Stroke Event[71]	-0.052	-0.053	-0.052	Beta
Disutility: Prior Cardiovascular Event[71]	-0.034	-0.034	-0.033	Beta

SA: sensitivity analysis; *Utility range overlap between health states was programmatically avoided in sensitivity analyses

Economic Inputs

Drug Acquisition Costs

Because OCA is still under FDA review for this indication, a published wholesale acquisition cost (WAC) does not exist for this indication. We assumed the same WAC as for Ocaliva® (currently marketed for primary biliary cholangitis) from Redbook.[72] Net price data for OCA are not available from SSR Health data. We therefore used the FSS price of Ocaliva® as a placeholder net price estimate.[73]

Table 5.9. Drug Cost Inputs

Drug	WAC per dose	FSS/Net Price Per Dose	Discount From WAC	Placeholder Net Price per year
Obeticholic Acid*	$230.33	$219.96	4.5%	$80,340**

WAC: wholesale acquisition cost

*Price assumed to be the same as Ocaliva® (obeticholic acid, indicated for the treatment of primary biliary cholangitis).

**Price estimated using FSS discount, assuming 365.25 days per year, and rounded to the nearest dollar.

Treatment Discontinuation

We were limited to modeling the per protocol efficacy and safety from the interim results of the REGENERATE trial, as the ITT analysis results are not yet available. Thus, treatment discontinuation is not reflected in the model results. If the ITT results become available, we will derive a monthly discontinuation rate from the REGENERATE trial based on discontinuation at 18 months (11.7%; monthly probability of discontinuation = 0.007).[6] After 18 months, patients in fibrosis stages F0 to F3 who have not previously discontinued will be assumed to remain on OCA treatment for their remaining lifetime.

We assumed that 50% of patients in the F4 health state could still improve their fibrosis stage and thus continue treatment after the first 18 months, while the remaining 50% could not improve and discontinued treatment. All patients who transitioned to either the decompensated cirrhosis or HCC health states were assumed to discontinue treatment.

Non-Drug Costs

We used liver disease state-specific costs from the published economic and clinical burden of NAFLD model by Younossi et. al., who derived annual costs based on recent publications, resource use inputs from hepatology experts mapped to national fee schedules, and Medicare.[65] CV disease costs were obtained from the published cost-effectiveness analysis of PCSK9 inhibitor therapy by Kazi et al.[63] and a cost estimation of CV disease study by O'Sullivan et al.[64]

Table 5.10. Annual Non-Drug Costs

Annual Cost	Base Case	Lower Value (-20%)	Upper Value (+20%)	Modeled SA Distribution
F0-F2[65]	$447	$358	$536	Log Normal
F3[65]	$551	$441	$661	Log Normal
Compensated Cirrhosis[65]	$19,603	$15,682	$23,524	Log Normal
Decompensated Cirrhosis[65]	$36,989	$29,591	$44,387	Log Normal
Hepatocellular Carcinoma[65]	$96,681	$77,345	$116,017	Log Normal
Liver Transplant Year 1[65]	$368,148	$294,519	$441,778	Log Normal
Liver Transplant Year 2+[65]	$50,645	$40,516	$60,774	Log Normal
MI Event[63]	$55,316	$44,253	$66,379	Log Normal
Stroke Event[63]	$58,932	$47,146	$70,718	Log Normal
Post-MI Annual Cost[63]	$2,728	$2,182	$3,274	Log Normal
Post-Stroke Annual Cost[63]	$5,742	$4,594	$6,890	Log Normal
CV Death Event[64]	$18,341	$14,673	$22,009	Log Normal

MI: myocardial infarction; CV: cardiovascular; SA: sensitivity analysis

Adverse Events

We included costs for Grade 3 pruritus and increased LDL-C as documented in the REGENERATE trial.[6] We also applied a multiplicative factor for pruritus based on the previous ICER report on OCA for NASH; to determine the overall utility for a patient with pruritus, we took the product of the calculated health state utility and the pruritus utility.[54] Adverse event costs were estimated by combining costs from CMS (CPT 99213) and generic drug treatment WAC (simvastatin/atorvastatin for increased LDL-C and hydroxyzine for pruritus) [74].

Table 5.11. Included Adverse Events

Adverse Event	OCA %[6]	Standard Care %[6]	Utility Multiplier[54]	Cost/Year[74]
Grade 3 pruritus	5.5%	0.5%	0.79 (±20%)	$301
Increased LDL-C	17.5%	7.2%	-	$117

OCA: obeticholic acid

Societal Perspective Costs

NASH fibrosis health state-specific societal costs were derived from the GAIN study, a retrospective, cross-sectional study in which physicians recruited NASH patients to provide demographic, clinical, and economic information on direct (e.g., caregiver costs, over-the-counter medication costs, transportation costs, etc.) and indirect (i.e. productivity loss) non-medical costs via an online survey.[70] GAIN study patients diagnosed by liver biopsy were stratified by fibrosis score (F0-F4), and direct non-medical and indirect costs were reported for each stratified by multiple European

countries plus the U.S. We also assessed annual productivity loss costs due to nonfatal CV events based on the societal perspective analysis from a previous ICER report on cardiovascular disease.[63]

Table 5.12. Societal Perspective Annual Costs

Annual Societal Cost	Base Case	Lower Value (-20%)	Upper Value (+20%)	Modeled SA Distribution
NASH Direct Non-Medical Costs				
NASH Fibrosis Stage 0-2[70]	$2,775	$2,220	$3,330	Log Normal
NASH Fibrosis Stage 3[70]	$4,841	$3,873	$5,809	Log Normal
NASH Fibrosis Stage 4[70]	$7,466	$5,973	$8,959	Log Normal
NASH Indirect Costs				
NASH Fibrosis Stage 0-2[70]	$7,929	$6,343	$9,515	Log Normal
NASH Fibrosis Stage 3[70]	$13,833	$11,067	$16,600	Log Normal
NASH Fibrosis Stage 4[70]	$21,333	$17,067	$25,600	Log Normal
Productivity				
CV Event Productivity Loss (Year of Event)[63]	$4,522	$3,618	$5,427	Log Normal

CV: cardiovascular; SA: sensitivity analysis

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Additionally, we performed a threshold analysis by systematically altering the price of OCA to estimate the maximum prices that would correspond to given cost-effectiveness thresholds. These threshold prices were calculated for the base case, as well as for the two scenarios separately modeling treatment initiation at stage F2 and F3.

Scenario Analyses

We performed the following scenario analyses:

1) *Modified societal perspective that included direct non-medical costs, indirect costs, and productivity loss*. The societal perspective costs described above were added to the base case scenario.

2) *An evaluation comparing non-invasive only versus non-invasive with biopsy diagnostic strategies*. We compared the use of a fibrosis non-invasive diagnostic alone vs. that non-

invasive diagnostic combined with liver biopsy prior to treatment initiation. The non-invasive diagnostic test's characteristics were assumed to be 91% sensitivity and 92% specificity.[75] We needed to estimate the percentage of patients believed to have advanced fibrosis by non-invasive testing who did not (false positives). A meta-analysis found that in patients undergoing liver biopsy for NAFLD with abnormal liver function tests, only about 60% of patients actually had NASH.[1] Based on expert input, we assumed that no more than one-quarter of those patients with NASH would have advanced fibrosis, giving a prevalence of 15% advanced fibrosis. Applying the above sensitivity and specificity to a population with this prevalence gives a positive predictive value of testing of 67%. Thus, 33% of patients undergoing non-invasive testing were assumed to be false positives who might be treated if confirmatory biopsy were not performed. This scenario compared the costs and outcomes of OCA treatment that are generated by treating a subset of false positives from the non-invasive diagnostic only pathway with the costs and harms of biopsy added to only treating true positive NASH with fibrosis patients. We modeled a cost of $1,441 for liver biopsy,[76] a 0.2% mortality associated with biopsy,[77] and assumed a one-month disutility of -0.05 associated with biopsy. Both true- and false-negative subjects were modeled in the F0 health state for their lifetime, with the false-negatives accruing drug costs.

3) *Modeling treatment initiation separately among F2 patients or F3 patients*. We modeled two distinct scenarios, where all base case input parameters and assumptions were included, with the exception of the initial fibrosis stage distribution. We created one scenario where 100% of the cohort began the first cycle in F2, and then a separate scenario where 100% of the cohort began the first cycle in F3, in order to evaluate the impact of stage at treatment initiation on the comparative value estimate.

4) *Initiating treatment where the cohort has a history of CV events*. We modeled a scenario where treatment for NASH with fibrosis was initiated among people with a history of CV events. All base case input parameters and assumptions were included. Additionally, during this scenario, we also tested adjusting the relative risk for CV events modeled with LDL-C.

We are considering including the following additional scenario analyses in the final report:

- Varying the rates of treatment discontinuation, including discontinuation upon improvement to F0 or discontinuation at F4.

Model Validation

We used several approaches to validate the model. First, we provided preliminary methods and results to the manufacturer, patient groups, and clinical experts. Based on feedback from these groups, we refined the data inputs and model assumptions. Second, we varied model input

parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. Finally, we compared results to other cost-effectiveness models in this therapeutic area.

5.3 Results

Base Case Results

OCA (based on the placeholder price) had higher total costs ($1,291,000 over lifetime) compared to standard care ($419,000 over lifetime) but resulted in more LYs (14.54 vs. 13.97), evLYG (10.23 vs. 9.63), and QALYs (10.13 vs. 9.63), respectively (Table 5.13). OCA had fewer patients with advanced liver disease (decompensated cirrhosis, HCC, and liver transplant) outcomes over a lifetime (14% vs. 27%) and fewer liver-related deaths (9% vs. 19%) compared to standard care, but more patients with CV events over a lifetime (94% vs. 77%) and more CV-related deaths (22% vs. 18%). Based on the placeholder price, the OCA incremental cost-effectiveness ratios compared to standard care were $1,756,000/QALY, $1,531,000/LY, and $1,459,000/evLYG (Table 5.14).

Table 5.13. Discounted Results for the Base-Case for Obeticholic Acid Compared to Standard Care

Treatment	Drug Cost	Total Cost	Advanced Liver Disease‡	CV Events	Life Years	evLYG	QALY
Obeticholic Acid*	$1,051,000	$1,291,000	14%	94%	14.54	10.23	10.13
Standard Care	$-	$419,000	27%	77%	13.97	9.63	9.63
Incremental	$1,051,000	$872,000	-13%	17%	0.57	0.60	0.50

*Using the placeholder price for obeticholic acid
‡Advanced liver disease includes lifetime decompensated cirrhosis, HCC, and liver transplant outcomes
CV: cardiovascular; evLYG: equal value life year gained; QALY: quality-adjusted life years

Table 5.14. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Cost per LY Gained	Cost per evLYG	Cost per QALY Gained
Obeticholic Acid*	$1,531,000	$1,459,000	$1,756,000
Standard Care			Reference

*Using the placeholder price for obeticholic acid
LY: life year; evLYG: equal value life year gained; QALY: quality-adjusted life year

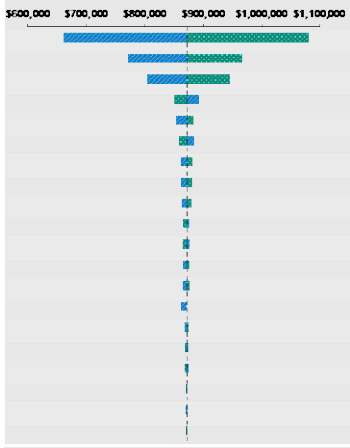
Sensitivity Analysis Results

To demonstrate the effects of parameter uncertainty on both costs and health outcomes, we varied input parameters using standard errors (if available) or reasonable ranges to evaluate changes in

incremental cost and QALYs for OCA versus standard care. The key drivers of incremental costs were the placeholder price for OCA, standard care efficacy, probability of discontinuing OCA, and the cost of liver transplantation. The key drivers of incremental QALYs were the OCA efficacy relative risks, the utility value for fibrosis stage 0 to 3, and the standard care probability of fibrosis improvement.

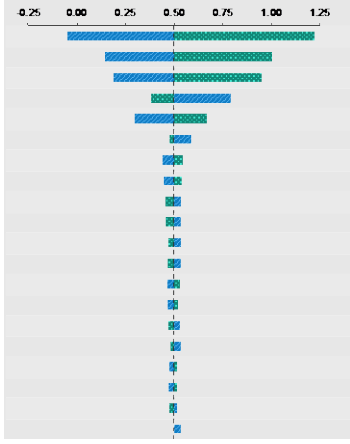
Figure 5.2. Tornado Diagram(s) for One-Way Sensitivity Analyses of Obeticholic Acid versus Standard Care

Incremental Cost: OCA vs. Standard Care



Parameter	Low Value	High Value	Low Result	High Result	Spread
Obeticholic Acid Net Price	$176	$264	$661,297	$1,081,694	$420,397
Standard Care Improvement of fibrosis	**0.18**	**0.28**	**$770,854**	**$967,635**	**$196,781**
Standard Care No change of fibrosis	0.50	0.62	$805,253	$946,286	$141,033
Cost: Liver Transplant Year 1	**$294,519**	**$441,778**	**$893,446**	**$849,546**	**$43,900**
Obeticholic Acid RR: Improvement of fibrosis	1.29	2.12	$853,962	$882,472	$28,510
Proportion of MIs that are fatal	**0.19**	**0.29**	**$885,817**	**$857,723**	**$28,095**
Obeticholic Acid RR: No change of fibrosis	0.75	1.02	$861,499	$880,832	$19,333
Standard Care Transition Weight: F3 to F1	**0.40**	**0.60**	**$861,929**	**$880,490**	**$18,561**
Standard Care Transition Weight: F2 to F3	0.40	0.60	$863,043	$879,863	$16,820
Health State Annual Cost: Compensated Cirrhosis	**$15,682**	**$23,524**	**$877,947**	**$865,045**	**$12,902**
Health State Annual Cost: HCC	$77,345	$116,017	$877,745	$865,247	$12,498
Standard Care Transition Weight: F3 to F2	**0.40**	**0.60**	**$865,526**	**$877,133**	**$11,607**
Transition Probability: Decompensated Cirrhosis to Liver-Related Death	0.10	0.16	$865,337	$876,488	$11,150
Standard Care Transition Weight: F4 to F3	**0.80**	**1.00**	**$861,815**	**$871,496**	**$9,681**
Non-statins: RR per 1mmol/L reduction	0.66	0.86	$867,845	$874,930	$7,085
Proportion of strokes that are fatal	**0.17**	**0.25**	**$874,875**	**$868,148**	**$6,727**
Standard Care Transition Weight: F1 to F3	0.27	0.40	$874,788	$868,332	$6,456
OCA LDLc Difference from PBO at 12 weeks	**13.8 mg/dL**	**20.6 mg/dL**	**$874,040**	**$868,957**	**$5,084**
On statins: RR per 1mmol/L reduction	0.71	0.84	$869,291	$873,674	$4,383
Standard Care Transition Weight: F1 to F2	**0.48**	**0.72**	**$873,640**	**$869,471**	**$4,169**

Incremental QALYs: OCA vs. Standard Care



Parameter	Low Value	High Value	Low Result	High Result	Spread
Obeticholic Acid RR: Improvement of fibrosis	1.29	2.12	-0.05	1.23	1.27
Utility: NASH Fibrosis Stage 0-2	**0.61**	**0.91**	**0.15**	**1.00**	**0.86**
Obeticholic Acid RR: No change of fibrosis	0.75	1.02	0.18	0.95	0.77
Utility: Compensated Cirrhosis	**0.49**	**0.83**	**0.79**	**0.38**	**0.41**
Standard Care Improvement of fibrosis	0.18	0.28	0.30	0.67	0.38
Utility: NASH Fibrosis Stage 3	**0.64**	**0.82**	**0.59**	**0.48**	**0.11**
Non-statins: RR per 1mmol/L reduction	0.66	0.86	0.44	0.55	0.11
Transition Probability: Compensated Cirrhosis to Liver-Related Death	**0.02**	**0.03**	**0.45**	**0.54**	**0.10**
OCA LDLc Difference from PBO at 12 weeks	13.8 mg/dL	20.6 mg/dL	0.53	0.46	0.08
Standard Care Transition Weight: F2 to F3	**0.40**	**0.60**	**0.53**	**0.46**	**0.07**
Utility: Hepatocellular Carcinoma	0.40	0.60	0.54	0.47	0.07
Utility: Liver Transplantation	**0.45**	**0.68**	**0.53**	**0.46**	**0.07**
On statins: RR per 1mmol/L reduction	0.71	0.84	0.46	0.53	0.07
Obeticholic Acid Transition Weight: F3 to F1	**0.40**	**0.60**	**0.47**	**0.52**	**0.06**
Standard Care Transition Weight: F3 to F1	0.40	0.60	0.53	0.47	0.06
Utility: Decompensated Cirrhosis	**0.46**	**0.68**	**0.53**	**0.48**	**0.05**
Obeticholic Acid Transition Weight: F2 to F3	0.40	0.60	0.47	0.52	0.04
Transition Probability: Decompensated Cirrhosis to Liver-Related Death	**0.10**	**0.16**	**0.47**	**0.52**	**0.04**
Proportion of MIs that are fatal	0.19	0.29	0.52	0.48	0.04
Standard Care Transition Weight: F4 to F3	**0.80**	**1.00**	**0.54**	**0.50**	**0.04**

The probabilistic sensitivity analysis produced a range of uncertainty that included both positive and negative incremental QALYs, with a mean incremental cost-effectiveness ratio of $2,070,000/QALY (95% credible range: -$16,520,000 to $20,790,000) using the placeholder price for OCA. None of the simulations predicted OCA to be cost-effective, using the placeholder price, at a threshold between $50,000/QALY and $250,000/QALY.

Table 5.15. Probabilistic Sensitivity Analysis Results: Obeticholic Acid versus Standard Care

	$50,000 per QALY	$100,000 per QALY	$150,000 per QALY	$200,000 per QALY	$250,000 per QALY
Probability of OCA being cost-effective	0%	0%	0%	0%	0.04%

*Using the placeholder price for obeticholic acid

Scenario Analyses Results

Modified Societal Perspective

Adding societal costs for NASH fibrosis stages and cardiovascular events increased the total cost for both OCA and standard care compared to the base case (Table 5.16). However, despite higher productivity loss due to CV events for OCA, the total societal cost of standard care was higher than that for OCA due to more time spent in the F3 and F4 health states. As a result, the incremental costs per LY, evLYG, and QALY gained decreased, but nonetheless still did not achieve commonly-cited cost-effectiveness thresholds when using the placeholder price for OCA (Table 5.17).

Table 5.16. Results for the Societal Perspective Analysis for Obeticholic Acid Compared to Standard Care

Treatment	Drug Cost	Societal Cost	Total Cost	Advanced Liver Disease‡	CV Events	Life Years	evLYG	QALY
Obeticholic Acid*	$1,051,000	$191,000	$1,482,000	14%	94%	14.54	10.23	10.13
Standard Care	$-	$212,000	$419,000	27%	77%	13.97	9.63	9.63
Incremental	$1,051,000	-$21,000	$1,063,000	-13%	17%	0.57	0.60	0.50

*Using the placeholder price for obeticholic acid

‡Advanced liver disease includes lifetime decompensated cirrhosis, HCC, and liver transplant outcomes

CV: cardiovascular; evLYG: equal value life year gained; QALY: quality-adjusted life years

Table 5.17. Incremental Cost-Effectiveness Ratios for the Societal Perspective Analysis

Treatment	Cost per LY Gained	Cost per evLYG	Cost per QALY Gained
Obeticholic Acid*	$1,494,000	$1,424,000	$1,713,000
Standard Care			Reference

*Using the placeholder price for obeticholic acid

LY: life year; evLYG: equal value life year gained; QALY: quality-adjusted life year

Diagnostic Pathways Comparison Scenario

We compared the use of a fibrosis non-invasive diagnostic alone vs. that non-invasive diagnostic combined with liver biopsy prior to treatment initiation (Table 5.18). The non-invasive diagnostic alone generated slightly less LYs, evLYG, and QALYs, and an additional cost of $317,000 compared to non-invasive diagnosis with biopsy confirmation.

Table 5.18. Results for the Diagnostic Pathways Comparison Scenario

Treatment with Obeticholic Acid*	Drug Cost	Total Cost	Advanced Liver Disease‡	CV Events	Life Years	evLYG	QALY
Non-Invasive Only	$1,110,000	$1,286,000	9.7%	96.9%	14.79	10.63	10.58
Non-Invasive with Biopsy Confirmation	$785,000	$960,000	9.6%	92.9%	14.83	10.67	10.60

*Using the placeholder price for obeticholic acid
‡Advanced liver disease includes lifetime decompensated cirrhosis, HCC, and liver transplant outcomes
CV: cardiovascular; evLYG: equal value life year gained; QALY: quality-adjusted life years

Patients Initiating Treatment at F2 Scenario

All patients entering the cohort in this scenario began with F2 fibrosis, holding all other base case input parameters and assumptions constant (Table 5.19 and 5.20).

Table 5.19. Results for the Patients Initiating Treatment at F2 Scenario for Obeticholic Acid Compared to Standard Care

Treatment	Drug Cost	Total Cost	Advanced Liver Disease‡	CV Events	Life Years	evLYG	QALY
Obeticholic Acid*	$1,095,000	$1,282,000	11%	96%	14.75	10.39	10.31
Standard Care	$-	$419,000	23%	79%	14.28	9.88	9.88
Incremental	$1,095,000	$863,000	-12%	17%	0.47	0.51	0.43

*Using the placeholder price for obeticholic acid
‡Advanced liver disease includes lifetime decompensated cirrhosis, HCC, and liver transplant outcomes
CV: cardiovascular; evLYG: equal value life year gained; QALY: quality-adjusted life years

Table 5.20. Incremental Cost-Effectiveness Ratios for the Patients Initiating Treatment at F2 Scenario

Treatment	Cost per LY Gained	Cost per evLYG	Cost per QALY Gained
Obeticholic Acid*	$1,997,000	$1,816,000	$2,168,000
Standard Care			Reference

*Using the placeholder price for obeticholic acid

LY: life year; evLYG: equal value life year gained; QALY: quality-adjusted life year

Patients Initiating Treatment at F3 Scenario

All patients entering the cohort in this scenario began with F3 fibrosis, holding all other base case input parameters and assumptions constant (Tables 5.21 and 5.22).

Table 5.21. Results for the Patients Initiating Treatment at F3 Scenario for Obeticholic Acid Compared to Standard Care

Treatment	Drug Cost	Total Cost	Advanced Liver Disease‡	CV Events	Life Years	evLYG	QALY
Obeticholic Acid*	$1,015,000	$1,298,000	17%	93%	14.37	10.10	9.98
Standard Care	$-	$419,000	31%	75%	13.72	9.43	9.43
Incremental	$1,015,000	$879,000	-14%	18%	0.65	0.67	0.55

*Using the placeholder price for obeticholic acid
‡Advanced liver disease includes lifetime decompensated cirrhosis, HCC, and liver transplant outcomes
CV: cardiovascular; evLYG: equal value life year gained; QALY: quality-adjusted life years

Table 5.22. Incremental Cost-Effectiveness Ratios for the Patients Initiating Treatment at F3 Scenario

Treatment	Cost per LY Gained	Cost per evLYG	Cost per QALY Gained
Obeticholic Acid*	$1,256,000	$1,232,000	$1,490,000
Standard Care			Reference

*Using the placeholder price for obeticholic acid
LY: life year; evLYG: equal value life year gained; QALY: quality-adjusted life year

Patients Initiating Treatment with History of Cardiovascular Event

All patients entering the cohort in this scenario began in the history of CV event submodel, holding all other base case input parameters and assumptions constant. This scenario resulted in fewer LYs, evLYG, and QALYs for OCA than for standard care (Tables 5.23 and 5.24). We additionally adjusted the relative risk of CV events associated with increases in LDL-C, which generated equal outcomes between OCA and standard care in this scenario.

Table 5.23. Results for the Patients Initiating Treatment with History of Cardiovascular Event for Obeticholic Acid Compared to Standard Care

Treatment	Drug Cost	Total Cost	Advanced Liver Disease‡	CV Events	Life Years	evLYG	QALY
Obeticholic Acid*	$1,021,000	$1,280,000	14%	114%	14.11	6.94	6.94
Standard Care	$-	$260,000	14%	102%	14.33	7.13	7.06
Incremental	$1,021,000	$1,020,000	0%	12%	-0.21	-0.19	-0.12

*Using the placeholder price for obeticholic acid
‡Advanced liver disease includes lifetime decompensated cirrhosis, HCC, and liver transplant outcomes
CV: cardiovascular; evLYG: equal value life year gained; QALY: quality-adjusted life years

Table 5.24. Incremental Cost-Effectiveness Ratios for the Patients Initiating Treatment with History of Cardiovascular Event Scenario

Treatment	Cost per LY Gained	Cost per evLYG	Cost per QALY Gained
Obeticholic Acid*	Dominated	Dominated	Dominated
Standard Care			Reference

*Using the placeholder price for obeticholic acid
LY: life year; evLYG: equal value life year gained; QALY: quality-adjusted life year

Threshold Analyses Results

Annual prices necessary to reach cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY are listed in Table 5.25. We also present the threshold prices for the scenarios in which patients initiate treatment at F2 (Table 5.26) and at F3 (Table 5.27). We strongly caution the readers against assuming that the values provided in this section will approximate the health benefit price benchmarks (HBPBs) that will be presented in the next iteration of this report. These results may change substantially based on reviewer and public input, as well as manufacturer and internal model review.

Table 5.25. Threshold Analysis Results

	Annual Price to Achieve $50,000 per QALY	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY
Obeticholic Acid	$15,620	$17,510	$19,410

Table 5.26. Threshold Analysis Results for Patients Initiating Treatment at F2 Scenario

	Annual Price to Achieve $50,000 per QALY	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY
Obeticholic Acid	$13,390	$14,970	$16,550

Table 5.*27*. Threshold Analysis Results for Patients Initiating Treatment at F3 Scenario

	Annual Price to Achieve $50,000 per QALY	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY
Obeticholic Acid	$17,600	$19,780	$21,950

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

We utilized a recently published systematic review of cost-effectiveness analyses in NAFLD and NASH by Johansen and colleagues to inform our comparisons with prior economic models.[53] With a lack of FDA approved treatments for NASH with fibrosis, there are no directly comparable models aside from the prior ICER model. Johansen identified 16 unique cost-effectiveness models in this clinical area. Most published models have focused on screening and diagnostic strategies for either NASH, NAFLD, or both. Additionally, two studies evaluated the value of surgical treatments for NASH.

Limitations

As with any modeling exercise, there are many limitations to be considered when evaluating these findings. First, we are unable to accurately identify the effectiveness parameters to directly inform transition probabilities from the REGENERATE trial. As such, our transformation of the trial-reported outcomes may be biased based on the outcome distributions we assumed. Furthermore, those effectiveness parameters are based on 18 months of trial data and extrapolated to a lifetime horizon, which assumes continued effectiveness (along with adherence to treatment). And because

the available REGENERATE trial data only span 18 months, we were unable to observe progression to advanced liver disease in the vast majority of the population, requiring additional external transition probabilities.

We assumed that the treated population has the characteristics of the REGENERATE trial, including the fibrosis stage distribution. In scenario analyses, we demonstrated that the incremental value of obeticholic acid may depend on the patient population in which it is used.

We also assumed the underlying risk of CV events could be accurately predicted by the Framingham equation, along with adjustment for the increased LDL-C that has been observed to be associated with OCA. However, we did not model the observed decrease in HDLc that has also been observed, as we did not want to simultaneously model two uncertainties related to cholesterol. Additionally, we made assumptions regarding subsequent CV event risk that did not increase patient's risk of events after the second CV event, which may have underestimated CV events.

Conclusions

OCA appears to improve outcomes in people with NASH with fibrosis. At a placeholder price of $80,000 per year, OCA is not cost-effective at traditional cost-effectiveness thresholds. Treating patients with F3 fibrosis without a prior history of CV events may be the population with the highest chance of showing value to the health care system at the placeholder price.

5.4 Summary and Comment

We created a *de novo* Markov model to evaluate the comparative value of obeticholic acid compared to current standard care for patients with NASH with fibrosis from the US health care system perspective. Treating NASH patients with fibrosis with OCA at the assumed placeholder price resulted in increased costs, along with increased life expectancy, evLYG, and QALYs gained compared to standard care. The ultimate cost-effectiveness of OCA will be determined by the price that is set by the manufacturer and its long-term effectiveness.

6. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of OCA to placebo. We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Council of clinicians, patients, and health services researchers. As part of their deliberations, Council members will judge whether a treatment may substantially impact the considerations listed in Table 6.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Council member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Council member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's value assessment framework. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Council's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 6.1 Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

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

6.1 Potential Other Benefits

As discussed elsewhere in the report, it is unclear whether NASH with fibrosis (and particularly F3 fibrosis) is a symptomatic condition with significant levels of fatigue, and if so whether treatments for NASH fibrosis will reduce this fatigue. It is possible that OCA and/or pioglitazone could reduce patient fatigue and potentially improve productivity.

6.2 Contextual Considerations

If approved, OCA will be the first drug in the US with an FDA indication for NASH.

There is significant uncertainty about the long-term risks of side effects with both OCA and pioglitazone, however the uncertainties are greater with OCA, both around potential CV side effects and around the risk for liver decompensation and death. Pioglitazone has been used in many more patients for many more years and so side effects are better understood.

There is significant uncertainty around the magnitude and durability of the long-term benefits of both OCA and pioglitazone for NASH. These uncertainties are somewhat greater for pioglitazone

than for OCA since the trials have not typically been of as high quality, but there are large uncertainties with both therapies given that this is a long-term disorder and trials are relatively very short in comparison.

An additional contextual consideration with NASH is the experience of patients of believing themselves healthy and then finding that they have a life-altering liver disease (cirrhosis) often with few options for treatment. We heard about this experience from multiple stakeholders.

7. Health Benefit Price Benchmarks

ICER does not provide Health Benefit Price Benchmarks (HBPBs) as part of the draft report because results are likely to change based on public comment. We strongly caution the readers against assuming that the values provided in Threshold Analysis Results section will approximate the health benefit price benchmarks (HBPBs) that will be presented in the next iteration of this report. These results may change substantially based on reviewer and public input, as well as manufacturer and internal model review. HBPBs will be included in the revised Evidence Report.

8. Potential Budget Impact

8.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of obeticholic acid for prevalent individuals in the United States (US) with advanced fibrosis due to NASH who do not have cirrhosis. This population was selected to follow the anticipated FDA label indication. In our estimates of potential budget impact, we used the wholesale acquisition cost (WAC) and net price of the currently marketed Ocaliva, and the $50,000, $100,000, and $150,000 cost-effectiveness threshold prices calculated for obeticholic acid.

8.2 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 differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

This potential budget impact analysis includes the estimated number of individuals with advanced fibrosis due to NASH who do not have cirrhosis, who would be eligible for treatment with obeticholic acid. To estimate the size of the potential candidate population for treatment, we used an estimate based on Estes et al., who used a Markov model to project NAFLD and NASH prevalence in the US through 2030. Estes et al. estimated an average of approximately 3 million individuals with F3 fibrosis from 2020-2024 in the US, whom we assumed would be eligible for treatment with obeticholic acid. When spread over five years, this results in an estimate of approximately 600,000 patients eligible for treatment with obeticholic acid each year over five years. We assumed that obeticholic acid would be added to standard care without displacing other treatments.

ICER's methods for estimating potential budget impact are described in detail elsewhere[78] and have been recently updated. The intent of our revised approach to budgetary impact is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the U.S. economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

8.3 Results

Table 8.1 illustrates the five-year annualized per-patient potential budget impact of obeticholic acid compared to standard care in this population. These results are based on the WAC list price of Ocaliva ($84,128 per year), the net price ($80,340), and the annual threshold prices for cost-effectiveness thresholds of $150,000, $100,000, and $50,000 per QALY versus usual care (approximately $19,410, $17,510, and $15,620, respectively).

Table 8.1. Annualized Per-Patient Potential Budget Impact Over a Five-year Time Horizon for Obeticholic Acid Plus Standard Care versus Standard Care Alone

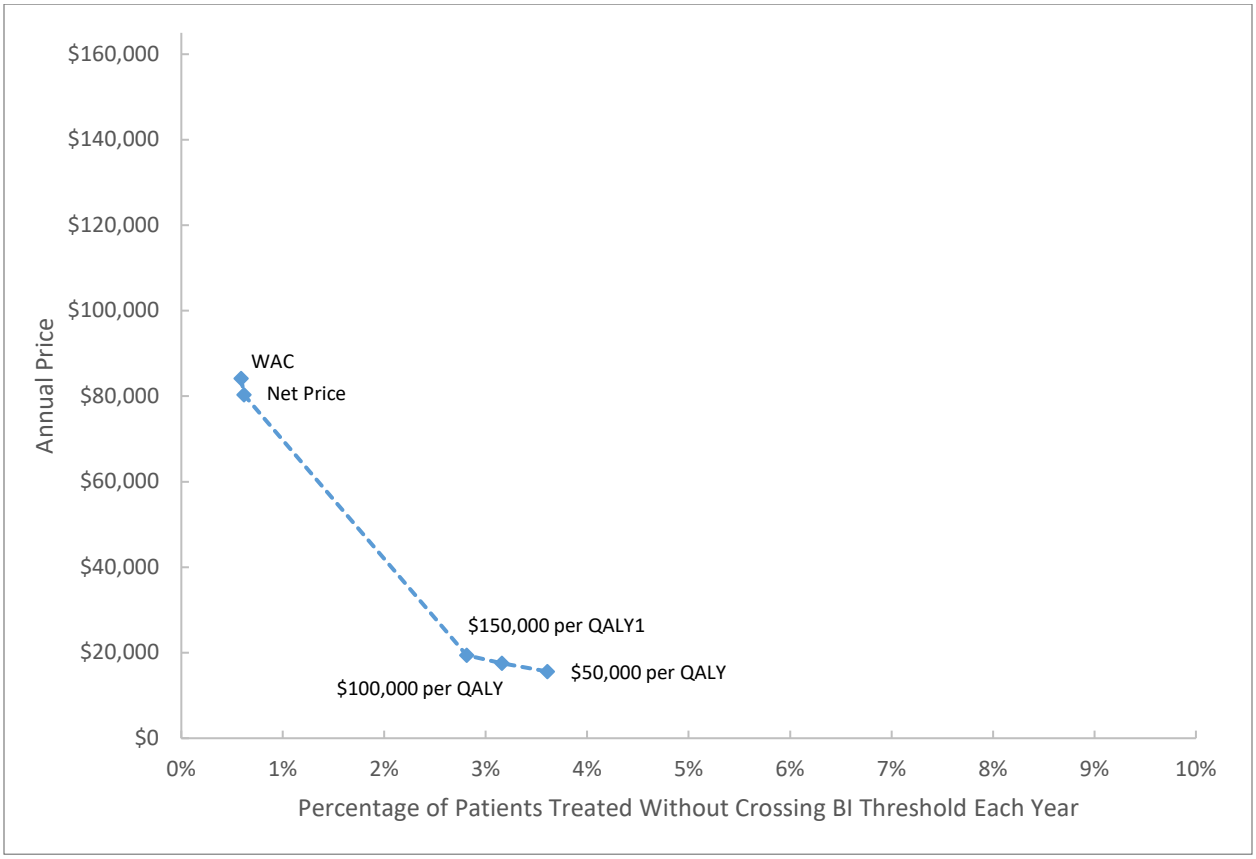
	Average Annual Per Patient Budget Impact				
	At WAC*	At Net Price*	At $150,000/QALY Price	At $100,000/QALY Price	At $50,000/QALY Price
Obeticholic Acid	$84,900	$81,300	$23,100	$21,300	$19,500
Usual Care			$6,300		
Net Impact	$78,600	$75,000	$16,900	$15,100	$13,300

*Assumed same WAC and discounted net price as for Ocaliva.
All annualized costs include drug and non-drug health care costs. Numbers may not sum due to rounding.
QALY: quality-adjusted life year

For obeticholic acid, the average annualized potential budgetary impact when using WAC was an additional per-patient cost of approximately $78,600 versus standard care alone, and approximately $75,000 at its assumed net price. Its average annualized potential budget impact versus standard care at the threshold prices for $50,000 to $150,000 per QALY ranged from approximately $13,300 to approximately $16,900 per patient over this time horizon.

In the NASH population eligible for obeticholic acid, as shown in Figure 8.1, only approximately 0.6% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million at the WAC or net prices. The budget impact threshold would also be crossed at the $150,000, $100,000 and $50,000 threshold prices, with only 2.8% of eligible patients treated at the $150,000 threshold price, up to 3.6% at the $50,000 threshold price.

Figure 8.1. Potential Budget Impact Scenarios of Obeticholic Acid Plus Standard Care vs. Standard Care Alone at Different Acquisition Prices*



*Assumed same WAC and discounted net price as for Ocaliva.
BI: budget impact, QALY: quality-adjusted life year

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This is the second ICER review of treatments for NASH.

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APPENDICES

Appendix A. Search Strategies and Results

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.

	#	Checklist item
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		

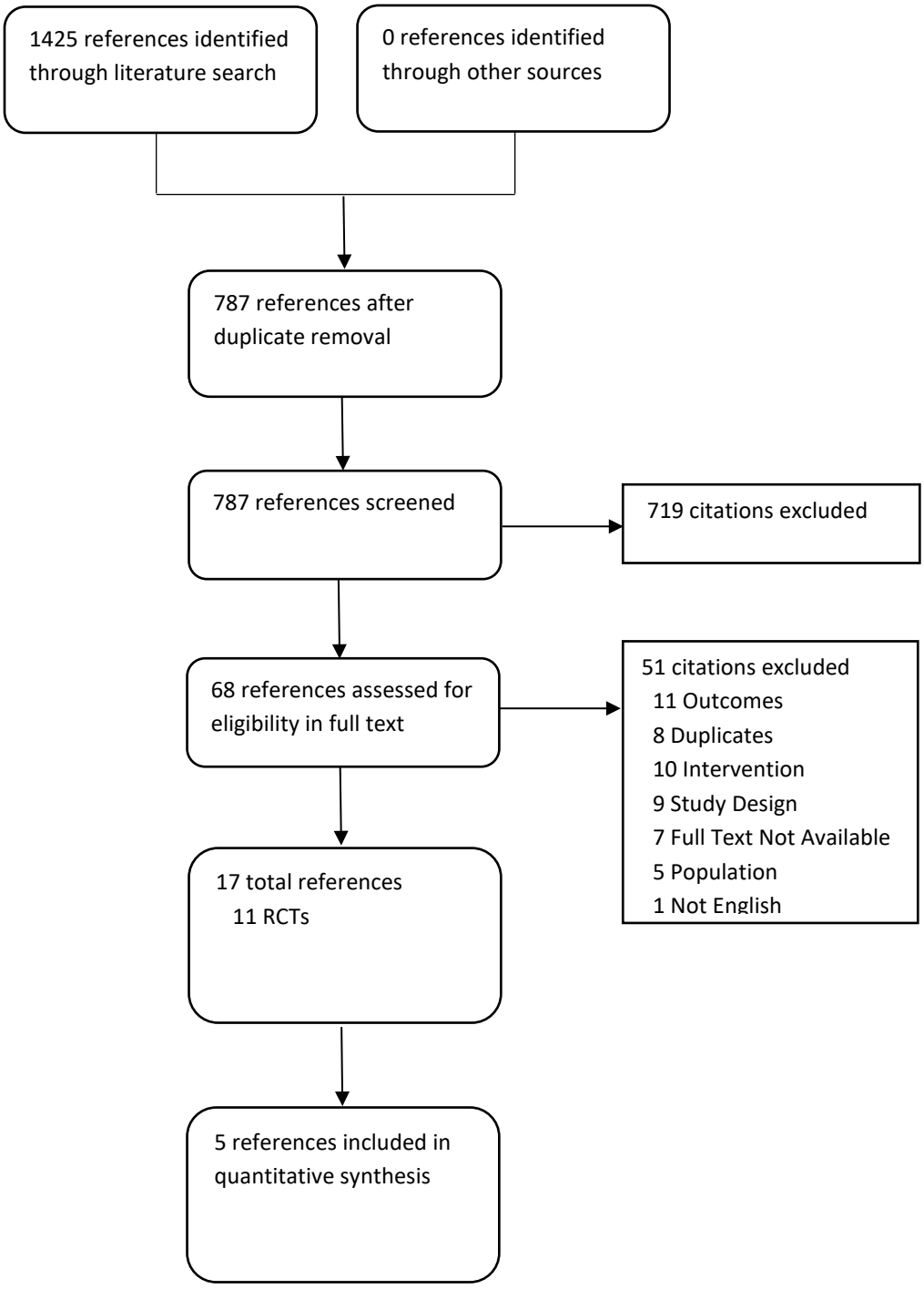
Table A2.1. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled trials

	Search Terms
1	exp fatty liver/
2	(liver and (fatty or steato*)).mp.
3	(non-alcoholic fatty liver disease or nonalcoholic fatty liver disease).mp.
4	(NASH* or NAFL*).mp.
5	(non?alcoholic steatohep*).mp.
6	1 or 2 or 3 or 4 or 5
7	(obeticholic acid or OCA or INT-747 or thiazolidinediones or pioglitazone).mp.
8	6 and 7
9	(animals not (humans and animals)).sh.
10	8 NOT 9
11	(addresses or autobiography or bibliography or biography or clinical trial, phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt.
12	10 NOT 11
13	Limit 12 to English language
14	Remove duplicates from 13

Table A2.2. Search strategy of EMBASE SEARCH

	Search Terms
#1	'fatty liver'/exp or (fatty AND (liver or hepat*) or steatohepat* or nafl* or nash*)
#2	'obeticholic acid' or oca or 'int 747' or thiazolidinediones or pioglitazone
#3	#1 and #2
#4	#3 and [humans]/lim and [english]/lim
#5	#4 NOT (‘case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey’/it)

Figure A1. PRISMA flow Chart Showing Results of Literature Search for NASH



Appendix B. Previous Systematic Reviews and Technology Assessments

We identified two previously conducted systematic reviews which are summarized below. One review focused on diabetes drugs for the treatment of non-alcoholic fatty liver disease (NAFLD), while the other one compared pharmacological interventions for non-alcoholic steatohepatitis by means of a network meta-analysis.

Previous Systematic Reviews

Lombardi R, Onali S, Thorburn D, Davidson BR, Gurusamy K, Tsochatzis E. Pharmacological interventions for non-alcohol related fatty liver disease (NAFLD): an attempted network meta-analysis. Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD011640. DOI: 10.1002/14651858.CD011640.pub2

The investigators conducted a systematic review of 77 studies of medical management of NAFLD and non-alcoholic steatohepatitis (NASH). In the bile acid trials (including obeticholic acid and ursodeoxycholic acid), the investigators found no evidence of difference in mortality or SAEs for bile acids versus placebo (GRADE of evidence was very low). In the thiazolidinedione trials, the investigators also found no evidence of difference in mortality or SAEs for thiazolidinediones versus placebo (GRADE of evidence was very low).

Blazina I, Selph S. Diabetes drugs for non-alcoholic fatty liver disease: a systematic review. Syst Rev. (2019) 8:295.

The investigators conducted a systematic review to determine whether the off-label use of medications approved by the US Food and Drug Administration for the treatment of diabetes would lead to weight loss and improvements in steatohepatitis in patients with NAFLD. Drugs developed specifically for treatment of NAFLD, including obeticholic acid, were excluded. A total of 18 head-to-head and placebo-controlled randomized controlled studies of adults with NAFLD (including NASH) were included in the analysis. Of these, 5 studies randomized NASH patients (in 2 studies patients were additionally diagnosed with prediabetes or diabetes, and 3 studies randomized NASH patients without diabetes) to pioglitazone or placebo. Pioglitazone was found to be superior with regards to improvements in liver function, liver fat, and NASH resolution in comparison to placebo. However, treatment with pioglitazone lead to significant increases in weight when compared to placebo. These findings are consistent with another recent systematic review and network meta-analysis. The investigators concluded that trial evidence supports the efficacy of some diabetes drugs (especially pioglitazone) in patients with NAFLD or NASH, though weight gain with some diabetes drugs may warrant caution.

Singh S, Khera R, Allen AM, et al. Comparative Effectiveness of Pharmacological Interventions for Nonalcoholic Steatohepatitis: A Systematic Review and Network Meta-analysis. Hepatology.2015; 62(5):1417-1432.

A Bayesian network meta-analysis combining direct and indirect treatment comparisons was conducted to assess the comparative effectiveness of vitamin E, thiazolidinediones, pentoxifylline, obeticholic acid and placebo for the treatment of NASH. Nine randomized controlled trials including 964 patients with biopsy-proven NASH were identified in this review. Three of these studies compared pioglitazone with placebo and one study compared obeticholic acid with placebo. Efficacy was evaluated based on improvement in fibrosis stage. Improvement in ballooning degeneration, lobular inflammation, and steatosis were also evaluated. Key observations from this analysis is there is moderate confidence in the superiority of obeticholic acid and pentoxifylline to placebo for improving fibrosis. The analysis also observed a high confidence in estimating that vitamin E, thiazolidinediones and obeticholic acid are superior to placebo for improving ballooning degeneration. High-quality evidence supports the effect of vitamin E, TZDs, and obeticholic acid over placebo in improving ballooning degeneration. All four interventions seemed to have at least moderate-quality evidence over placebo to improve steatosis.

Technology Assessments

We identified one ongoing health technology assessment (HTA) of obeticholic acid (OCA) for the treatment of non-alcoholic steatohepatitis (NASH) conducted by the National Institute for Health and Care Excellence (NICE). We also identified two completed HTAs of OCA for the treatment of primary biliary cholangitis (PBC); one by the Canadian Agency for Drugs and Technologies in Health (CADTH) and NICE each. These reviews are summarized below.

We were unable to identify any HTAs of pioglitazone for the treatment of NASH.

NICE

Obeticholic acid for treating liver fibrosis in people with steatohepatitis [GID-TA10606] - TBC

https://www.nice.org.uk/guidance/proposed/gid-ta10606

NICE is currently conducting an appraisal of the clinical and cost effectiveness of obeticholic acid for the treatment of liver fibrosis in people with NASH. The expected publication date is to be confirmed (TBC).

Obeticholic acid for treating primary biliary cholangitis [Technology appraisal guidance [TA443] – April 26, 2017

https://www.nice.org.uk/guidance/ta443/chapter/1-Recommendations

NICE recommends OCA as a treatment option for primary biliary cholangitis; either in combination with ursodeoxycholic acid (UDCA) for people whose disease has not responded adequately to UDCA monotherapy, or as a monotherapy for people who cannot tolerate treatment with UDCA. NICE bases its recommendation on the agreed upon discount in the patient access scheme. Furthermore, NICE recommends assessing a patient's response to OCA after 12 months and only continue treatment if there is proof of clinical benefit.

CADTH

Common Drug Review - Obeticholic Acid (Ocaliva) [SR0509-000] – July 25, 2017

https://www.cadth.ca/sites/default/files/cdr/complete/SR0509_complete_Ocaliva_Jul_27_17_e.pdf

CADTH recommends OCA be reimbursed for the treatment of primary biliary cholangitis; either in combination with UDCA in adults with an inadequate response to treatment with UDCA alone, or as monotherapy in those who are unable to tolerate UDCA. CADTH also stipulated the condition that patients ought to be under the care of a specialist, as well as the price of Ocaliva be decreased by at least 60%.

Appendix C. Ongoing Studies

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Outcomes	Estimated Completion Date
Obeticholic Acid (OCA)					
Study Evaluating the Efficacy and Safety of Obeticholic Acid in Subjects With Compensated Cirrhosis Due to Nonalcoholic Steatohepatitis (REVERSE) **NCT03439254** **Intercept Pharmaceuticals**	Phase 3, Randomized, Double-Blind, parallel assignment Estimated N: 900	Intervention – OCA 10 mg – OCA 25 mg Comparator – Placebo	Inclusions – ≥18 years of age – Confirmed NASH diagnosis and a fibrosis score of 4 based upon the NASH CRN scoring system determined by central reading Exclusions – History of a clinically evident hepatic decompensation event – History of CP score ≥7 points – MELD score > 12 – ALT ≥ 5 X ULN – Calculated creatinine clearance <60mL/min – HbA1c ≥ 9.5 % – Other known forms of chronic liver disease, drug-induced liver injury, known or suspected hepatocellular carcinoma – History of liver transplant, or current placement on a liver transplant list	*[Time Frame: 18 months]* Primary Outcome – Percentage of subjects with improvement in fibrosis by at least 1 stage with no worsening of NASH, using NASH CRN scoring system Secondary Outcomes – Percentage of subjects with improvement in fibrosis by ≥2 stages, using Ishak scoring criteria – Percentage of subjects with NASH resolution, using the NASH CRN scoring	June 2021
Phase 3 Study to Evaluate the Impact on NASH With Fibrosis of Obeticholic Acid Treatment (REGENERATE)	Phase 3, Randomized, Double-Blind, parallel assignment	Intervention – OCA 10 mg – OCA 25 mg Comparator – Placebo	Inclusions – 18-85 years – Histologic evidence of NASH upon central read of a liver biopsy obtained no more than 6 months before Day 1 (defined by presence of all 3 key histological features of NASH according to NASH CRN criteria)	Primary Outcomes - The proportion of OCA treated patients relative to placebo achieving ≥1 stage of liver fibrosis improvement with no worsening of NASH *[Time Frame: 18 months]*	October 2022

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Outcomes	Estimated Completion Date
NCT02548351 **Intercept Pharmaceuticals**	Estimated N: 2,480			- The proportion of OCA treated patients relative to placebo achieving NASH resolution with no worsening of liver fibrosis *[Time Frame: 18 months]* - Time to first occurrence of: Death (all cause), MELD score ≥15, liver transplant, ascites requiring medical intervention, histological progression to cirrhosis, hospitalization for variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis *[Time Frame: Estimated to be 7 years]*	
Role of Obeticholic Acid in the Patients of NAFLD With Raised ALT (NAFLD) **NCT03836937** **Sir Salimullah Medical College Mitford Hospital**	Randomized, Open-Label, parallel assignment trial Estimated N: 70	Intervention – OCA 10 mg Comparator – Lifestyle modification	Inclusions – 18 – 65 years – NAFLD (by USG) – Raised ALT (>40 U/L) Exclusions – Patient with significant alcohol intake – Patient with history of taking drugs that may cause fatty liver or history of taking drugs that have shown benefit in previous NASH pilot studies – Chronic viral hepatitis – Patient with co-morbid condition – Patient with history of recent MI – Patient with liver failure – Patient with hypothyroidism	*[Time Frame: 12 Weeks]* Primary Outcomes – Change in fibroscan score and CAP value which signifies fibrosis and steatosis status respectively – Change in BMI – Change in ALT, AST – Fasting blood sugar – 2 hours after 75 gm glucose – Serum bilirubin / Serum albumin – Gamma glutamyle transpeptidase – Prothrombin time – Total cholesterol/ Triglyceride/ LDL/ HDL	March 2020

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Outcomes	Estimated Completion Date
Pioglitazone (PIO)					
A 5-year Longitudinal Observational Study of Patients With Nonalcoholic Fatty Liver (NAFL) or Nonalcoholic Steatohepatitis (NASH) **NCT02815891** **Target PharmaSolutions, Inc.**	Observational Cohort, non-probability sample Estimated N: 15,000	---	Inclusions – ≥2 years – Adults and children with NAFL or NASH who are being seen specifically to address this disease process Exclusions – Simultaneous enrollment in another registry, study, or clinical trial where NASH treatment outcomes are reported, except where approved or conducted as an adjunct project of TARGET-NASH	*[Time Frame: up to 5 years]* Primary Outcomes – Understanding of the natural history of NASH – Evaluate NASH treatment regimens being used in clinical practice – Examine populations underrepresented in phase II-III clinical trials – Optimal duration and combination of NASH therapies – Examine liver histology – Estimate adverse event frequency and severity – Impact of NASH therapies on medical co-morbidities	July 2026
The Efficacy and Safety of Pioglitazone in Patients With Nonalcoholic Steatohepatitis **NCT01068444** **Kaohsiung Medical University Chung-Ho Memorial Hospital**	Phase 2, Randomized, Double-Blind, Placebo-controlled, parallel assignment Estimated N: 90	Intervention – PIO 30 mg Comparator – Placebo	Inclusions – 18 – 70 years – Liver biopsy findings consistent with the diagnosis of NASH with or without compensated cirrhosis within one year before baseline – Compensated liver disease – ALT level between 1.3-5 x ULN during 6 months before screening – HbA1C ≦ 8.0 during screening Exclusions	*[Time Frame: 9 months]* Primary Outcomes – Comparison between Pioglitazone and placebo groups in terms of steatosis and liver function tests – Evaluation of clinical safety of Pioglitazone Secondary Outcome – Comparison between Pioglitazone and placebo groups in terms of liver necroinflammation and fibrosis	March 2019

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Outcomes	Estimated Completion Date
			– Therapy with any systemic anti-neoplastic or immunomodulatory treatment in 6 months prior – Medical condition associated with chronic liver disease other than NASH – Hepatocellular carcinoma – History or other evidence of bleeding from esophageal varices – Serum creatinine level >1.5 times the ULN – History of ischemic heart disease – Albumin <3.2g/dL during screening – Total bilirubin >1.2 x ULN – Organ, stem cell, or bone marrow transplant – Active systemic autoimmune disorder – Participation in another clinical trial – Therapy with insulin within 1 week – History of metformin use within 3 months		
Comparison of The Effects of Thiazolidinediones (TZD), Sodium- Glucose Cotransporter 2 Inhibitors (SGLT2i) Alone and TZD / SGLT2i Combination Therapy on Non-alcoholic Fatty Liver Disease in Type 2 Diabetic Patients With Fatty Liver	Open-Label, Randomized, parallel assignment Estimated N: 60	Interventions – PIO 15 mg – Empagliflozin 10 mg – Combination of PIO (15 mg) and Empagliflozin (10 mg)	Inclusions – 19 – 75 years – NAFL or fatty liver diagnosis – Type 2 Diabetes diagnosis Exclusions – Acute or chronic metabolic acidosis – Alcoholic liver disease – People who take drugs that can cause fatty liver – Malignant tumors – History of substance abuse or alcohol intoxication within 12 weeks	*[Time Frame: 6 months]* Primary Outcome – Liver fat change measured by MRI-PDFF in co-localized regions of interest within each of nine liver segments Secondary Outcome – Liver fibrosis – Changes in lipid profile, liver enzymes, glucose metabolism, inflammation status	February 2021

Title/ Trial Sponsor	Study Design	Interventions	Patient Population	Outcomes	Estimated Completion Date
NCT03646292 **Yonsei University**			– HIV – People with renal failure, chronic renal disease – Cardiac failure within 6 months, or acute cardiovascular disease within 12 weeks		

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

ALT: Alanine Aminotransferase, CRN: Clinical Research Network, HbA1c: Hemoglobin A1c, HDL: high-density cholesterol, HIV: Human Immunodeficiency Virus, LDL; low-density cholesterol, MELD: model of end stage liver disease, mg: milligram, min: minute, MRI-PDFF: magnetic resonance imaging-derived proton density fat fraction, N: total number, NAFLD: Non-alcoholic Fatty Liver Disease, NASH: Non-Alcoholic Steatohepatitis, ULN: upper limit of normal, U/L: units per liter

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. 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. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2)[29] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

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.*

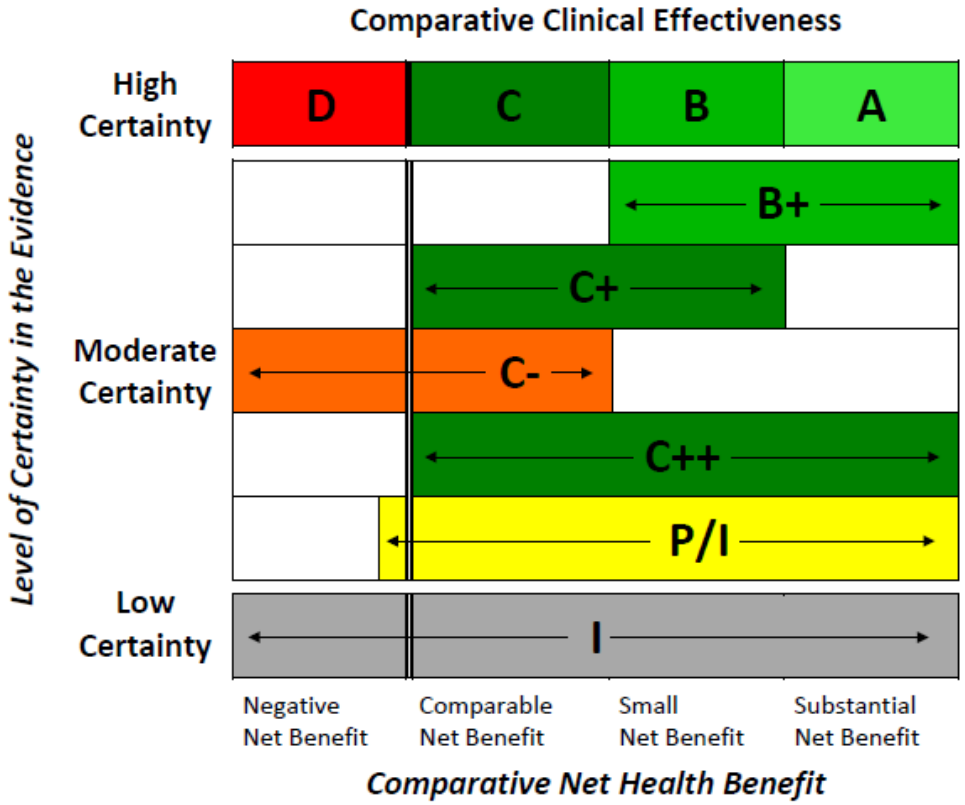
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) 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.[79]

Figure D1. 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 or substantial net health benefit, with high certainty of at least a small net health benefit*
***C+ = "Comparable or Incremental"** - Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
***C- = "Comparable or Inferior"** – Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
***C++ = "Comparable or Better"** - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a 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"** – Any situation in which the level of certainty in the evidence is low*

Table D1. Study Design

Trial & Author	Design & Duration of Follow-up	Interventions	Inclusion Criteria	Exclusion Criteria
Obeticholic Acid (OCA)				

REGENERATE
 	
Younossi 2019[6]
 	
Younossi 2019[33]
	Phase 3, Randomized, Double-Blind, Parallel Assignment
	
	N: 931
	
	Follow-up
	18 months
		Intervention
		- OCA 25 mg
		- OCA 10 mg
		
		Comparator
		- Placebo
			- Ages 18-85 years
			- Biopsy confirmed NASH
			- Stable body weight
			- Histologic evidence of fibrosis stage 2 or stage 3, or histologic evidence of fibrosis stage 1a or stage 1b if accompanied by ≥1 of the following risk factors:
			  - Obesity (BMI ≥30 kg/m2)
			  - Type 2 Diabetes Mellitus
			  - ALT >1.5× ULN
			- Subjects with a historical biopsy, either not taking or on stable doses of TZDs/glitazones or vitamin E for 6 months before Day 1
				- MELD score >12; ALT ≥10× ULN; HbA1c >9.5; Total bilirubin >1.5 mg/dL; BMI >45 kg/m2
				- Evidence of other known forms of known chronic liver disease, or known or suspected hepatocellular carcinoma
				- History of liver transplant, or current placement on a liver transplant list
				- Current or history of significant alcohol consumption
				- History of biliary diversion
				- Prior or planned ileal resection, or prior or planned bariatric surgery
				- Histological presence of cirrhosis
				- HIV; acute cholecystitis or biliary obstruction

FLINT **Neuschwander-Tetri 2015[30]** **Hameed 2018[80]** **Clinicaltrials.gov 2015[81]**	Phase 2, Double-blind, Randomized, Multicentre, Parallel Assignment N: 283 Follow-Up - 72 weeks Treatment Period - 24 weeks Post-treatment measurements	Intervention - OCA 25 mg Comparator - Placebo	- Ages ≥18 years - Biopsy confirmed NASH	- Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year - Use of drugs historically associated with NAFLD for more than 2 weeks in the year prior - Bariatric surgery (prior or planned during study) - Uncontrolled diabetes within 60 days - Presence of cirrhosis on liver biopsy - A platelet count below 100,000/mm3 - Clinical evidence of hepatic decompensation as defined by the presence of any of the following abnormalities - Serum albumin <3.2 g/dL, INR >1.3, direct bilirubin >1.3 mg/dL

Trial & Author	Design & Duration of Follow-up	Interventions	Inclusion Criteria	Exclusion Criteria
				- History of esophageal varices, ascites or hepatic encephalopathy - Evidence of other forms of chronic liver disease - History of hemochromatosis or iron overload - Any other type of liver disease other than NASH - ALT >300 U/L; Serum creatinine ≥2.0 mg/dL, Use of ursodeoxycholic acid within 90 days prior; History of biliary diversion - HIV; Active substance abuse in year prior - Participation in an IND trial in 30 days prior - Any other condition which would impede compliance or hinder completion of the study
CONTROL **Pockros 2019[31]** **Clinicaltrials.gov 2015[82]**	Phase 2, Randomized, Double-Blind N: 84 Follow-Up - Screening Period: 5 weeks - Double-Blind Period: 16 weeks - Open-Label Safety Extension: up to 2 years	Intervention - OCA 25 mg - OCA 10 mg Comparator - Placebo **all participants were on OL background atorvastatin*	- Ages 18-85 years - Biopsy confirmed NASH - Histologic evidence of fibrosis (stages 1-4) without hepatic decompensation - On stable anti-diabetic medication if subject has Type 2 Diabetes Mellitus - Either not taking or on stable doses of TZDs and/or Vitamin E for ≥6 months prior to day 1	- Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to Screening Visit 1 - LDL cholesterol ≥190 mg/dL and on statin therapy at Screening - LDL cholesterol >200 mg/dL in subjects who are not on statin therapy, or in statin washout subjects - Total bilirubin ≥2x ULN; Creatine phosphokinase >5x ULN; Serum creatinine ≥1.5 mg/dL; ALT >300 U/L - Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures - History of biliary diversion - Uncontrolled diabetes within 60 days prior to randomization - Acute cholecystitis or acute biliary obstruction

Trial & Author	Design & Duration of Follow-up	Interventions	Inclusion Criteria	Exclusion Criteria
				- HIV infection - Known substance abuse in the year before Screening - Evidence of other forms of chronic liver disease - History of liver transplant, current placement on a liver transplant list, or current MELD score >12 - Presence of hepatic decompensation - Subjects with recent history of CVD or with history or planned cardiovascular interventions to treat atherosclerotic CVD - Previous exposure to OCA - Participation in a clinical research study with any investigational product in the 6 months
Mudaliar 2013[32] **Clinicaltrials.gov 2012[83]**	Phase 2, Randomized, Double-blind, Placebo controlled, Multicenter N: 64 Follow-up 6 weeks	Intervention - OCA 50 mg - OCA 25 mg Comparator - Placebo	- Ages 18-75 years - Type 2 Diabetes Mellitus - Presumed NAFLD findings shown on prior biopsy (in the last 5 years)	- Bilirubin >2 × ULN - ALT >155 U/L for females and >185 U/L for males - AST >155 U/L for females and >200 U/L for males - Patients taking any antidiabetic medications, except for metformin and sulfonylureas
Pioglitazone (PIO)				
Cusi 2016[41] **Bril 2018[34]**	Phase 4, Randomized, Double-Blind, Single-center, Placebo-controlled N: 101	Intervention - PIO 45 mg Comparator - Placebo **both groups were on hypocaloric diet*	- Ages 18-70 years - Biopsy confirmed NASH diagnosis within past 6 months Participants must have the following laboratory values: - Hemoglobin ≥ 12 gm/dl in males, or ≥ 11 gm/dl in females	- Any cause of chronic liver disease other than NASH - Any clinical evidence or history of ascitis, bleeding varices, or spontaneous encephalopathy - Current history of alcohol abuse - Prior surgical procedures to include gastroplasty, jejuno-ileal or jejunocolic bypass - Prior exposure to organic solvents

Trial & Author	Design & Duration of Follow-up	Interventions	Inclusion Criteria	Exclusion Criteria
	Follow-Up - Run-in Phase: 1 month (mean duration) - Double-blind, randomized Phase: 18 months - Open label: 18 months		- WBC count ≥ 3,000/mm3 - Neutrophil count ≥ 1,500/mm3 - Platelets ≥ 100,000/mm3, Albumin ≥3.0 g/dl - Serum creatinine ≤ 1.8 mg/dl - Creatinine phosphokinase ≤ 2 x ULN - AST and ALT ≤ 3.0x ULN - Alkaline phosphatase ≤ 2.5x ULN	- Subjects with Type 1 Diabetes Mellitus - Patients on chronic medications with known adverse effects on glucose tolerance levels unless the patient has been on a stable dose of such agents for 4 weeks before study - Patients with a history of clinically significant heart disease, peripheral vascular disease, or diagnosed pulmonary disease - Patients with severe osteoporosis
PIVENS **Sanyal 2010[37]** **Clinicaltrials.gov 2012[84]**	Phase 3, Randomized, Double-Blind N: 247 Follow-up 96 weeks	Intervention - PIO 30 mg - Vitamin E 800 IU Comparator - Placebo	- Ages 18 years and older - Histologic evidence of NASH based on a liver biopsy obtained within 6 months of randomization	- Alcohol consumption of more than 20g per day for women and more than 30g per day form men for at least 3 consecutive months during the previous 5 years - Cirrhosis, hepatitis C or other liver diseases - Heart failure - Diabetes
Belfort 2006[43]	Phase 4, Randomized, Double-Blind, parallel assignment N: 55 Follow-up - 4 weeks run-in period - 6 months double-blind	Intervention - Months 1 -2: PIO 30 mg - Months 3-6: 45 mg Comparator - Placebo **both groups were on hypocaloric diet*	- Ages 21 - 70 years - NASH confirmed by liver biopsy - Subjects must meet the criteria for impaired glucose tolerance or Type 2 Diabetes Mellitus - Diabetic patients will be allowed to be on sulfonylureas or repaglinide but not on metformin, a thiazolidinedione or insulin All participants must have the following laboratory values: - Hemoglobin ≥ 13 gm/dL in males, or ≥ 12 gm/dL in females - WBC count ≥ 3,000/mm3 - Neutrophil count ≥ 1,500/mm3	- Any cause of chronic liver disease other than NASH - Any clinical evidence or history of ascitis, bleeding varices, or spontaneous encephalopathy - Past (for at least for 1 year) or current history of alcohol abuse - Prior surgical procedures to include gastroplasty, jejuno-ileal or jejunocolic bypass - Diabetics with a fasting plasma glucose level greater than 260 mg/dL on initial visit - Diabetics who are taking metformin, a thiazolidinedione or insulin - Subjects with Type 1 Diabetes Mellitus

Trial & Author	Design & Duration of Follow-up	Interventions	Inclusion Criteria	Exclusion Criteria
			- Platelets ≥ 100,000/mm3 - Prothrombin time within 3 seconds of control - Albumin ≥3.0 g/dl, Serum creatinine ≤ 1.6 mg/dl - Creatinine phosphokinase ≤ 2x ULN - AST or ALT ≤ 2.5x ULN - Alkaline phosphatase ≤ 2.5x ULN	- Patients on chronic medications with known adverse effects on glucose tolerance levels - Patients with a history of clinically significant heart disease
Aithal 2008[44]	Phase 2, Randomized, Double-Blind, Placebo-controlled N: 74 Follow-up - 3 months run-in period - 12 months DB randomized	Intervention - PIO 30 mg Comparator - Placebo **both groups were on standard diet and exercise*	- Ages 18-70 years - Biopsy confirmed NASH - Lipid lowering drugs if stable for at least 3 months	- History of excessive alcohol consumption - Liver diseases other than NASH - Use of drugs associated with fatty liver disease, weight loss medication - Patients diagnosed with Diabetes Mellitus - Current or previous heart failure - Renal impairment
Anushiravani 2019[85]	Randomized, Double-blinded, Placebo-controlled trial N: 150 Follow-Up 3 months	Interventions* - PIO 15 mg - Vitamin E 400 IU - Metformin - Silymarin Comparator - Placebo	- Ages 18-65 years - Probable NAFLD diagnosis - With or without increased AST or ALT levels	- Secondary causes of hepatic steatosis - History of alcohol consumption - Diabetes Mellitus - Chronic liver disease - Patients with positive results for tests of autoimmune hepatitis and virus markers
Yan 2015[86]	Randomized, parallel controlled, open-label clinical trial	Intervention - LSI + PIO 15 mg	- Impaired glucose tolerance - T2DM duration < 1 year	- Alcohol consumption ≥10 g/d for women and ≥20 g/d for men - Hepatitis B or C, or other liver diseases - Severe metabolic abnormalities

Trial & Author	Design & Duration of Follow-up	Interventions	Inclusion Criteria	Exclusion Criteria
	N: 184 Follow-Up 16 weeks	Comparator - LSI		- Organ dysfunction - Treatment with the following drugs within 4 weeks of study enrollment: hypoglycemic or lipid-regulating drugs, the drugs that may impact hepatic fat content and Chinese herbs
Bril 2019[42]	Multicenter, parallel-group, double-blind, randomized, placebo-controlled trial N: 105 Follow-Up 18 months	Intervention - PIO 45 mg + Vitamin E 400 IU - Vitamin E 400 IU Comparator - Placebo	- Diagnosis of Type 2 Diabetes Mellitus - Histologically confirmed NASH	- Use of thiazolidinediones, glucagon-like peptide 1 agonists, sodium–glucose cotransporter 2 inhibitors, or vitamin E - Other etiologies of liver disease - Drugs that can produce hepatic steatosis - Type 1 Diabetes Mellitus - Severe heart, pulmonary, or renal disease

*: only PIO, Vitamin E and PBO abstracted

ALT: Alanine Aminotransferase, AST: Aspertate Aminotransferase, BMI: body mass index, CVD: cardiovascular disease, dL: deciliter, HbA1c: Hemoglobin A1c, HIV: Human Immunodeficiency Virus, IND: investigational new drug, INR: International Normalized Ratio, IU: international unit, MELD: model for end-stage liver disease, mg: milligram, N: total number, NAFLD: Non-Alcoholic Fatty Liver Disease, NASH: Non-Alcoholic Steatohepatitis, TZD: Thiazolidinediones, ULN: upper limit of normal, U/L: units per liter, WBC: white blood cell

Table D2. Baseline Characteristics I

Trial	Arms	N	Male, n (%)	Age, mean years (SD)	T2DM, n (%)	BMI, mean kg/m2 (SD)	Weight, mean kg (SD)	LDL Cholesterol, mg/dL
Obeticholic Acid (OCA)								
REGENERATE **Younossi 2019[6]**	OCA 25 mg	308	133 (43.2)	55 (11)	171 (55.5)	NR	95.4 (19.5)	113.3 (38.8)
	OCA 10 mg	312	135 (43.3)	55 (11)	171 (54.8)	NR	95.2 (19.1)	113.8 (38.4)
	Placebo	311	124 (39.9)	56 (12)	175 (56.3)	NR	95.3 (19.0)	114.8 (38.2)
FLINT **Neuschwander-Tetri 2015[30]** **Clinicaltrials.gov 2015[81]** **Hameed 2018[80]**	OCA 25 mg	141	43 (30.5)	52 (11)	75.0 (53.0)	35.0 (7.0)	100.0 (23.0)	2.9 (1.0) mmol/L
	Placebo	142	53 (37.3)	51 (12)	74.0 (52.0)	34.0 (6.0)	96.0 (18.0)	2.9 (1.1) mmol/L
CONTROL **Pockros 2019[31]** **Clinicaltrials.gov 215[82]**	OCA 25 mg	22	12 (54.5)	62.2 (11.1)	9 (40.9)	33.7 (5.4)	NR	125.2 (36.3)
	OCA 10 mg	21	9 (42.9)	57.1 (11.6)	8 (38.1)	34.0 (6.6)	NR	119.3 (36.4)
	Placebo	21	8 (38.1)	59.8 (9.9)	10 (47.6)	33.6 (6.7)	NR	117.5 (42.2)
Mudaliar 2013[32]	OCA 50 mg	21	9 (42.9)	50.5 (10.8)	21 (100)	36.5 (7.9)	106.4 (25.1)	NR
	OCA 25 mg	20	14 (70.0)	52.7 (8.7)	20 (100)	36.5 (6.2)	108.6 (23.0)	NR
	Placebo	23	10 (43.5)	53.1 (12.1)	23 (100)	36.1 (7.4)	104.2 (25.6)	NR
Pioglitazone (PIO)								
Cusi 2016[41]	PIO 45 mg	50	36 (72.0)	52 (10)	24 (48.0)	34.3 (4.8)	98.2 (16.5)	109 (44)
	Placebo	51	35 (68.6)	49 (11)	28 (54.9)	34.5 (4.8)	99.2 (17.0)	109 (33)
Bril 2018[34]	Prediabetes	49	34 (69.0)	47 (12)	NR	34.4 (4.1)	100.0 (16.8)	NR
	T2DM	52	37 (71.0)	54 (8)	NR	34.4 (5.4)	97.5 (16.6)	NR
PIVENS **Sanyal 2010[37]** **Clinicaltrials.gov 2012[84]**	PIO 30 mg	80	33 (41.2)	47.0 (12.6)	0 (0)*	34 (6)	97 (23)	120 (31)
	Vitamin E 800 IU	84	32 (38.1)	46.6 (12.1)	0 (0)*	34 (7)	94 (24)	119 (35)
	Placebo	83	35 (42.2)	45.4 (11.2)	0 (0)*	35 (7)	99 (21)	125 (35)
Belfort 2006[43]	PIO 45 mg	26	14 (53.8)	51 (7)	NR	33.5 (4.9)	93.7 (18.1)	118 (31)

Trial	Arms	N	Male, n (%)	Age, mean years (SD)	T2DM, n (%)	BMI, mean kg/m2 (SD)	Weight, mean kg (SD)	LDL Cholesterol, mg/dL
	Placebo	21	7 (33.3)	51 (10)	NR	32.9 (4.4)	90.2 (15.4)	117 (37)
Aithal 2008[44]	PIO 30 mg	37	19 (51.4)	52 (Range: 28-71)	0 (0)	29.8 (3.0)	88.6 (10.7)	3.3 (1.0) mmol/L
	Placebo	37	26 (70.2)	55 (Range: 27-73)	0 (0)	30.8 (4.1)	92.8 (21.1)	3.4 (1.1) mmol/L
Anushiravani 2019[85]	PIO 15 mg	30	NR	NR	NR	25.1 (3.7)	NR	113.7 (34.3)
	Vitamin E 400 IU	30	NR	NR	NR	26.1 (3.5)	NR	106.1 (39.3)
	Placebo	30	NR	NR	NR	26.1 (3.1)	NR	131.2 (48.8)
Yan 2015[86]	PIO 15 mg + LSI	60	28	53.5 (8.6)	NR	27.47 (3.74)	74.98 (12.73)	3.25 (0.94) mmol/L
	LSI	62	32	50.6 (10.7)	NR	27.27 (2.80)	75.73 (11.13)	2.91 (0.68) mmol/L
Bril 2019[42]	PIO 45 mg + Vitamin E 400 IU	37	30 (81.1)	60 (6)	37 (100)	35.2 (4.3)	107.4 (3.1)†	91 (44)
	Vitamin E 400 IU	36	33 (91.7)	60 (9)	36 (100)	33.8 (4.6)	102.8 (2.8)†	98 (39)
	Placebo	32	30 (93.8)	57 (11)	30 (100)	33.6 (4.0)	104.3(2.9)†	94 (33)

* Assumption made based on study protocol, † numbers are digitized and should be interpreted with caution

BMI: body mass index, IU: international unit, kg: kilogram, LDL: Low-density lipoprotein, LSI: lifestyle intervention, mg: milligram, mmol/L: millimole per deciliter, N: total number, n: number, T2DM: Type 2 Diabetes Mellitus, SD: standard deviation

Table D3. Baseline Characteristics II

Trial	Arms	N	Fibrosis Stage, n (%)					NAS (NAFLD activity score)			NAS Parameters, mean score (SD)			
			mean (SD)	Stage 1	Stage 2	Stage 3	Stage 4	mean (SD)	NAS<6, n (%)	NAS≥6, n (%)	Hepatocellular Ballooning	Lobular Inflammation	Portal Inflammation	Steatosis
Obeticholic Acid (OCA)														
REGENERATE Younossi 2019[6]	OCA 25 mg	308	NR	0 (0)*	139 (45.1)	169 (54.9)	0 (0)*	NR	100 (32.5)	208 (67.5)	NR			
	OCA 10 mg	312	NR	0 (0)*	130 (41.7)	182 (58.3)	0 (0)*	NR	101 (32.4)	211 (67.6)	NR			
	Placebo	311	NR	0 (0)*	142 (45.7)	169 (54.3)	0 (0)*	NR	94/309 (30.4)	215/309 (69.6)	NR			
FLINT Neuschwander-Tetri 2015[30] Hameed 2018[80] Clinicaltrials.gov 2015[81]	OCA 25 mg	141	1.9 (1.1)	NR		63/282 (22.3)	2/282 (<1.0)	5.3 (1.3)	NR		1.4 (0.7)	1.8 (0.7)	1.2 (0.6)	2.1 (0.8)
	Placebo	142	1.8 (1.0)	NR				5.1 (1.3)	NR		1.3 (0.7)	1.8 (0.7)	1.1 (0.6)	2.0 (0.8)
CONTROL Pockros 2019[31] Clinicaltrials.gov 2015[82]	OCA 25 mg	22	NR	7 (31.8)	4 (18.2)	4 (18.2)	7 (31.8)	NR	14 (63.6)	8 (36.4)	NR			
	OCA 10 mg	21	NR	3 (14.3)	7 (33.3)	4 (19.0)	7 (33.3)	NR	12 (57.1)	9 (42.9)	NR			
	Placebo	21	NR	4 (19.0)	6 (28.6)	7 (33.3)	4 (19.0)	NR	11 (52.4)	10 (47.1)	NR			
Mudaliar 2013[32] Clinicaltrials.gov 2012[83]	OCA 50 mg	21	NR					NR			NR			
	OCA 25 mg	20	NR					NR			NR			
	Placebo	23	NR					NR			NR			
Pioglitazone (PIO)														
Cusi 2016[41]	PIO 45 mg	50	1.1 (1.1)	22 (44.0)	6 (12.0)	7 (14.0)		4.5 (1.5)	NR		0.8 (0.4)	1.7 (0.6)	NR	2.0 (0.8)
	Placebo	51	0.9 (0.9)	22 (43.1)	4 (7.8)	5 (9.8)		4.5 (1.2)	NR		0.9 (0.4)	1.7 (0.5)	NR	1.9 (0.8)
Bril 2018[34]	Prediabetes	49	0.8 (0.9)	NR				4.3 (1.4)	NR		0.8 (0.4)	1.5 (0.5)	NR	1.9 (0.9)

Trial	Arms	N	Fibrosis Stage, n (%)					NAS (NAFLD activity score)			NAS Parameters, mean score (SD)			
			mean (SD)	Stage 1	Stage 2	Stage 3	Stage 4	mean (SD)	NAS<6, n (%)	NAS≥6, n (%)	Hepatocellular Ballooning	Lobular Inflammation	Portal Inflammation	Steatosis
	T2DM	52	1.2 (1.1)	NR				4.7 (1.3)	NR		0.9 (0.4)	1.8 (0.5)	NR	2.0 (0.7)
PIVENS Sanyal 2010[37] Clinicaltrials.gov 2012[87]	PIO 30 mg	80	1.4 (0.9)	35 (43.8)	19 (23.8)	11 (13.8)	1 (1.2)	5.0 (1.4)	52 (64.4)	28 (35.6)	1.1 (0.8)	1.8 (0.7)	NR	2.0 (0.8)
	Vitamin E 800 IU	84	1.5 (1.0)	32 (38.1)	18 (21.7)	17 (20.5)	1 (1.2)	5.1 (1.4)	50 (59.6)	34 (40.4)	1.3 (0.8)	1.8 (0.7)	NR	1.9 (0.9)
	Placebo	83	1.6 (1.1)	24 (28.9)	23 (27.7)	16 (19.3)	3 (3.6)	4.8 (1.4)	55 (66.3)	28 (33.7)	1.3 (0.7)	1.6 (0.7)	NR	1.9 (0.8)
Belfort 2006[43]	PIO 45 mg	26	1.6 (0.2)†	12 (46.2)	5 (19.2)	7 (26.9)	0 (0)	NR			NR	1.7 (0.1)†	NR	2.3 (0.2)†
	Placebo	21	1.1 (0.2)†	9 (42.8)	4 (19.0)	2 (9.5)	0 (0)	NR			NR	1.7 (0.1)†	NR	2.1 (0.3)†
Aithal 2008[44]	PIO 30 mg	37	NR	2 (6.5)	14 (45.2)	5 (16.1)	2 (6.5)	NR			NR			
	Placebo	37	NR	2 (6.7)	12 (40.0)	7 (23.3)	4 (13.3)	NR			NR			
Anushiravani 2019[85]	PIO 15 mg	30	NR					NR			NR			
	Vitamin E 400 IU	30	NR					NR			NR			
	Placebo	30	NR					NR			NR			
Yan 2015[86]	PIO 15 mg + LSI	60	NR					NR			NR			
	LSI	62	NR					NR			NR			
Bril 2019[42]	PIO 45 mg + Vitamin E 400 IU	37	1.4 (1.1)	NR				3.7 (1.3)	NR		0.7 (0.6)	1.4 (0.5)	NR	1.6 (0.8)
	Vitamin E 400 IU	36	1.6 (1.2)	NR				3.9 (1.6)	NR		0.9 (0.8)	1.3 (0.5)	NR	1.7 (0.8)
	Placebo	32	1.5 (1.0)	NR				4.2 (1.6)	NR		0.9 (0.8)	1.6 (0.6)	NR	1.8 (0.7)

* Assumption made based on study protocol, † numbers are digitized and should be interpreted with caution: international unit, mg: milligram, N: total number, n: number, NAFLD: Non-alcoholic Fatty Liver Disease, NR: not reported, T2DM: Type 2 Diabetes Mellitus, SD: standard deviation

Table D4. Baseline Characteristics III

Trial	Arms	N	Laboratory parameters, mean U/L (SD)			Concomitant Medication Use, n (%)			
			ALT	AST	Total Bilirubin	Lipid Lowering / Statins	Antidiabetic Medication / TZD	Pioglitazone	Vitamin E
Obeticholic Acid (OCA)									
REGENERATE **Younossi 2019[6]**	OCA 25 mg	308	80.2 (56.4)	57.0 (34.1)	0.7 (0.3) mg/dL	160 (51.9) / 127 (41.2)	159 (51.1) / 4 (1.3)	NR	32 (10.4)
	OCA 10 mg	312	75.6 (47.0)	56.6 (34.0)	0.7 (0.3) mg/dL	170 (54.5) / 142 (45.5)	171 (54.8) / 9 (2.9)	NR	34 (10.9)
	Placebo	311	79.6 (56.6)	58.9 (40.5)	0.6 (0.3) mg/dL	175 (56.7) / 144 (46.3)	167 (54.2) / 5 (1.6)	NR	42 (13.5)
FLINT **Neuschwander-Tetri 2015[30]** **Hameed 2018[80]** **Clinicaltrials.gov 2015[81]**	OCA 25 mg	141	83 (49)	64 (38)	11.5 (5.9)	72 (51.1) / NR	67 (47.5) / 3 (2.1)	1 (0.7)	29 (20.6)
	Placebo	142	82 (51)	58 (34)	11.3 (7.5)	64 (45.1) / NR	73 (51.4) / 5 (3.5)	6 (4.2)	32 (22.5)
CONTROL **Pockros 2019[31]** **Clinicaltraisl.gov 2015[82]**	OCA 25 mg	22	58.3 (47.1)†	53.5 (19.1)†	0.8 (0.3) mg/dL†	NR			
	OCA 10 mg	21	60.8 (36.1)†	48.4 (28.8)†	0.9 (0.7) mg/dL†	NR			
	Placebo	21	79.5 (59.3)†	60.3 (57.0)†	0.7 (0.4) mg/dL†	NR			
Mudaliar 2013[32] **Clinicaltrials.gov 2012[83]**	OCA 50 mg	21	NR			NR			
	OCA 25 mg	20	NR			NR			
	Placebo	23	NR			NR			
Pioglitazone (PIO)									
Cusi 2016[41]	PIO 45mg	50	62 (33)	47 (21)	NR	NR / 19 (38.0)	NR / 0 (0)*	0 (0)	0 (0)*
	Placebo	51	57 (33)	43 (22)	NR	NR / 19 (37.3)	NR / 0 (0)*	0 (0)	0 (0)*
Bril 2018[34]	Prediabetes	49	66 (30)	44 (18)	NR	NR			
	T2DM	52	71 (47)	53 (35)	NR	NR			
PIVENS	PIO 30 mg	80	82 (45)	54 (26)	0.8 (0.4) mg/dL	0 (0)*	0 (0)*	0 (0)*	0 (0)*

Trial	Arms	N	Laboratory parameters, mean U/L (SD)			Concomitant Medication Use, n (%)			
			ALT	AST	Total Bilirubin	Lipid Lowering / Statins	Antidiabetic Medication / TZD	Pioglitazone	Vitamin E
Sanyal 2010[37] Clinicaltrials.gov 2012[84]	Vitamin E 800 IU	84	86 (52)	59 (33)	0.8 (0.4) mg/dL	0 (0)*	0 (0)*	0 (0)*	0 (0)*
	Placebo	83	81 (48)	55 (30)	0.8 (0.4) mg/dL	0 (0)*	0 (0)*	0 (0)*	0 (0)*
Belfort 2006[43]	PIO 45 mg	26	67 (26)	47 (15)	NR	NR	NR / 0 (0)*	0 (0)*	NR
	Placebo	21	61 (33)	42 (16)	NR	NR	NR / 0 (0)*	0 (0)*	NR
Aithal 2008[44]	PIO 30 mg	37	93.6 (61.3)	NR	11.7 (5.3) µmol/L	NR	0 (0)	0 (0)*	NR
	Placebo	37	84.1 (37.7)	NR	13.6 (7.4) µmol/L	NR	0 (0)	0 (0)*	NR
Anushiravani 2019[85]	PIO 15 mg	30	30.2 (18.1)	23.3 (11.1)	NR	NR / 0 (0)	NR	0 (0)*	0 (0)*
	Vitamin E 400 IU	30	23.3 (14.2)	19.4 (7.8)	NR	NR / 0 (0)	NR	0 (0)*	0 (0)*
	Placebo	30	22.8 (15.9)	19.6 (11.7)	NR	NR / 0 (0)	NR	0 (0)*	0 (0)*
Yan 2015[86]	PIO 15 mg + LSI	60	41‡ (IQR: 26-65)	28(20–43)	NR	NR	NR	0 (0)	NR
	LSI	62	34‡ (IQR: 20-54)	25(20–30)	NR	NR	NR	0 (0)	NR
Bril 2019[42]	PIO 45 mg + Vitamin E 400 IU	37	40 (25)	32 (18)	NR	NR / 29 (78.4)	0 (0)*	0 (0)*	0 (0)*
	Vitamin E 400 IU	36	53 (32)	41 (22)	NR	NR / 26 (72.3)	0 (0)*	0 (0)*	0 (0)*
	Placebo	32	53 (33)	40 (23)	NR	NR / 25 (78.2)	0 (0)*	0 (0)*	0 (0)*

* Assumption made based on study protocol, † numbers are digitized and should be interpreted with caution, ‡medianALT: Alanine aminotransferase, AST: Aspartate aminotransferase, IQR: interquartile range, IU: international unit, LSI: lifestyle intervention, mg: milligram, mg/dL: milligram per deciliter, N: total number, n: number, NR: not reported, SD: standard deviation, TZD: Thiazolidinediones, U/L: units per liter

Table D5. Patient Reported Outcomes at Baseline

Trial	Arms	N	Patient Reported Outcomes					
			SF-36 (PCS), mean score (SD)	SF (MCS), mean score (SD)	EQ-5D Utility Score (SD)	CLDQ-NASH total score	NASH-related work productivity impairment	NASH-related activity impairment
Obeticholic Acid (OCA)								
REGENERATE Younossi 2019[6] Younossi 2019[33]	OCA 25 mg	308	NR	NR	0.81 (0.17)	5.16 (1.13)	0.16	0.251
	OCA 10 mg	312	NR	NR				
	Placebo	311	NR	NR				
FLINT Neuschwander-Tetri 2015[30]	OCA 25 mg	141	45 (11)	48 (12)	NR	NR	NR	NR
	Placebo	142	44 (11)	48 (12)	NR	NR	NR	NR
Pioglitazone (PIO)								
PIVENS Sanyal 2010[37]	PIO 30 mg	80	49 (9)	49 (8)	NR	NR	NR	NR
	Vitamin E 800 IU	84	49 (10)	49 (10)	NR	NR	NR	NR
	Placebo	83	47 (11)	47 (12)	NR	NR	NR	NR

CLDQ-NASH: chronic liver disease questionnaire – NASH, EQ-5D: EuroQol five dimension scale, IU: international units, MCS: mental component summary, mg: milligram, N: total number, n: number, NASH: non-alcohol steatohepatitis, NR: not reported, PCS: Physical component summary, SD: standard deviation, SF-36: 36-item short form survey

Table D6. Efficacy Outcomes I

Trial	Follow-Up	Arms	N	Fibrosis			NASH Resolution		NAS		
				Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value	n (%)	RR (95% CI), p-value	Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value
Obeticholic Acid (OCA)											
REGENERATE **Younossi 2019[6]**	18 months	OCA 25 mg (ITT)	308	NR	71 (23.1)	1.9 (1.4, 2.8), p=0.0002	36 (11.7)	1.5 (0.9, 2.4), p=0.13	NR	112 (36.4)	1.5 (1.2, 1.9), p=0.0012
		OCA 10 mg (ITT)	312	NR	55 (17.6)	1.5 (1.0, 2.2), p=0.045	35 (11.2)	1.4 (0.9, 2.3), p=0.18	NR	94 (30.1)	1.2 (1.0, 1.6), p=0.11
		Placebo (ITT)	311	NR	37 (11.9)	---	25 (8.0)	---	NR	76 (24.4)	---
	18 months	OCA 25 mg (ITT + Stage 1)	404	NR	85 (21.0)	NR, p<0.0001	60 (14.9)	NR, p=0.0013	NR		
		OCA 10 mg (ITT + Stage 1)	407	NR	64 (15.7)	NR, p=0.03	46 (11.3)	NR, p=0.09	NR		
		Placebo (ITT + Stage 1)	407	NR	43 (10.6)	---	32 (7.9)	---	NR		
	18 months	OCA 25 mg (pP)	218	NR	60 (28.0)	2.2 (1.4, 3.2), p<0.0001	31 (14.0)	1.4 (0.9, 2.3), p=0.18	NR	96 (44.0)	1.4 (1.1, 1.8), p=0.004
		OCA 10 mg (pP)	226	NR	47 (21.0)	1.6 (1.1, 2.5), p=0.025	34 (15.0)	1.5 (0.9, 2.4), p=011	NR	82 (36.3)	1.2 (0.9, 1.5), p=0.19
		Placebo (pP)	224	NR	29 (13.0)	---	23 (10.0)	---	NR	69 (30.8)	---
FLINT **Neuschwander-Tetri 2015[30]**	72 weeks (≈18 months)	OCA 25 mg	102	-0.2 (1.0), p=0.01	36 (35.3)	1.8 (1.1, 2.7), p=0.004	22 (21.6)*	1.5 (0.9, 2.6), p=0.08	-1.7 (1.8), p<0.0001	50/110 (45.5)	1.9 (1.3, 2.8), p=0.0002
		Placebo	98	-0.1 (0.9)	19 (19.3)		13 (13.3)*		-0.7 (1.8)	23/109 (21.1)	
	96 weeks (≈24 months)	OCA 25 mg	122	NR			NR		NR		
		Placebo	120	NR			NR		NR		

Trial	Follow-Up	Arms	N	Fibrosis			NASH Resolution		NAS		
				Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value	n (%)	RR (95% CI), p-value	Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value
FLINT sub-group analysis Hameed 2018[80]	72 weeks (≈18 months)	OCA ≥2% Weight Loss	45	-0.3 (NR), p=0.2**	NR		10 (22.0)	NR, p=0.89	-2.4 (NR), p<0.001**	NR	
		OCA <2% Weight Loss	57	-0.1 (NR)	NR		12 (21.0)		-1.2 (NR)	NR	
		Placebo ≥2% Weight Loss	31	0.2 (NR), p=0.51††	NR		4 (13.0)	NR, p=0.94	-1.2 (NR), p=0.29††	NR	
		Placebo <2% Weight Loss	67	0.1 (NR)	NR		9 (13.0)		-0.5 (NR)	NR	
CONTROL Pockros 2019[31]	16 weeks	OCA 25 mg	22	NR			NR		NR		
		OCA 10 mg	21	NR			NR		NR		
		Placebo	21	NR			NR		NR		
Mudaliar 2013[32]	6 weeks	OCA 50 mg	21	NR			NR		NR		
		OCA 25 mg	20	NR			NR		NR		
		Placebo	23	NR			NR		NR		
Pioglitazone (PIO)											
Cusi 2016[41]	18 months	PIO 45 mg	50	−0.5 (1.0), p=0.039	20 (40.0), p=0.13		26 (52.0)	NR, p<0.001	NR	29 (58.0)	NR, p<0.001
		Placebo	51	0 (1.2)	13 (25.5)		10 (19.6)	---	NR	9 (17.6)	
	36 months	PIO 45 mg	34	0 (95%CI: -0.2, 0.3), p=0.80	NR		19 (55.9)	NR, p=0.96	0.1 (95%CI: -0.4, 0.6), p=0.70	NR	
Bril 2018[34]	18 months	PIO - prediabetes	21	-0.4 (0.7), p=0.86‡	NR		11 (55.0)	NR	-2.2 (2.1), NR	13 (60.0)	NR
		Placebo - prediabetes	17	-0.2†; NR	NR		6 (29.0)	NR	NR	2 (12.0)	NR
		PIO - T2DM	20	-0.4 (0.8)	NR		12 (60.0)	NR	-2.6 (1.7), NR	14 (70.0)	NR
		Placebo - T2DM	25	0.1†, NR	NR		10 (16.0)	NR	NR	6 (24.0)	NR
	36 months	PIO - prediabetes	16	-0.4 (0.6), p=0.92‡	NR		NR		-2.6 (1.6); p=0.57	NR	NR
		PIO - T2DM	18	-0.4 (1.1)	NR		NR		-2.3 (1.5)	NR	NR

Trial	Follow-Up	Arms	N	Fibrosis			NASH Resolution		NAS		
				Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value	n (%)	RR (95% CI), p-value	Mean Change (SD), p-value	Improvement , n (%)	RR (95% CI), p-value
PIVENS Sanyal 2010[37]	96 weeks (≈24 months)	PIO 30 mg	80	-0.4 (NR), p=0.1; p=0.78#	35 (44.0)	p=0.12	38 (47.0)*	NR, p=0.001; p=0.19#	-1.9 (NR), p<0.001; p=0.27#	65 (81.0)	NR
		Vitamin E	84	-0.3 (NR), p=0.19	34 (41.0)	NR, p=0.24	30 (36)*	NR, p=0.05	-1.9 (NR), p<0.001	63 (75)	NR
		Placebo	83	-0.1 (NR)	26 (31.0)	---	17 (21)*	---	-0.5 (NR)	42 (50.0)	NR
Belfort 2006[43]	6 months	PIO 45 mg	26	-0.6†, p=0.08	12 (46.0)	NR, p=0.08	NR		NR		
		Placebo	21	-0.2†	7 (33.0)		NR		NR		
Aithal 2008[44]	12 months	PIO 30 mg	31	NR	9 (29.0)	NR, p=0.05	NR		NR		
		Placebo	30	NR	6 (20.0)		NR		NR		
Anushiravani 2019[85]	3 months	PIO 15 mg	30	NR			N/A¤		NR		
		Vitamin E 400 IU	30	NR			N/A¤		NR		
		Placebo	30	NR			N/A¤		NR		
Yan 2015[86]	4 months	PIO 15 mg + LSI	47	NR			NR		NR		
		LSI	53	NR			NR		NR		
Bril 2019[42]	18 months	PIO 45 mg + Vitamin E 400 IU	37	-0.6 (0.9), p=0.22	19 (51.4)	NR, p=0.07	16 (43.2)	NR, p=0.005	NR	20 (54.1)	NR, p=0.003
		Vitamin E 400 IU	36	-0.6 (1.0), p=0.39	19 (52.8)	NR, p=0.09	12 (33.3)	NR, p=0.04	NR	11 (30.6)	NR, p=0.26
		Placebo	32	-0.3 (1.1)	10 (31.3)	---	4 (12.5)	---	NR	6 (18.8)	---

*Definite NASH, † numbers are digitized and should be interpreted with caution, ‡ versus PIO T2DM, # versus Vitamin E, ¤ patients had NAFLD, ** versus OCA <2% weight loss, †† versus placebo <2% weight loss

95%CI: 95% Confidence Interval, ITT: intention-to-treat, IU: international unit, mg: milligram, N: total number, n: number, N/A: not available, NASH: non-alcoholic steatohepatitis, NAS: NAFLD activity score, NR: not reported, pP: per protocol, RR: response ratio, SD: standard deviation, T2DM: type 2 diabetes mellitus

Table D7. Efficacy Outcomes II

Trial	Follow-Up	Arms	N	NAS Parameter Improvement					
				Hepatocellular Ballooning			Lobular Inflammation		
				Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value	Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value
Obeticholic Acid (OCA)									
REGENERATE **Younossi 2019[6]**	18 months	OCA 25 mg (ITT)	308	NR	108 (35.1)	1.5 (1.2, 2.0), p=0.0011	NR	136 (44.2)	1.2 (1.0, 1.5), p=0.032
		OCA 10 mg (ITT)	312	NR	85 (27.2)	1.2 (0.9, 1.5), p=0.24	NR	123 (39.4)	1.1 (0.9, 1.4), p=0.34
		Placebo (ITT)	311	NR	72 (23.2)	---	NR	111 (35.7)	---
	18 months	OCA 25 mg (ITT + Stage 1)	404	NR			NR		
		OCA 10 mg (ITT + Stage 1)	407	NR			NR		
		Placebo (ITT + Stage 1)	407	NR			NR		
	18 months	OCA 25 mg (pP)	218	NR	95 (43.6)	0.0008	NR	114 (52.3)	1.3 (1.0, 1.5), p=0.03
		OCA 10 mg (pP)	226	NR	77 (34.1)	0.19	NR	104 (46.0)	1.1 (0.9, 1.4), p=0.38
		Placebo (pP)	224	NR	64 (28.6)	---	NR	94 (42.0)	---
FLINT **Neuschwander-Tetri 2015[30]**	72 weeks (≈18 months)	OCA 25 mg	102	-0.5 (0.9), p=0.03	47 (46.1)	1.5 (1.0, 2.1), p=0.03	-0.5 (0.8), p=0.0006	54 (52.9)	1.6 (1.1, 2.2), p=0.0016
		Placebo	98	-0.2 (0.9)	30 (30.6)		-0.2 (0.9)	34 (34.7)	
	96 weeks (≈24 months)	OCA 25 mg	122	NR			NR		
		Placebo	120	NR			NR		
FLINT sub-group analysis		OCA ≥2% Weight Loss	45	-0.6 (NR), p=0.07*	NR		-0.7 (NR), p<0.001*	NR	

Trial	Follow-Up	Arms	N	NAS Parameter Improvement					
				Hepatocellular Ballooning			Lobular Inflammation		
				Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value	Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value
Hameed 2018[80]	72 weeks (≈18 months)	OCA <2% Weight Loss	57	-0.3 (NR)	NR		-0.3 (NR)	NR	
		Placebo ≥2% Weight Loss	31	-0.2 (NR), p=0.49‡	NR		-0.3 (NR), p=0.23‡	NR	
		Placebo <2% Weight Loss	67	-0.1 (NR)	NR		-0.1 (NR)	NR	
CONTROL **Pockros 2019[31]**	16 weeks (4 months)	OCA 25 mg	22	NR			NR		
		OCA 10 mg	21	NR			NR		
		Placebo	21	NR			NR		
Pioglitazone (PIO)									
Mudaliar 2013[32]	6 weeks	OCA 50 mg	21	NR			NR		
		OCA 25 mg	20	NR			NR		
		Placebo	23	NR			NR		
Cusi 2016[41]	18 months	PIO 45 mg	50	−0.6 (0.6), p=0.001	25 (50.0)	NR, p=0.004	−0.6 (0.9), p<0.001	25 (50.0)	NR, p=0.004
		Placebo	51	−0.2 (0.7)	12 (23.5)		−0.1 (0.8)	11 (21.6)	
	36 months	PIO 45 mg	34	0 (95%CI: -0.2, 0.2), p=0.99	NR		NR		
Bril 2018[34]	18 months	PIO - prediabetes	21	-0.6 (0.5), p=0.94#	NR		-0.5 (1.0), p=0.26#	NR	
		Placebo - prediabetes	17	-0.05†, NR	NR		NR		
		PIO - T2DM	20	-0.6 (0.5)	NR		-0.8 (0.7)	NR	
		Placebo - T2DM	25	-0.3†, NR	NR		NR		
	36 months	PIO - prediabetes	16	-0.6 (0.5), p=0.88	NR		NR		
		PIO - T2DM	18	-0.6 (0.6)	NR		NR		
PIVENS **Sanyal 2010[37]**	96 weeks (≈24 months)	PIO 30 mg	80	-0.4 (NR), p=0.01; p=0.59¤	35 (44.0)	NR, p=0.08	-0.7 (NR), p<0.001; p=0.59¤	48 (60.0)	NR, 0.004
		Vitamin E	84	-0.5 (NR), p=0.03	42 (50.0)	NR, p=0.01	-0.6 (NR), p=0.008	45 (54.0)	NR, 0.02
		Placebo	83	-0.2 (NR)	24 (29.0)	---	-0.2 (NR)	29 (35.0)	---
Belfort 2006[43]	6 months	PIO 45 mg	26	NR			-0.7†, p=0.008	17 (65.0)	NR, 0.008

Trial	Follow-Up	Arms	N	NAS Parameter Improvement					
				Hepatocellular Ballooning			Lobular Inflammation		
				Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value	Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value
		Placebo	21	NR			-0.3†	6 (29.0)	
Aithal 2008[44]	12 months	PIO 30 mg	31	NR			NR	14/31 (45.2)	NR, p=0.25
		Placebo	30	NR			NR	8/30 (26.7)	
Anushiravani 2019[85]	3 months	PIO 15 mg	30	NR			NR		
		Vitamin E 400 IU	30	NR			NR		
		Placebo	30	NR			NR		
Yan 2015[86]	16 weeks (4 months)	PIO 15 mg + LSI	47	NR			NR		
		LSI	53	NR			NR		
Bril 2019[42]	18 months	PIO 45 mg + Vitamin E 400 IU	37	-0.6 (0.9), p=0.022	23 (62.2)	NR, p=0.03	-0.6 (0.7), p=0.018	25 (67.6)	NR, p=0.05
		Vitamin E 400 IU	36	-0.5 (0.9), p=0.1	18 (50.0)	NR, p=0.21	-0.4 (0.7), p=0.29	13 (36.1)	NR, p=0.54
		Placebo	32	-0.1 (0.9)	11 (34.4)	---	-0.2 (0.8)	14 (43.8)	---

* versus OCA <2% weight loss, † numbers are digitized and should be interpreted with caution, ‡ versus placebo <2% weight loss, # versus PIO T2DM, ¤ versus Vitamin E
95% CI: 95% Confidence Interval, ITT: intention to treat, IU: international units, mg: milligram, N: total number, n: number, NAS: NAFLD Activity Score, NR: not reported, pP: per-Protocol, RR: response ratio, SD: standard deviation, T2DM: Type 2 Diabetes Mellitus

Table D8. Efficacy Outcomes III

Trial	Follow-Up	Arms	N	NAS Parameter Improvement					
				Portal Inflammation			Steatosis		
				Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value	Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value
Obeticholic Acid (OCA)									
REGENERATE **Younossi 2019[6]**	18 months	OCA 25 mg (ITT)	308	NR			NR	127 (41.2)	1.1 (0.9, 1.3), p=0.40
		OCA 10 mg (ITT)	312	NR			NR	127 (40.7)	1.1 (0.9, 1.3), p=0.49
		Placebo (ITT)	311	NR			NR	118 (37.9)	---
	18 months	OCA 25 mg (ITT + Stage 1)	404	NR			NR		
		OCA 10 mg (ITT + Stage 1)	407	NR			NR		
		Placebo (ITT + Stage 1)	407	NR			NR		
	18 months	OCA 25 mg (pP)	218	NR			NR	113 (51.8)	1.2 (1.0, 1.5), p=0.072
		OCA 10 mg (pP)	226	NR			NR	108 (47.8)	1.1 (0.9, 1.4), p=0.33
		Placebo (pP)	224	NR			NR	97 (43.3)	---
FLINT **Neuschwander-Tetri 2015[30]**	72 weeks (≈18 months)	OCA 25 mg	102	0.2 (0.7), p=0.59	12 (11.8)	1.0 (0.6, 1.7), p=0.9	-0.8 (1.0), p=0.0004	62 (60.8)	1.7 (1.2, 2.3), p=0.001
		Placebo	98	0.2 (0.7)	13 (13.3)		-0.4 (0.8)	37 (37.8)	
	96 weeks (≈24 months)	OCA 25 mg	122	NR			NR		
		Placebo	120	NR			NR		

Trial	Follow-Up	Arms	N	NAS Parameter Improvement					
				Portal Inflammation			Steatosis		
				Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value	Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value
FLINT sub-group analysis **Hameed 2018[80]**	72 weeks (≈18 months)	OCA ≥2% Weight Loss	45	0.2 (NR), p=0.91*	NR		-1.1 (NR), p<0.001*	NR	
		OCA <2% Weight Loss	57	0.2 (NR)	NR		-0.5 (NR), NR	NR	
		Placebo ≥2% Weight Loss	31	0.2 (NR), p=0.83‡	NR		-0.8 (NR), p<0.001‡	NR	
		Placebo <2% Weight Loss	67	0.1 (NR)	NR		-0.2 (NR), NR	NR	
CONTROL **Pockros 2019[31]**	16 weeks (4 months)	OCA 25mg	22	NR			NR		
		OCA 10mg	21	NR			NR		
		Placebo	21	NR			NR		
Mudaliar 2013[32]	6 weeks	OCA 50mg	21	NR			NR		
		OCA 25mg	20	NR			NR		
		Placebo	23	NR			NR		
Pioglitazone (PIO)									
Cusi 2016[41]	18 months	PIO 45mg	50	NR			−1.1 (1.0), p<0.001	35 (70.0)	NR, p<0.001
		Placebo	51	NR			−0.2 (0.8)	13 (25.5)	
	36 months	PIO 45mg	34	NR			0.2 (95%CI: -0.1, 0.5), p=0.184	NR	
Bril 2018[34]	18 months	PIO - prediabetes	21	NR			-1.1 (1.1), p=0.89#	NR	
		Placebo - prediabetes	17	NR			-0.2†, NR	NR	
		PIO - T2DM	20	NR			-1.1 (0.8)	NR	
		Placebo - T2DM	25	NR			-0.2†, NR	NR	

Trial	Follow-Up	Arms	N	NAS Parameter Improvement					
				Portal Inflammation			Steatosis		
				Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value	Mean Change (SD), p-value	Improvement, n (%)	RR (95% CI), p-value
	36 months	PIO - prediabetes	16	NR			-1.1 (1.1), p=0.48	NR	
		PIO - T2DM	18	NR			-0.9 (0.9)	NR	
PIVENS Sanyal 2010[37]	96 weeks (≈24 months)	PIO 30 mg	80	NR	13 (16.0)	NR	-0.8 (NR), p<0.001; p=0.41¤	55 (69.0)	NR, p<0.001
		Vitamin E 800 IU	84	NR	15 (18.0)	NR	-0.7 (NR), p<0.001	45 (54.0)	NR, p=0.005
		Placebo	83	NR	9 (11.0)	NR	-0.1 (NR)	26 (31.0)	---
Belfort 2006[43]	6 months	PIO 45 mg	26	NR	NR	NR	-1.1†, p=0.003	17 (65.0)	NR, p=0.003
		Placebo	21	NR	NR		-0.2†	8 (38.0)	
Aithal 2008[44]	12 months	PIO 30 mg	31	NR	8/31 (25.8)	NR, p=0.67	NR	15/31 (48.4)	NR, p=0.19
		Placebo	30	NR	7/30 (23.3)		NR	11/30 (36.7)	
Anushiravani 2019[85]	3 months	PIO 15 mg	30	NR			NR		
		Vitamin E 400 IU	30	NR			NR		
		Placebo	30	NR			NR		
Yan 2015[86]	16 weeks (4 months)	PIO 15 mg + LSI	47	NR			NR		
		LSI	53	NR			NR		
Bril 2019[42]	18 months	PIO 45 mg + Vitamin E 400 IU	37	NR			-1.3 (1.0), p<0.001	32 (86.4)	NR, p<0.001
		Vitamin E 400 IU	36	NR			-1.0 (1.0), p=0.018	24 (66.7)	NR, p=0.07
		Placebo	32	NR			-0.4 (0.9)	15 (46.9)	---

* versus OCA <2% weight loss, † numbers are digitized and should be interpreted with caution, ‡ versus placebo <2% weight loss, # versus PIO T2DM, ¤ versus Vitamin E
95%CI: 95% Confidence Interval, IU: international unit, LSI: lifestyle intervention, N: total number, n: number, NR: not reported, U/L: units per liter, SD: standard deviation

Table D9. Efficacy Outcomes IV

Trial	Follow-Up	Arms	N	ALT		AST		Bilirubin		LDL
				Normalization, n (%)	Change from Baseline, mean U/L (SD); p-value	Normalization, n (%)	Change from Baseline, mean U/L (SD); p-value	Normalization, n (%)	Change from Baseline, U/L (SD); p-value	Change from Baseline, mg/dL (SD); p-value
Obeticholic Acid (OCA)										
REGENERATE **Younossi 2019[6]**	18 months	OCA 25mg (ITT)	308	124/187 (66.3)	-36.0 (SE: 3.6), NR	109/224 (48.7)	-20.4 (SE: 2.3), NR	NR		6.6 (NR)*, NR
		OCA 10mg (ITT)	312	88/178 (49.4)	-23.8 (SE: 2.6), NR	95/227 (41.9)	-14.1 (SE: 2.1), NR	NR		1.6 (NR)*, NR
		Placebo (ITT)	311	65/181 (35.9)	-15.6 (SE: 3.3)	60/214 (28.0)	-9.8 (SE: 2.4)	NR		-7.9 (NR)*
		OCA 25mg (ITT + Stage 1)	404	NR		NR		NR		NR
		OCA 10mg (ITT + Stage 1)	407	NR		NR		NR		NR
		Placebo (ITT + Stage 1)	407	NR		NR		NR		NR
		OCA 25mg (pP)	218	86/131 (65.6)	NR	88/161 (54.7)	NR	NR		NR
		OCA 10mg (pP)	226	71/129 (55.0)	NR	74/165 (44.8)	NR	NR		NR
		Placebo (pP)	224	50/134 (37.3)	NR	46/157 (29.3)	NR	NR		NR
FLINT Neuschwander-Tetri 2015[30]	72 weeks (≈18 months)	OCA 25mg	102	NR	-38 (47), p<0.0001	NR	-27 (37), p=0.0001	NR	-1.0 (4.1) p=0.002	0.2 (0.9) mmol/L, p<0.0001

Trial	Follow-Up	Arms	N	ALT		AST		Bilirubin		LDL
				Normalization, n (%)	Change from Baseline, mean U/L (SD); p-value	Normalization, n (%)	Change from Baseline, mean U/L (SD); p-value	Normalization, n (%)	Change from Baseline, U/L (SD); p-value	Change from Baseline, mg/dL (SD); p-value
		Placebo	98	NR	-18 (44)	NR	-10 (31)	NR	0.6 (3.7)	-0.2 (0.8) mmol/L
	96 weeks (≈24 months)	OCA 25mg	122	NR	-27 (49), p=0.36	NR	-20 (39), p=0.24	NR	0.5 (4.6) mmol/L, p=0.66	-0.3 (0.9), P=0.86
		Placebo	120	NR	-21 (34)	NR	-11 (26)	NR	0.4 (3.7)	-0.3 (0.8)
FLINT sub-group analysis (Hameed 2017)	72 weeks (≈18 months)	OCA ≥2% Weight Loss	45	NR	-43 (NR), p=0.12	NR	-29, p=0.15	NR	-0.06 (NR), p=0.66	18 (NR), p=0.04
		OCA <2% Weight Loss	57	NR	-34 (NR), NR	NR	-23 (NR), NR	NR	-0.4 (NR), NR	4 (NR), NR
		Placebo ≥2% Weight Loss	31	NR	-29 (NR), p=0.02	NR	-14 (NR), p=0.14	NR	0.01 (NR), p=0.79	-12 (NR), p=0.01
		Placebo <2% Weight Loss	67	NR	-10 (NR), NR	NR	-5 (NR), NR	NR	0.02 (NR), NR	-3 (NR), NR
CONTROL	16 weeks (4 months)	OCA 25mg	22	NR	-21.9 (28.1)*, n.s.	NR	-7.3 (13.7)*, n.s.	NR	0.02 (0.05)*, n.s.	-44.7 (SE: 5.7), n.s.
		OCA 10mg	21	NR	-17.9 (24.8)*, n.s.	NR	-9.6 (19.3)*, n.s.	NR	0.01 (0.05)*, n.s.	-40.0 (SE: 5.9), p=0.05
		Placebo	21	NR	-1.6 (29.6)*	NR	6.3 (46.0)*	NR	0.07 (0.4)*	-48.1 (SE: 5.9)
Mudaliar 2013	6 weeks	OCA 50mg	21	NR	10 (47), p=0.84	NR	4 (24), p=0.43	NR		NR
		OCA 25mg	20	NR	-10 (14), p=0.003	NR	-2 (7), p=0.12	NR		NR
		Placebo	23	NR	11 (48)	NR	5 (46)	NR		NR
Pioglitazone (PIO)										

Trial	Follow-Up	Arms	N	ALT		AST		Bilirubin		LDL
				Normalization, n (%)	Change from Baseline, mean U/L (SD); p-value	Normalization, n (%)	Change from Baseline, mean U/L (SD); p-value	Normalization, n (%)	Change from Baseline, U/L (SD); p-value	Change from Baseline, mg/dL (SD); p-value
Cusi 2016	18 months	PIO 45mg	50	NR	-35 (NR), NR	NR	-18 (NR), NR	NR		-25 (NR), NR
		Placebo	51	NR	-13 (NR)		-5 (NR)	NR		-30.0 (NR)
	36 months	PIO 45mg	34	NR	0 (95%CI: -5, 4), p=0.97	NR	-1 (95%CI: -5, 3), p=0.63	NR		-3 (95%CI: -12, 7), p=0.57
Bril 2018	18 months	PIO - prediabetes	21	NR	-36 (21), p=0.07	NR	-16 (4), p=0.29	NR		NR
		Placebo - prediabetes	17	NR	-21 (27)	NR	-10 (17)	NR		NR
		PIO - T2DM	20	NR	-50 (47), p=0.03	NR	-32 (36), p=0.02	NR		NR
		Placebo - T2DM	25	NR	-17 (48)	NR	-5 (40)	NR		NR
	36 months	PIO - prediabetes	16	NR	-34 (24)	NR	-15 (14)	NR		NR
		PIO - T2DM	18	NR	-54 (43), p=0.10	NR	-35 (33), p=0.03	NR		NR
PIVENS	96 weeks (≈24 months)	PIO 30mg	80	NR	-40.8 (NR), p<0.0001; p=0.19†	NR	-20.4 (NR), p<0.0001; p=0.30†	NR	-0.040 (NR), p=0.07; p=0.23†	-8.1 (NR); p=0.26, p=0.33†
		Vitamin E	84	NR	-37.0 (NR), p<0.001	NR	-21.3 (NR), p<0.001	NR	0.037 (NR), p=0.56	-12.0 (NR), p=0.07
		Placebo	83	NR	-20.1 (NR)	NR	-3.8 (NR)	NR	0.064 (NR)	-5.8 (NR)
Belfort 2006	6 months	PIO 45mg	26	NR	-39 (NR), p<0.001	NR	-19 (NR), p=0.04	NR		2 (NR), p=0.58
		Placebo	21	NR	-21 (NR)	NR	-9 (NR)	NR		-2 (NR)

Trial	Follow-Up	Arms	N	ALT		AST		Bilirubin		LDL
				Normalization, n (%)	Change from Baseline, mean U/L (SD); p-value	Normalization, n (%)	Change from Baseline, mean U/L (SD); p-value	Normalization, n (%)	Change from Baseline, U/L (SD); p-value	Change from Baseline, mg/dL (SD); p-value
Aithal 2008	12 months	PIO 30mg	31	NR	-37.7 (NR), p=0.009	NR		NR	-2.7 (NR), p=0.06	-0.1 (NR), p=0.17
		Placebo	30	NR	-6.9 (NR)	NR		NR	1.3 (NR)	-0.2 (NR)
Anushiravani 2019	3 months	PIO 15 mg	30	NR	-8.6 (NR), p<0.001	NR	-6.7 (NR), p<0.001	NR		-1.1 (NR), p=0.02
		Vitamin E 400 IU	30	NR	-3.3 (NR), p=0.05	NR	-2.3 (NR), p=0.32	NR		-2.3 (NR), p=0.26
		Placebo	30	NR	-0.6 (NR)	NR	-0.9 (NR)	NR		-0.6 (NR)
Yan 2015	16 weeks (4 months)	PIO 15 mg + LSI	47	NR	-20.5(95%CI: -24.8, -16.2)	NR	-8.3 (95% CI: -10.2, -6.4)	NR		-0.05 (95% CI: -0.25, 0.14), NR
		LSI	53	NR	-14.1(95% CI: -18.0, -10.2)	NR	-6.5 (95% CI: -8.2, -4.8)	NR		-0.14 (95% CI: -0.32, 0.04)
Bril 2019	18 months	PIO 45 mg + Vitamin E 400 IU	37	NR	-20.8 (NR)*, NR	NR	-10.9 (NR)*, NR	NR		-4 (31), p=0.45
		Vitamin E 400 IU	36	NR	-24.7 (NR)*, NR	NR	-14.9 (NR)*, NR	NR		0 (30), p=0.12
		Placebo	32	NR	-7.2 (NR)*	NR	-8.5 (NR)*	NR		-12 (31)

* numbers are digitized and should be interpreted with caution, † versus Vitamin E

95%CI: 95% Confidence Interval, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ITT: intention to treat, IU: international units, mg: milligram, mg/dL: milligram per deciliter, mmol/L: millimole per liter, N: total number, n: number, NR: not reported, n.s.: not significant, pP: per protocol, U/L: units per liter, SD: standard deviation, SE: standard error

Table D10. Patient Reported Outcomes

Trial	Follow-Up	Arms	N	Change from baseline, SF36 (PCS), mean (SD); p-value	Change from baseline, SF36 (MCS), mean (SD); p-value	EQ-5D Utility Score	CLDQ-NASH total score	NASH-related work productivity impairment	NASH-related activity impairment
Obeticholic Acid (OCA)									
REGENERATE	18 months	OCA 25 mg	404	NR	NR	NR	0.30 (0.10)	NR	NR
		OCA 10 mg	407	NR	NR	NR	0.16 (0.10)	NR	NR
		Placebo	407	NR	NR	NR	0.18 (0.8)	NR	NR
FLINT	72 weeks	OCA 25mg	102	0 (7), p=0.22	0 (9), p=065	NR	NR	NR	NR
		Placebo	98	-1 (7)	1 (9)	NR	NR	NR	NR
	96 weeks	OCA 25mg	122	0 (8), p=0.19	0 (9), p=0.14	NR	NR	NR	NR
		Placebo	120	-1 (7)	-1 (10)	NR	NR	NR	NR
Pioglitazone (PIO)									
PIVENS		PIO 30mg	70	-0.9 (NR), p=0.93; p=0.54*	-1.9 (NR), p=0.23; p=0.47*	NR	NR	NR	NR
		Vitamin E	78	0.4 (NR), p=0.45	-0.5 (NR), p=0.76	NR	NR	NR	NR
		Placebo	74	-0.3 (NR)	0.4 (NR)	NR	NR	NR	NR

*Versus Vitamin E

CLDQ-NASH: chronic liver disease questionnaire – NASH, EQ-5D: EuroQol five dimension scale, IU: international units, MCS: mental component summary, mg: milligram, N: total number, n: number, NASH: non-alcohol steatohepatitis, NR: not reported, PCS: Physical component summary, SD: standard deviation, SF-36: 36-item short form survey

Table D11. Harms I

Trial	Arms	N	Any AE, n (%)	TEAEs, n (%)	SAE, n (%)	TEAEs leading to D/C, n (%)	Death, n (%)	Pruritus, n (%)	Cardiovascular, n (%)	LDL increase, n (%)	Weight increase, n (%)
Obeticholic Acid (OCA)											
REGENERATE Yanoussi 2019[6]	OCA 25 mg	658	NR	601 (91.3)	93 (14.1)	83 (12.6)	1 (<1.0)	336 (51.1)	42 (6.4)	115 (17.5)	NR
	OCA 10 mg	653	NR	579 (88.7)	72 (11.0)	39 (6.0)	0 (0)	183 (28.0)	43 (6.6)	109 (16.7)	NR
	Placebo	657	NR	548 (83.4)	75 (11.4)	41 (6.2)	2 (<1.0)	123 (18.7)	30 (4.6)	47 (7.2)	NR
FLINT Neuschwander-Tetri 2015[30]	OCA 25 mg	141	99 (70.2)	NR	30 (21.3)	1 (<1.0)	2 (1.4)	33 (23.4)	7 (5.0)	NR	NR
	Placebo	142	68 (47.9)	NR	21 (14.8)	0 (0)	0 (0)	9 (6.3)	5 (3.5)	NR	NR
FLINT - subgroup analysis Hameed 2018[80]	OCA ≥2% Weight Loss	45	NR	NR	NR	NR	NR	12 (27.0)	NR	NR	NR
	OCA <2% Weight Loss	57	NR	NR	NR	NR	NR	11 (19.0)	NR	NR	NR
	Placebo ≥2% Weight Loss	31	NR	NR	NR	NR	NR	0 (0)	NR	NR	NR
	Placebo <2% Weight Loss	67	NR	NR	NR	NR	NR	5 (7.0)	NR	NR	NR
CONTROL Pockros 2019[31]	OCA 25 mg	22	20 (90.9)	NR	1 (4.6)	2 (9.2)	0 (0)	12 (54.5)	NR	NR	0 (0)
	OCA 10 mg	21	14 (66.7)	NR	1 (4.8)	0 (0)	0 (0)	3 (14.3)	NR	NR	0 (0)
	Placebo	21	17 (81.0)	NR	0 (0)	0 (0)	0 (0)	1 (4.8)	NR	NR	0 (0)
Mudaliar 2013[32]	OCA 50 mg	21	16 (76.2)	8 (38.1)	0 (0)	1 (4.8)	0 (0)	1 (4.8)	0 (0)	NR	NR
	OCA 25 mg	20	9 (45.0)	1 (5.0)	0 (0)	0 (0)	0 (0)	2 (10.0)	2 (10.0)	NR	NR
	Placebo	23	14 (60.9)	6 (26.1)	0 (0)	1 (4.3)	0 (0)	2 (8.7)	0 (0)	NR	NR
Pioglitazone (PIO)											
Cusi 2016[41]	PIO 45 mg	50	NR	NR	0 (0)	0 (0)	0 (0)	NR	14 (28.0)	NR	NR
	Placebo	51	NR	NR	0 (0)	1 (2.0)	0 (0)	NR	11 (21.6)	NR	NR

Trial	Arms	N	Any AE, n (%)	TEAEs, n (%)	SAE, n (%)	TEAEs leading to D/C, n (%)	Death, n (%)	Pruritus, n (%)	Cardiovascular, n (%)	LDL increase, n (%)	Weight increase, n (%)
PIVENS Sanyal 2010[37]	PIO 30 mg	80	43 (53.8)	NR	2 (2.5)	0 (0)	0 (0)	NR	10 (12.5)	NR	>20%: 3 (3.8)
	Vitamin E 800 IU	84	53 (63.1)	NR	7 (8.3)	0 (0)	1 (1.2)	NR	12 (14.3)	NR	>20%: 0 (0)
	Placebo	83	50 (60.2)	NR	10 (12.0)	0 (0)	0 (0)	NR	12 (14.5)	NR	>20%: 0 (0)
Belfort 2006[43]	PIO 45mg	26	NR	NR	0 (0)	1 (3.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Placebo	21	NR	NR	0 (0)	2 (9.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Aithal 2008[44]	PIO 30 mg	37	NR	NR	NR	4 (10.8)	NR	0 (0)	0 (0)	NR	1 (2.7)
	Placebo	37	NR	NR	NR	4 (10.8)	NR	1 (2.7)	1 (2.7)	NR	2 (5.4)
Anushiravani 2019[85]	PIO 15 mg	30	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Vitamin E 400 IU	30	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	30	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yan 2015[86]	PIO 15 mg + LSI	47	19 (40.4)	NR	0 (0)	4 (8.5)	NR	0 (0)	Palpitations: 2 (10.5)	NR	NR
	LSI	53	0 (0)	NR	0 (0)	0 (0)	NR	0 (0)	Palpitations: 0 (0)	NR	NR
Bril 2019[42]	PIO 45 mg + Vitamin E 400 IU	37	NR	NR	NR	0 (0)	2 (5.4)	NR	8 (21.6)	NR	NR
	Vitamin E 400 IU	36	NR	NR	NR	0 (0)	2 (5.6)	NR	6 (16.7)	NR	NR
	Placebo	32	NR	NR	NR	1 (3.1)	0 (0)	NR	4 (12.5)	NR	NR

AE: adverse event, D/C: discontinuation, IU: international units, LDL: low-density lipoprotein, LSI: lifestyle intervention, mg: milligram, N: total number, n: number, NR: not reported, TEAE: treatment-emergent adverse event, SAE: serious adverse event

Table D12. Harms II

Trial	Arms	N	Fatigue, n (%)	Headache, n (%)	Nausea, n (%)	Constipation, n (%)	Abdominal pain, n (%)	Diarrhea, n (%)	Upper Resp. Tract Infection, n (%)
Obeticholic Acid (OCA)									
REGENERATE Younossi 2019[6]	OCA 25 mg	658	71 (10.8)	34	83 (12.6)	70 (10.6)	67 (10.2)	49 (7.4)	54
	OCA 10 mg	653	78 (11.9)	42	72 (11.0)	65 (10.0)	66 (10.1)	44 (6.7)	47
	Placebo	657	88 (13.4)	51	77 (11.7)	36 (5.5)	62 (9.4)	79 (12.0)	44
FLINT Neuschwander Tetri 2015[30]	OCA 25 mg	141	NR	2 (1.4)	NR	5 (3.5)	7 (5.0)	NR	NR
	Placebo	142	NR	5 (3.5)	NR	1 (<1)	9 (6.3)	NR	NR
FLINT - subgroup analysis Hameed 2018[80]	OCA ≥2% Weight Loss	45	NR	NR	NR	NR	NR	NR	NR
	OCA <2% Weight Loss	57	NR	NR	NR	NR	NR	NR	NR
	Placebo ≥2% Weight Loss	31	NR	NR	NR	NR	NR	NR	NR
	Placebo <2% Weight Loss	67	NR	NR	NR	NR	NR	NR	NR
CONTROL Pockros 2019[31]	OCA 25 mg	22	3 (13.6)	1 (4.8)	NR	3 (13.6)	NR	2 (9.1)	1 (4.6)
	OCA 10 mg	21	3 (14.3)	0 (0)	NR	2 (9.5)	NR	0 (0)	0 (0)
	Placebo	21	1 (4.8)	1 (4.8)	NR	0 (0)	NR	3 (14.3)	1 (4.8)
Mudaliar 2013[32]	OCA 50 mg	21	NR	3 (14)	NR	5 (23.8)	NR	0 (0)	1 (4.8)
	OCA 25 mg	20	NR	1 (5.0)	NR	0 (0)	NR	0 (0)	0 (0)
	Placebo	23	NR	1 (4.3)	NR	0 (0)	NR	2 (8.7)	2 (8.7)
Pioglitazone (PIO)									
Cusi 2016[41]	PIO 45 mg	50	NR	NR	NR	NR	NR	NR	NR
	Placebo	51	NR	NR	NR	NR	NR	NR	NR
PIVENS	PIO 30 mg	80	NR	NR	NR	NR	NR	NR	NR

Trial	Arms	N	Fatigue, n (%)	Headache, n (%)	Nausea, n (%)	Constipation, n (%)	Abdominal pain, n (%)	Diarrhea, n (%)	Upper Resp. Tract Infection, n (%)
Sanyal 2010[37]	Vitamin E	84	NR	NR	NR	NR	NR	NR	NR
	Placebo	83	NR	NR	NR	NR	NR	NR	NR
Belfort 2006[43]	PIO 45 mg	26	1 (3.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PBO	21	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Aithal 2008[44]	PIO 30 mg	37	NR	1 (2.7)	NR	1 (2.7)	NR	NR	NR
	Placebo	37	NR	2 9 %.4)	NR	2 (5.4)	NR	NR	NR
Anushiravani 2019[85]	PIO 15 mg	30	NR	NR	NR	NR	NR	NR	NR
	Vitamin E 400 IU	30	NR	NR	NR	NR	NR	NR	NR
	Placebo	30	NR	NR	NR	NR	NR	NR	NR
Yan 2015[86]	PIO 15 mg + LSI	47	3 (15.8)	1 (5.3)	1 (5.3)	0 (0)	0 (0)	1 (5.3)	NR
	LSI	53	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NR
Bril 2019[42]	PIO 45 mg + Vitamin E 400 IU	37	NR	NR	NR	NR	NR	NR	10 (27.0)
	Vitamin E 400 IU	36	NR	NR	NR	NR	NR	NR	9 (25.0)
	Placebo	32	NR	NR	NR	NR	NR	NR	8 (25.0)

IU: international units, mg: milligram, N: total number, n: number, NR: not reported, Resp.: respiratory

Table D13. Study Quality

Trial	Comparable Groups	Non-differential Follow-up	Patient/Investigator Blinding (Double-Blind)	Clear Definition of Outcomes	Selective outcome reporting	Measurements Valid	Intention to treat analysis	Appropriate Approach to Missing Data	USPSTF Rating
Obeticholic Acid (OCA)									
REGENERATE[6]	yes	yes	yes	yes	no	yes	yes	yes	good
FLINT[30]	yes	yes	yes	yes	no	yes	mITT	yes	good
CONTROL[31]	no	yes	yes	yes	no	yes	per Protocol	N/A	fair
Mudaliar 2013[32]	yes	yes	yes	yes	no	yes	yes	no	fair
Pioglitazone (PIO)									
Cusi 2016[41]	yes	yes	yes	yes	no	yes	yes	yes	good
PIVENS[37]	yes	yes	yes	yes	no	yes	yes	yes	good
Belfort 2016[43]	no	yes	yes	yes	no	yes	yes	yes	fair
Aithal 2008[44]	yes	yes	yes	yes	no	yes	yes	yes	good
Bril 2019[42]	yes	no	yes	yes	no	yes	yes	yes	fair

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	X	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-related costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Neumann, Sanders et al.[66]

Description evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[88]
2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).
3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.
4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.
5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.
6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

Table E2. Base Case Analysis Per Regimen Results of Probabilistic Sensitivity Analysis for Obeticholic Acid versus Standard Care

	Obeticholic Acid			Standard Care		
	Base Case	PSA Mean	Credible Range	Base Case	PSA Mean	Credible Range
Total Costs	**$1,290,904**	**$1,287,520**	**($1,074,034 - $1,531,737)**	**$419,408**	**$426,428**	**($247,801 - $662,909)**
Drug Cost	$1,050,992	$1,036,948	($748,953 - $1,361,058)	--	--	--
Without Fibrosis	$7,802	$8,268	($2,430 - $17,599)	$4,357	$4,596	($1,737 - $9,094)
With Fibrosis	$6,856	$6,126	($1,477 - $8,134)	$6,733	$6,394	($4,746 - $7,700)
Compensated Cirrhosis	$28,511	$29,991	(-$4,328 - $75,094)	$61,156	$59,632	($33,235 - $89,508)
Decompensated Cirrhosis	$7,868	$8,790	(-$412 - $23,139)	$14,791	$16,222	($7,947 - $32,665)
Hepatocellular Carcinoma	$34,720	$35,616	(-$292 - $88,397)	$69,416	$69,053	($26,460 - $127,584)
Liver Transplant	$127,387	$135,110	(-$1,182 - $324,354)	$240,838	$248,492	($123,675 - $426,882)
Cardiovascular Events	$26,768	$26,670	($21,904 - $32,237)	$22,118	$22,040	($18,433 - $26,195)
Adverse Events	$37	$37	($29 - $46)	$10	$10	($7 - $13)
Total QALYs	**10.13**	**10.09**	**(8.09 - 12.20)**	**9.63**	**9.52**	**(7.97 - 10.86)**
Without Fibrosis	4.29	4.53	(1.41 - 9.60)	1.90	1.98	(0.90 - 3.60)
With Fibrosis	4.38	4.05	(2.19 - 5.02)	4.67	4.56	(3.60 - 5.33)
Compensated Cirrhosis	0.92	0.93	(-0.14 - 2.35)	2.00	1.89	(1.04 - 2.84)
Decompensated Cirrhosis	0.12	0.13	(-0.01 - 0.34)	0.22	0.24	(0.12 - 0.48)
Hepatocellular Carcinoma	0.22	0.22	(0.00 - 0.56)	0.42	0.41	(0.15 - 0.78)
Liver Transplant	0.23	0.26	(0.00 - 0.59)	0.44	0.47	(0.24 - 0.79)
Cardiovascular Events	-0.02	-0.02	(-0.02 - -0.02)	-0.01	-0.01	(-0.02 - -0.01)
Adverse Events	-0.004	-0.004	(-0.005 - -0.003)	-0.0003	-0.0003	(-0.0007 - -0.0001)
Total Life Years	**14.54**	**14.49**	**(13.44 - 15.39)**	**13.97**	**13.93**	**(13.21 - 14.56)**
Equal Value Life Years	**10.23**	**10.18**	**(8.19 - 12.24)**	**9.63**	**9.53**	**(7.97 - 10.86)**
Advanced Liver Disease	**0.14**	**0.16**	**(-0.01 - 0.39)**	**0.27**	**0.29**	**(0.15 - 0.51)**
Decompensated Cirrhosis	0.06	0.07	(0.00 - 0.21)	0.11	0.13	(0.06 - 0.28)

	Obeticholic Acid			Standard Care		
	Base Case	PSA Mean	Credible Range	Base Case	PSA Mean	Credible Range
Hepatocellular Carcinoma	0.07	0.07	(0.00 - 0.18)	0.13	0.13	(0.06 - 0.23)
Liver Transplant	0.02	0.02	(0.00 - 0.09)	0.03	0.03	(0.00 - 0.13)
Liver Related Death	**0.09**	**0.10**	**(-0.01 - 0.24)**	**0.19**	**0.19**	**(0.11 - 0.30)**
From Comp. Cirrhosis	0.05	0.05	(-0.01 - 0.12)	0.10	0.09	(0.05 - 0.14)
From Decomp. Cirrhosis	0.04	0.04	(0.00 - 0.12)	0.07	0.08	(0.04 - 0.18)
From HCC	0.01	0.01	(0.00 - 0.04)	0.01	0.01	(0.00 - 0.07)
From Liver Transplant	0.00	0.00	(0.00 - 0.01)	0.00	0.00	(0.00 - 0.01)
Cardiovascular Events	**0.94**	**0.94**	**(0.82 - 1.05)**	**0.77**	**0.77**	**(0.69 - 0.83)**
Myocardial Infarction	0.74	0.74	(0.55 - 0.90)	0.61	0.60	(0.46 - 0.72)
Nonfatal MI	0.56	0.56	(0.41 - 0.70)	0.46	0.46	(0.34 - 0.56)
Fatal MI	0.18	0.18	(0.13 - 0.23)	0.15	0.14	(0.10 - 0.18)
Stroke	0.20	0.20	(0.08 - 0.37)	0.16	0.16	(0.06 - 0.30)
Nonfatal Stroke	0.16	0.16	(0.06 - 0.30)	0.13	0.13	(0.05 - 0.24)
Fatal Stroke	0.04	0.04	(0.02 - 0.08)	0.03	0.04	(0.01 - 0.07)
Cardiovascular Deaths	0.22	0.22	(0.18 - 0.26)	0.18	0.18	(0.15 - 0.21)

Table E3. Base Case Analysis Incremental Results of Probabilistic Sensitivity Analysis for Obeticholic Acid versus Standard Care

	Incremental		
	Base Case	PSA Mean	Credible Range
ICER (QALYs)	**$1,755,872**	**$2,065,739**	**(-$16,524,054 - $20,789,127)**
ICER (Life Years)	**$1,530,839**	**$538,726**	**(-$10,348,228 - $14,297,534)**
Cost per evLYG	**$1,452,260**	**-$22,617**	**(-$12,232,024 - $14,292,676)**
Total Costs	**$871,496**	**$861,092**	**($616,563 - $1,145,756)**
Drug Cost	$1,050,992	$1,036,948	($748,953 - $1,361,058)
Without Fibrosis	$3,445	$3,672	($400 - $8,998)
With Fibrosis	$123	-$267	(-$3,463 - $1,027)
Compensated Cirrhosis	-$32,645	-$29,641	(-$57,055 - -$1,617)
Decompensated Cirrhosis	-$6,922	-$7,431	(-$19,250 - -$209)
Hepatocellular Carcinoma	-$34,696	-$33,436	(-$80,015 - -$3,488)
Liver Transplant	-$113,451	-$113,382	(-$261,654 - -$8,214)
Cardiovascular Events	$4,650	$4,631	($2,541 - $7,086)
Adverse Events	$27	$27	($20 - $36)
Total QALYs	**0.50**	**0.57**	**(-0.15 - 1.74)**
Without Fibrosis	2.39	2.55	(0.24 - 6.32)
With Fibrosis	-0.29	-0.51	(-2.41 - 0.36)
Compensated Cirrhosis	-1.08	-0.95	(-1.84 - -0.06)
Decompensated Cirrhosis	-0.11	-0.11	(-0.28 - 0.00)
Hepatocellular Carcinoma	-0.20	-0.19	(-0.47 - -0.01)
Liver Transplant	-0.21	-0.21	(-0.47 - -0.02)
Cardiovascular Events	-0.003	0.00	(0.00 - 0.00)
Adverse Events	-0.003	-0.003	(-0.005 - -0.002)
Total Life Years	**0.57**	**0.55**	**(-0.15 - 1.28)**
Equal Value Life Years	**0.60**	**0.66**	**(-0.19 - 1.81)**
Advanced Liver Disease	**-0.13**	**-0.13**	**(-0.30 - -0.01)**

	Incremental		
	Base Case	PSA Mean	Credible Range
Decompensated Cirrhosis	-0.05	-0.06	(-0.16 - 0.00)
Hepatocellular Carcinoma	-0.06	-0.06	(-0.14 - 0.00)
Liver Transplant	-0.01	-0.01	(-0.07 - 0.00)
Liver Related Death	**-0.09**	**-0.09**	**(-0.19 - -0.01)**
From Comp. Cirrhosis	-0.05	-0.05	(-0.09 - 0.00)
From Decomp. Cirrhosis	-0.03	-0.04	(-0.10 - 0.00)
From HCC	-0.01	-0.01	(-0.04 - 0.00)
From Liver Transplant	0.00	0.00	(-0.01 - 0.00)
Cardiovascular Events	**0.17**	**0.17**	**(0.09 - 0.26)**
Myocardial Infarction	0.14	0.14	(0.07 - 0.21)
Nonfatal MI	0.10	0.10	(0.05 - 0.16)
Fatal MI	0.03	0.03	(0.02 - 0.05)
Stroke	0.04	0.04	(0.01 - 0.08)
Nonfatal Stroke	0.03	0.03	(0.01 - 0.06)
Fatal Stroke	0.01	0.01	(0.00 - 0.02)
Cardiovascular Deaths	0.04	0.04	(0.02 - 0.06)

Figure E1. Cost-Effectiveness Plane, Base Case Analysis Per Regimen Results of Probabilistic Sensitivity Analysis for Obeticholic Acid versus Standard Care

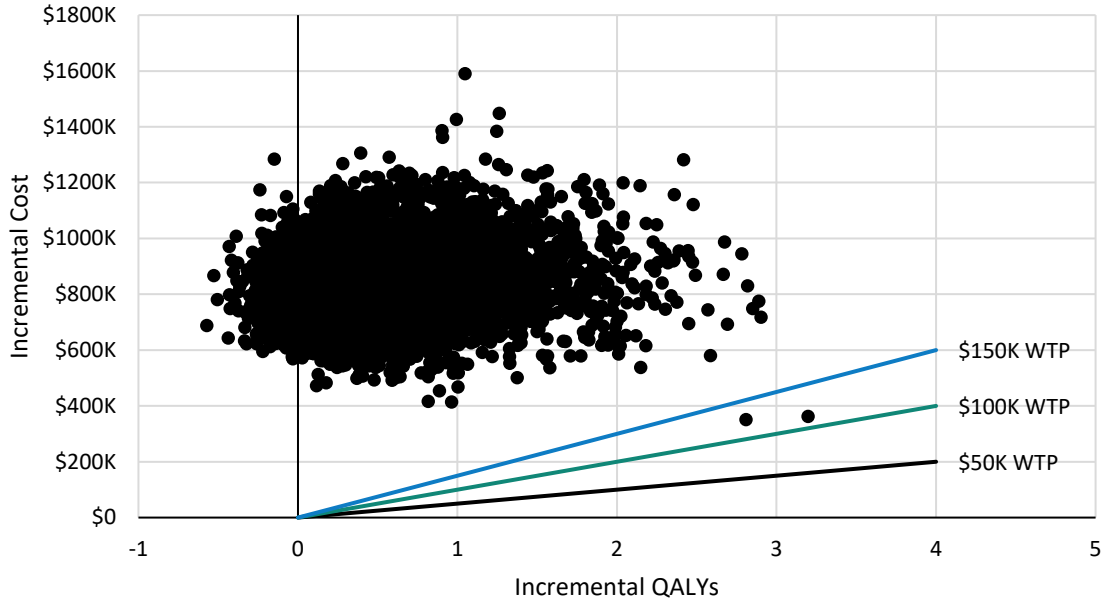


Figure E2. Cost-Effectiveness Acceptability Curve, Base Case Analysis Per Regimen Results of Probabilistic Sensitivity Analysis for Obeticholic Acid versus Standard Care

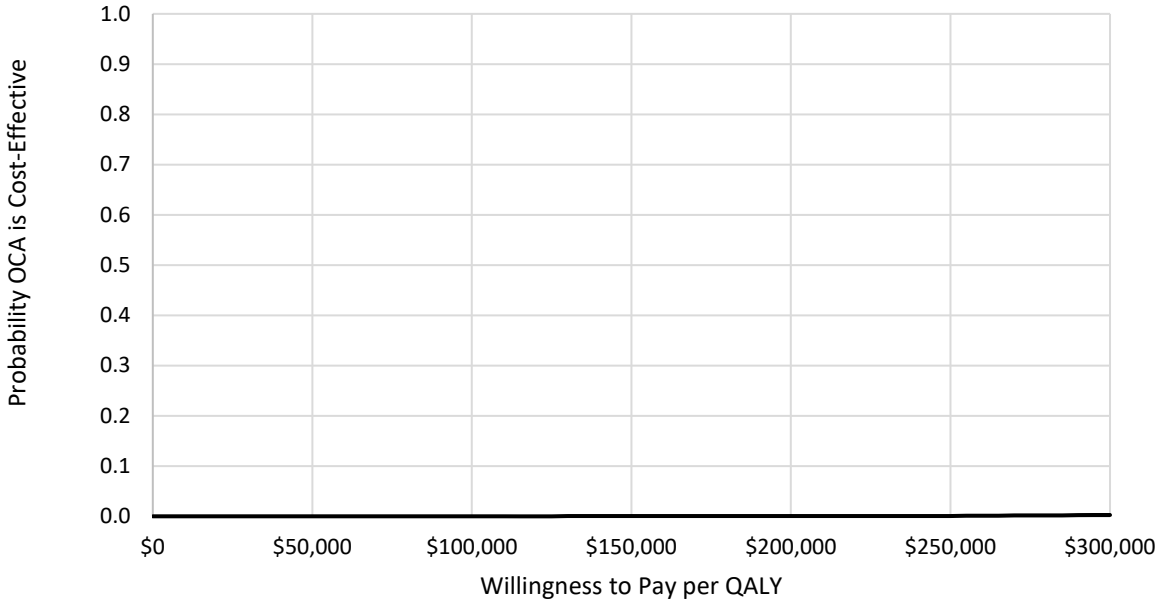


Table E4. Societal Analysis Per Regimen Results of Probabilistic Sensitivity Analysis for Obeticholic Acid versus Standard Care

	Obeticholic Acid			Standard Care		
	Base Case	PSA Mean	Credible Range	Base Case	PSA Mean	Credible Range
Total Costs	$1,481,826	$1,478,507	($1,261,054 - $1,725,081)	$631,468	$634,662	($454,449 - $878,181)
Drug Cost	$1,050,992	$1,037,693	($745,058 - $1,363,631)	--	--	--
Without Fibrosis	$7,802	$8,256	($2,342 - $17,615)	$4,357	$4,581	($1,708 - $9,181)
With Fibrosis	$6,856	$6,137	($1,786 - $8,080)	$6,733	$6,389	($4,843 - $7,680)
Compensated Cirrhosis	$28,511	$30,005	(-$3,667 - $73,951)	$61,156	$59,794	($32,814 - $90,781)
Decompensated Cirrhosis	$7,868	$8,810	(-$232 - $23,536)	$14,791	$16,284	($7,900 - $32,125)
Hepatocellular Carcinoma	$34,720	$35,663	($407 - $90,648)	$69,416	$68,940	($26,339 - $130,444)
Liver Transplant	$127,387	$134,999	($1,887 - $329,351)	$240,838	$247,609	($125,591 - $433,707)
Cardiovascular Events	$26,768	$26,727	($21,933 - $32,246)	$22,118	$22,057	($18,440 - $26,306)
Adverse Events	$37	$37	($29 - $46)	$10	$10	($7 - $13)
Societal Cost	$190,922	$190,218	($159,469 - $223,775)	$212,060	$209,009	($182,190 - $239,989)
Total QALYs	10.13	10.09	(8.10 - 12.29)	9.63	9.51	(7.93 - 10.88)
Without Fibrosis	4.29	4.52	(1.38 - 9.52)	1.90	1.97	(0.87 - 3.61)
With Fibrosis	4.38	4.06	(2.28 - 5.03)	4.67	4.55	(3.60 - 5.34)
Compensated Cirrhosis	0.92	0.93	(-0.11 - 2.37)	2.00	1.89	(1.02 - 2.87)
Decompensated Cirrhosis	0.12	0.13	(0.00 - 0.34)	0.22	0.24	(0.12 - 0.48)
Hepatocellular Carcinoma	0.22	0.22	(0.00 - 0.58)	0.42	0.41	(0.15 - 0.79)
Liver Transplant	0.23	0.26	(0.01 - 0.60)	0.44	0.47	(0.24 - 0.79)
Cardiovascular Events	-0.02	-0.02	(-0.02 - -0.02)	-0.01	-0.01	(-0.02 - -0.01)
Adverse Events	-0.004	-0.004	(-0.005 - -0.003)	-0.0003	-0.0003	(-0.0007 - -0.0001)
Total Life Years	14.54	14.49	(13.42 - 15.40)	13.97	13.93	(13.19 - 14.57)
Equal Value Life Years	10.23	10.19	(8.23 - 12.33)	9.63	9.52	(7.93 - 10.88)
Advanced Liver Disease	0.14	0.16	(0.00 - 0.40)	0.27	0.29	(0.15 - 0.50)

	Obeticholic Acid			Standard Care		
	Base Case	PSA Mean	Credible Range	Base Case	PSA Mean	Credible Range
Decompensated Cirrhosis	0.06	0.07	(0.00 - 0.21)	0.11	0.13	(0.07 - 0.28)
Hepatocellular Carcinoma	0.07	0.07	(0.00 - 0.18)	0.13	0.13	(0.06 - 0.24)
Liver Transplant	0.02	0.02	(0.00 - 0.09)	0.03	0.03	(0.00 - 0.13)
Liver Related Death	0.09	0.10	(-0.01 - 0.24)	0.19	0.19	(0.11 - 0.30)
From Comp. Cirrhosis	0.05	0.05	(-0.01 - 0.12)	0.10	0.09	(0.05 - 0.14)
From Decomp. Cirrhosis	0.04	0.04	(0.00 - 0.13)	0.07	0.08	(0.04 - 0.17)
From HCC	0.01	0.01	(0.00 - 0.04)	0.01	0.01	(0.00 - 0.07)
From Liver Transplant	0.00	0.00	(0.00 - 0.01)	0.00	0.00	(0.00 - 0.01)
Cardiovascular Events	0.94	0.94	(0.82 - 1.05)	0.77	0.77	(0.69 - 0.83)
Myocardial Infarction	0.74	0.74	(0.55 - 0.90)	0.61	0.60	(0.46 - 0.72)
Nonfatal MI	0.56	0.56	(0.42 - 0.70)	0.46	0.46	(0.34 - 0.56)
Fatal MI	0.18	0.18	(0.13 - 0.23)	0.15	0.14	(0.10 - 0.18)
Stroke	0.20	0.20	(0.07 - 0.37)	0.16	0.16	(0.06 - 0.30)
Nonfatal Stroke	0.16	0.16	(0.06 - 0.29)	0.13	0.13	(0.05 - 0.24)
Fatal Stroke	0.04	0.04	(0.02 - 0.08)	0.03	0.03	(0.01 - 0.07)
Cardiovascular Deaths	0.22	0.22	(0.18 - 0.26)	0.18	0.18	(0.15 - 0.21)

Table E5. Societal Analysis Incremental Results of Probabilistic Sensitivity Analysis for Obeticholic Acid versus Standard Care

	Incremental		
	Base Case	PSA Mean	Credible Range
ICER (QALYs)	$1,713,283	$2,143,791	(-$19,193,023 - $17,915,977)
ICER (Life Years)	$1,493,709	-$3,102,003	(-$9,057,217 - $12,488,519)
Cost per evLYG	$1,417,036	-$266,606	(-$15,075,939 - $14,486,039)
Total Costs	$850,358	$843,845	($599,664 - $1,126,466)
Drug Cost	$1,050,992	$1,037,693	($745,058 - $1,363,631)
Without Fibrosis	$3,445	$3,675	($398 - $8,974)
With Fibrosis	$123	-$252	(-$3,303 - $1,064)
Compensated Cirrhosis	-$32,645	-$29,789	(-$58,750 - -$1,925)
Decompensated Cirrhosis	-$6,922	-$7,475	(-$19,011 - -$274)
Hepatocellular Carcinoma	-$34,696	-$33,277	(-$83,081 - -$3,632)
Liver Transplant	-$113,451	-$112,610	(-$258,536 - -$8,550)
Cardiovascular Events	$4,650	$4,671	($2,584 - $7,005)
Adverse Events	$27	$27	($20 - $36)
Societal Cost	-$21,138	-$18,791	(-$42,176 - -$3,177)
Total QALYs	0.50	0.58	(-0.16 - 1.80)
Without Fibrosis	2.39	2.55	(0.24 - 6.29)
With Fibrosis	-0.29	-0.50	(-2.41 - 0.39)
Compensated Cirrhosis	-1.08	-0.96	(-1.85 - -0.07)
Decompensated Cirrhosis	-0.11	-0.11	(-0.28 - 0.00)
Hepatocellular Carcinoma	-0.20	-0.19	(-0.47 - -0.02)
Liver Transplant	-0.21	-0.21	(-0.47 - -0.02)
Cardiovascular Events	-0.003	0.00	(0.00 - 0.00)
Adverse Events	-0.003	-0.003	(-0.005 - -0.002)
Total Life Years	0.57	0.56	(-0.16 - 1.30)
Equal Value Life Years	0.60	0.67	(-0.18 - 1.87)

	Incremental		
	Base Case	PSA Mean	Credible Range
Advanced Liver Disease	-0.13	-0.13	(-0.30 - -0.01)
Decompensated Cirrhosis	-0.05	-0.06	(-0.16 - 0.00)
Hepatocellular Carcinoma	-0.06	-0.06	(-0.14 - 0.00)
Liver Transplant	-0.01	-0.01	(-0.07 - 0.00)
Liver Related Death	-0.09	-0.09	(-0.19 - -0.01)
From Comp. Cirrhosis	-0.05	-0.05	(-0.09 - 0.00)
From Decomp. Cirrhosis	-0.03	-0.04	(-0.10 - 0.00)
From HCC	-0.01	-0.01	(-0.04 - 0.00)
From Liver Transplant	0.00	0.00	(-0.01 - 0.00)
Cardiovascular Events	0.17	0.17	(0.09 - 0.26)
Myocardial Infarction	0.14	0.14	(0.07 - 0.21)
Nonfatal MI	0.10	0.10	(0.05 - 0.17)
Fatal MI	0.03	0.03	(0.02 - 0.05)
Stroke	0.04	0.04	(0.01 - 0.08)
Nonfatal Stroke	0.03	0.03	(0.01 - 0.06)
Fatal Stroke	0.01	0.01	(0.00 - 0.02)
Cardiovascular Deaths	0.04	0.04	(0.02 - 0.06)

Figure E1. Cost-Effectiveness Plane, Base Case Analysis Per Regimen Results of Probabilistic Sensitivity Analysis for Obeticholic Acid versus Standard Care

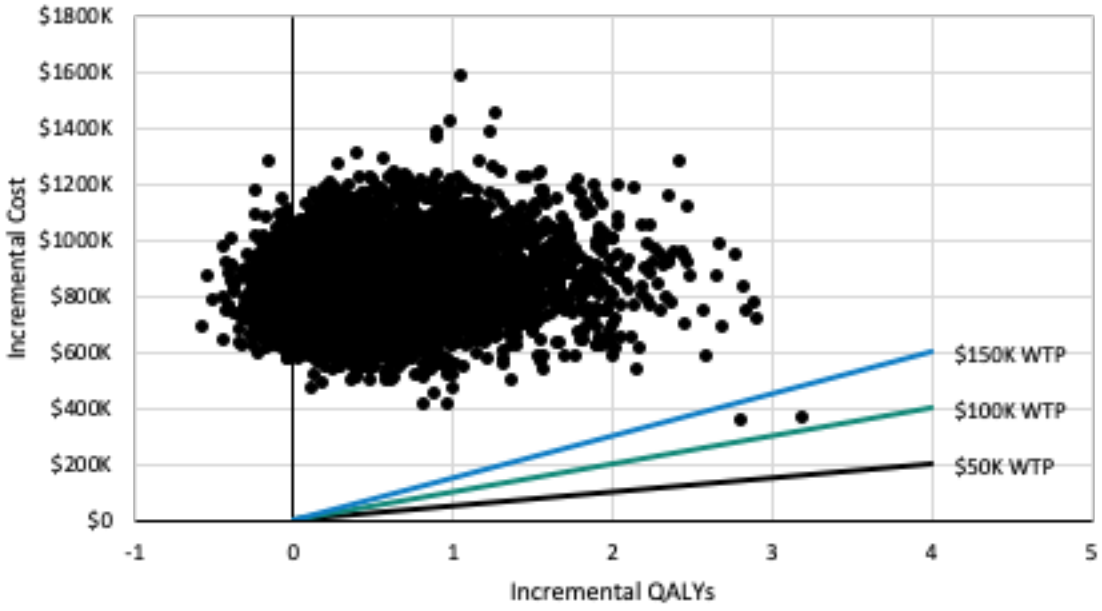


Figure E2. Cost-Effectiveness Acceptability Curve, Base Case Analysis Per Regimen Results of Probabilistic Sensitivity Analysis for Obeticholic Acid versus Standard Care