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

Revised Evidence Report

April 13, 2023

Prepared for

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Jeffrey A. Tice served as the lead author for the Report. Belen Herce-Hagiwara and Shahariar Mohammed Fahim led the systematic review and authorship of the comparative clinical effectiveness section of this Report. Janet Chu helped to edit and provided critical input for the clinical effectiveness section. Josh J. Carlson and Kangho Suh developed the cost-effectiveness model and authored the corresponding sections of the Report with assistance from Ronald Dickerson. Marina Richardson provided consultation on the cost-effectiveness analyses and conducted analyses for the budget impact model. David M. Rind and Steven D. Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Monica Frederick, Yasmine Kayali, Becca Piltch, and Liis Shea for their contributions to this Report.

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

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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 experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/wp-content/uploads/2022/11/ICER_NASH-Revised-Key-Stakeholders-List.pdf

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List of Acronyms and Abbreviations Used in this Report

AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine aminotransaminase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
BMI	Body mass index
CLDQ	Chronic Liver Disease Questionnaire
CV	Cardiovascular
CVD	Cardiovascular disease
DB	Double blind
evLY	Equal value life year
FDA	Food and Drug Administration
FXR	Farnesoid X-activated receptor
HBPB	Health Benefit Price Benchmark
HCC	Hepatocellular Carcinoma
HS	Hepatic Steatosis
HRQoL	Health-related quality of life
ICER	Institute for Clinical and Economic Review
ITT	Intention-to-treat
GGT	Gamma-Glutamyl Transpeptidase
LDL	Low density lipoprotein
LS	Least squares
LY	Life years
LYG	Life years gained
MACE	Major adverse cardiovascular event
MRI-PDFF	Magnetic resonance imaging-proton density fat fraction
NAFL	Nonalcoholic fatty liver
NAFLD	Nonalcoholic fatty liver disease
NAS	Nonalcoholic fatty liver disease activity score
NASH	Nonalcoholic steatohepatitis
NICE	National Institute for Health and Care Excellence
No.	Number
NS	Not significant
NR	Not reported
OCA	Obeticholic acid
OLE	Open label extension
PBC	Primary Biliary Cholangitis
PCSK-9	Proprotein convertase subtilisin/kexin 9
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
RES	Resmetirom
SAE	Serious adverse event
SF-36	Short Form Health Survey – 36
SOC	Standard of care
THR	Thyroid hormone receptor
T2DM	Type 2 Diabetes Mellitus
US	United States

WAC	Wholesale acquisition cost

Executive Summary

An estimated 24% of adults in the United States (US) have Nonalcoholic fatty liver disease (NAFLD).[1] NAFLD can be subcategorized as nonalcoholic fatty liver (NAFL), in which there is hepatic steatosis (HS) but no injury to liver cells, and as nonalcoholic steatohepatitis (NASH), in which HS is accompanied by hepatocellular injury.[2] 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 placing patients at high risk of death from liver failure or liver cancer. Some patients may need liver transplantation.[2] Despite an increased risk of death from liver-related causes, cardiovascular disease (CVD) is the most common cause of death in patients with NAFLD.[1] Obesity is a common risk factor in patients with NASH. Lifestyle interventions, including exercise and weight loss, can improve NASH, as can weight loss after bariatric surgery.[2,3] There are currently no FDA approved medications for NASH.

Two oral medications are currently being evaluated as treatments for NASH with fibrosis. Resmetirom (RES) is a small molecule agonist for the thyroid hormone receptor beta (THR-beta). Obeticholic Acid (OCA) is a bile acid analog that was approved for the treatment of patients with primary biliary cholangitis (PBC) in 2016. ICER had previously reviewed OCA as a treatment for NASH in 2020 and found the evidence inconclusive at that time. The prior report can be accessed, here: https://icer.org/wp-content/uploads/2020/10/ICER_NASH_Evidence_Report_072120.pdf.

Topline data from a phase 3 trial found that more patients treated with resmetirom 80 mg or 100 mg than placebo had ≥ 1 stage improvement in fibrosis without worsening of NASH (24% and 26% vs. 14%) and more had NASH resolution without worsening of fibrosis (26% and 30% vs. 10%).[4] The most frequent adverse event was diarrhea (28% to 34% vs. 16% placebo); LDL-cholesterol decreased with resmetirom compared with placebo.[4]

More patients treated with OCA 25 mg for 18 months than placebo had achieved ≥ 1 stage improvement in fibrosis without worsening of NASH (22% vs. 10%) without significant differences between groups in NASH resolution without worsening of fibrosis.[5] The discontinuation rate because of adverse events was higher with OCA than placebo (21.6% vs. 11.3%) with pruritus seen in 55% of patients receiving OCA; pruritus was the most common adverse event leading to treatment discontinuation.[6] LDL-cholesterol increased initially with OCA; these increases came down over time, but it is unclear whether this improvement was due to initiation of treatment with cholesterol-lowering medication.[6]

NASH is typically asymptomatic for most of its clinical course, and that course can be long; in many patients, NASH does not progress.[7] Since the existing trials are relatively short, there are important uncertainties about their actual long-term benefits. For both drugs, it remains unclear whether the

changes in the primary outcomes will translate into a reduction in cirrhosis, decompensated liver failure, hepatocellular carcinoma (HCC), liver transplantation and death or into improvements in quality of life. Treatments for a condition that may never become symptomatic must necessarily be quite safe and tolerable if they are to be used for many years. There are concerns about the safety of OCA because of the initial increases in LDL-cholesterol levels and because of reports of hepatic decompensation and death in patients with PBC-related cirrhosis treated with OCA. Tolerability is a concern because of pruritus, although patients may decide to continue therapy and manage their pruritus. We have fewer concerns about the safety and tolerability of resmetirom.

As such, for resmetirom we conclude that there is moderate certainty of comparable to substantial net health benefits with high certainty of at least comparable benefits compared with standard of care (C++). For OCA, we judge the evidence for OCA in NASH with F2 fibrosis to be insufficient ("I") and with F3 fibrosis, where patients are at higher risk of progression to cirrhosis, to be promising but inconclusive ("P/I").

In our lifetime economic model, treatment of patients with NASH with fibrosis with either resmetirom or OCA resulted in small gains in QALYs, evLYs, and life years along with reductions in disease-related costs. The cost-effectiveness of both drugs will depend on their price. If the price of OCA is not substantially reduced from the price of the approved (lower) doses used for PBC, it will not meet typical cost-effectiveness thresholds. ICER's Health Benefit Price Benchmark (HBPB) for resmetirom is $39,600 to $50,100 and the HBPB for OCA is $32,800 to $40,700. Because of the large number of adults in the US with NASH, the short-term budget impact of newly approved treatments may be a concern even for treatments that are cost-effective in the long run.

1. Background

ICER reviewed obeticholic acid for NASH in 2020.[8] Much of the background information in this report is updated from that review. Nonalcoholic fatty liver disease (NAFLD) is common in the general population. An estimated 24% of adults in the United States (US) have NAFLD.[1] NAFLD requires the presence of fat in the liver (hepatic steatosis [HS]) without another explanation such as significant alcohol consumption or use of medications that cause HS.[2] NAFLD can be subcategorized as nonalcoholic fatty liver (NAFL), in which there is HS but no injury to liver cells (hepatocellular injury), and as nonalcoholic steatohepatitis (NASH), in which HS is accompanied by hepatocellular injury.

The exact prevalence of NASH is uncertain since diagnosis requires liver biopsy and many patients with NAFLD do not undergo biopsy. It is estimated that the prevalence of NASH in the adult population is between 1.5% and 6.5%.[1] Patients with NASH may have liver fibrosis, and liver fibrosis can progress to cirrhosis. Patients with cirrhosis are at high risk of death from liver failure and liver cancer (hepatocellular carcinoma [HCC]) and may require liver transplantation.[2] NAFLD is associated with metabolic syndrome with or without type 2 diabetes mellitus (T2DM), and NAFLD and metabolic syndrome share the common risk factor of obesity. Metabolic syndrome is a major risk factor for cardiovascular disease (CVD), and despite an increased risk of death from liver-related causes, CVD is the most common cause of death in patients with NAFLD.[1] NASH has become a major cause of cirrhosis and, as effective treatment of hepatitis C is now available, it has become the leading reason for liver transplantation.[9]

The prognosis of NAFLD is variable. Most patients with NAFLD 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 improve 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.[10] 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.[11]

Lifestyle changes that result in improvement in the metabolic syndrome, including diet, exercise, and weight loss, can improve NASH, as can weight loss after bariatric surgery; bariatric surgery also improves T2DM and the metabolic syndrome.[2,3] There have been limited pharmacologic options for treating NASH, although many are now in development. Vitamin E and pioglitazone may improve the histologic changes of NASH[2], but are falling out of favor among patients and clinicians.[2]

Obeticholic acid (OCA; Ocaliva™; Intercept Pharmaceuticals) is a bile acid analog that selectively binds to the farnesoid X-activated receptor (FXR), which inhibits triglyceride synthesis and decreases fat deposition in the liver. It was approved for the treatment of patients with primary

biliary cholangitis in 2016. It is taken orally once daily. OCA is under review as a treatment for NASH with fibrosis, with a Food and Drug Administration (FDA) decision expected on June 22, 2023. ICER had previously reviewed OCA as a treatment for NASH in 2020 and found the evidence inconclusive at that time. The FDA issued a Complete Response Letter in 2020 stating that OCA's efficacy and safety data were insufficient to support accelerated approval at that time. The prior report can be accessed, here:

https://icer.org/wp-content/uploads/2020/10/ICER_NASH_Evidence_Report_072120.pdf

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

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 challenges 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 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, including liver transplantation. They also highlighted the additional burden of the fear and uncertainty that comes with living with a disease with no proven cure.

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. One person described the exhaustion as "feeling like I was walking through cement." 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 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.

An additional burden is the stigma experienced by patients living with cirrhosis. Patients described the assumption among the health care providers and the public that anyone with cirrhosis was either an alcoholic or drug user. This often adversely impacted their interactions with the health care system.

If patients do receive a liver transplant, the medications used to prevent transplant rejection can introduce new medical issues including new or worsening hypertension and diabetes as well as damage to the kidneys.

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 while 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 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 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 also heard from some in the community that they consider NASH to be a chronic, inexorably progressive disease.

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 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.

Patients are hopeful that there will finally be new therapies approved for NASH, though they expressed frustration about how long it has taken. They view OCA and resmetirom as steps in the right direction. They highlighted consensus among patients with NASH that the most important outcome is halting the progression of fibrosis. Any drug that halted fibrosis at stage F1 or F2 would be hailed as lifesaving. Patients also wanted us to highlight the willingness of some people living with NASH to tolerate side effects of effective therapy to prevent progression of their disease.

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. Comparative Clinical Effectiveness

3.1. Methods Overview

Detailed methods for the systematic literature review assessing the evidence on resmetirom and obeticholic acid for the treatment of NASH are detailed in Supplement Section D1.

Scope of Review

Resmetirom

We reviewed the clinical effectiveness of resmetirom for the treatment of NASH compared to no pharmacologic therapy, as represented by the placebo arm of the clinical trials.

Obeticholic Acid

We updated our prior review of the clinical effectiveness of obeticholic acid for the treatment of NASH compared to no pharmacologic therapy, as represented by the placebo arm of the clinical trials.

For both interventions, we searched for evidence in November 2022 on patient-important outcomes including all-cause mortality, cirrhosis, decompensated cirrhosis, health-related quality of life, cardiovascular events, and adverse events. Other outcomes included fibrosis stage, NASH resolution, quantitative measures of liver fat content, and changes in lipid levels. The full scope of the review is available in Supplement Section D1.

Evidence Base

Resmetirom

A total of seven references from three randomized, double-blind, placebo-controlled trials of resmetirom met our inclusion criteria.[4,12-16] Details about the study design of the trials can be found in Table 3.1 and in Supplement Table D6.

The key trial is MAESTRO-NASH, a large phase 3 trial.[4] Only topline results at 52 weeks are available. The investigators randomized 966 patients to receive once-daily resmetirom 80 mg, resmetirom 100 mg, or placebo. Adult patients were enrolled if they had biopsy-proven NASH based on a recent liver biopsy with fibrosis stages 1 to 3 and a NAFLD Activity Score (NAS) of ≥ 4, with a score of at least 1 in each component, and had ≥ 8% liver fat on magnetic resonance imaging-proton density fat fraction (MRI-PDFF).[16] Patients were also eligible if they had suspected or confirmed diagnosis of NASH with metabolic risk factors, AST ≥ 20 U/L, and liver fibrosis defined

using either biochemical test or Fibroscan or historical liver biopsy. The co-primary outcomes were ≥ 1 point improvement in fibrosis stage with no worsening of NAS and NASH resolution with ≥ 2 point reduction in NAS without worsening of fibrosis. All biopsies were read independently by two central pathologists.[16]

In the MAESTRO-NASH phase 3 trial, mean age for all participants (N = 966) was 57 years and 89% were White with a mean BMI of 36 kg/m^2.[4] Hispanics were well represented in this trial (21%).[4] Comorbidities including type 2 diabetes (67%), hypertension (78%), and dyslipidemia (71%) were common among the MAESTRO-NASH trial participants.[4] Approximately 95% of the MAESTRO-NASH trial participants had F2-F3 fibrosis stages, 33% F2 and 62% F3; the remaining 5% had stage F1B.[16] Other than the phase 2 trial and open label extension phase including a significant proportion of NASH participants with F1 stage, baseline characteristics were similar in all resmetirom trials included in this review. Details about the phase 2 trial including open label extension, and MAESTRO-NAFLD-1 trial are presented in the Supplement Section D2.

Table. 3.1 Overview of Key Studies

Trial & Design	Population	Primary Outcomes	Longest Follow-Up
Resmetirom			
MAESTRO-NASH[17] **Phase 3** **(N = 966)**	Adults ≥18 years with suspected or confirmed NASH and ≥ 8% fat content on MRI-PDFF	- ≥1 point improvement in fibrosis with no NAS worsening - NASH resolution with ≥2 point reduction in NAS without worsening of fibrosis	52 weeks
Phase 2 DB[18] **(N = 125)** **Phase 2 OLE[14]** **(N = 31)**	DB: Adults ≥18 years old with biopsy proven NASH and ≥10% MRI-PDFF fat fraction OLE: Phase 2 participants with 36-week MRI-PDFF and 36-week liver-biopsy in the parent study	DB: Change from baseline in hepatic fat fraction by MRI-PDFF OLE: Change in MRI-PDFF for an additional 36 weeks	DB: 36 weeks OLE: 36 weeks
MAESTRO-NAFLD-1[19] **Phase 3** **(N = 972)**	Adults ≥18 years with suspected or confirmed diagnosis of NASH or NAFLD and ≥8% MRI-PDFF fat fraction	Adverse events at 52 weeks	52 weeks
Obeticholic Acid (OCA)			
REGENERATE[20] **Phase 3** **(N = 2,477)**	Adults 18 to 65 years old with NASH and stage 2-3 fibrosis or stage 1 with additional risk factors	- ≥1 stage improvement in fibrosis and no worsening of NASH - NASH resolution and no worsening of fibrosis stages	18 months
FLINT[21] **Phase 2** **(N = 196)**	Adults ≥18 years with definite or probable NASH	≥2 point NAS reduction without worsening of fibrosis	96 weeks

DB: double blind, MRI-PDFF: magnetic resonance imaging proton density fat fraction, N: total number, NAS: non-alcoholic fatty liver disease activity score, OLE: open-label extension

Obeticholic Acid

Initially, the REGENERATE trial randomized a total of 2,477 patients 1:1:1 to receive once-daily OCA 25 mg, OCA 10 mg, or placebo.[6] Excluding an exploratory cohort with F1 stage (N=290), the manufacturers identified a total of 2,187 participants with fibrosis stages 2 or 3 as the intention-to-treat (ITT) efficacy population. A preplanned interim analysis was conducted in 2019 with a total of 931 F2-F3 participants and the results were included in the prior ICER review of OCA.[22] However, the FDA requested the manufacturer reread the liver biopsies using a consensus panel of pathologists to control inter- and intrareader variability. Using this consensus method, at least 2 of the 3 pathologists had to agree on all four histologic features. The manufacturer revised the primary endpoint results for those 931 participants and provided data on an additional 676 participants for a total of 1607 with histology results.[6]

The mean age for the 2,477 REGENERATE trial participants was 55 years and more than 80% of them were White with a mean BMI of 34 kg/m^2.[6] A significant proportion of the participants were Hispanic or Latino (27%). Approximately 58% of the participants had type 2 diabetes. Baseline liver biopsy confirmed that the ITT efficacy population (N = 2,187) had only fibrosis stages F2-F3 in all treatment arms, with 40% stage F2 stage and 60% stage F3.[6] Similar baseline characteristics were observed in the FLINT trial.[23] This report mainly focused on OCA 25 mg dose because we assume that the FDA submission for approval of this drug for the treatment of NASH only includes OCA 25 mg, not the 10 mg dose. Details about the OCA 10 mg dose are presented in Supplement Section D2.

3.2. Results

Clinical Benefits

Resmetirom

In MAESTRO-NASH, 24% (80 mg) and 26% (100 mg) of patients randomized to resmetirom had ≥ 1 stage improvement in fibrosis without worsening of NASH compared with 14% for the placebo group (P < 0.0001 for both comparisons).[4] In addition, 26% (80 mg) and 30% (100 mg) of patients randomized to resmetirom had NASH resolution without worsening of fibrosis stage compared to 10% of the placebo group (P < 0.0001 for both comparisons).[4] The phase 2 trial results at 12 weeks were similar for NASH resolution (Table 3.2).[12]

Table 3.2. Key Trial Results: Resmetirom

	MAESTRO-NASH[4]			Phase 2[12]	
	Placebo (N=318)	Resmetirom 80 mg (N=316)	Resmetirom 100 mg (N=321)	Placebo (N=41)	Resmetirom (N=84)
≥1 stage improvement in fibrosis with no worsening of NASH at 12 months	14%	24%†	26%*	NR	
NASH resolution without worsening of fibrosis stage at 12 months	10%	26%*	30%*	7%	25%‡

mg: milligram, n: total number, NR: not reported
* p<0.001 versus placebo
† p=0.0002 versus placebo
‡ p = 0.032 versus placebo

There were significant improvements in secondary outcomes including the individual histological measures that are used in the NAS score, MRI-PDFF fat content, liver enzymes, and LDL-cholesterol.[4] No data on health-related quality of life (HRQoL) were available for MAESTRO-NASH. Participants in the Phase 2 trial were assessed for changes in HRQoL using the Short Form Health Survey-36 (SF-36). At 36 weeks there were no differences between groups on any of the 10 SF-36 subscales.[12] (Supplement Table D13).

Obeticholic Acid

The primary outcomes were assessed at month 18 in a preplanned interim analyses on a population of 931 (47%) participants.[6] Using the consensus panel results, 22% of patients receiving OCA 25 mg achieved ≥ 1 stage improvement in fibrosis without worsening of NASH compared with 10% of the placebo group (p=0.0001).[6] The revised histology confirmed the prior findings that there were no significant differences in NASH resolution without worsening of fibrosis stage (Supplement Table D17).[5]

Table 3.3. Updated Results Based on New Analysis: REGENERATE trial[6]

	Revised Interim Analysis		Available Subset of ITT Population	
	Placebo (N=311)	OCA 25 mg (N=308)	Placebo (N=536)	OCA 25 mg (N=539)
≥1 stage improvement in fibrosis with no worsening of NASH at 18 months	9.6%	22.4%*	12.3%	21.0%*
NASH resolution without worsening of fibrosis stage at 18 months	3.5%	6.5%	NR	

ITT: intention-to-treat, mg: milligram, N: total number, NR: not reported, OCA: obeticholic acid
*p<0.0001 versus placebo

The initial increase in LDL-cholesterol levels with OCA returned to baseline after approximately 12 months and remained there through 54 months.[6] It is unclear if this was due to resolution of a short-term metabolic effect or increased use and dosage of cholesterol lowering medications. Participants receiving OCA 25 mg had a greater reduction in ALT compared to those randomized to placebo at 18 months (-30% vs. -12%, p<0.0001).[24] However, the between group difference was smaller at 48 months (-31% vs. -20%, p<0.0001).[24] Participants receiving OCA 25 mg also had a marginal reduction from baseline in liver stiffness, while the placebo group experienced an increase in liver stiffness value at 18 months (-1.1% vs. + 0.41%, p=0.004).[24] See Supplement Table D18. Quality of life was assessed in the REGNERATE trial using the Chronic Liver Disease Questionnaire (CLDQ)-NASH and EuroQol EQ-5D-5L. Baseline scores were similar between treatment groups. After 18 months of treatment, small numeric differences were seen between OCA 25 mg and placebo. The change in the itch domain score for the OCA 25 mg arm was statistically worse than the placebo arm but the difference was less than the minimum clinically important difference (Supplement Table D19).[25,26]

Harms

Resmetirom

In MAESTRO-NASH, more participants in the resmetirom 100 mg group (7.7%) discontinued because of adverse events compared to resmetirom 80 mg (2.8%) and placebo (3.7%).[4] Approximately 12% of participants in each of the three treatment arms experienced serious adverse events.[4] The most frequent adverse event in all the resmetirom trials was diarrhea. MAESTRO-NASH topline results reported around 34% and 28% of the participants having mild and transient diarrhea in resmetirom 100 mg and 80 mg arms, respectively, compared to only 16% of the placebo participants.[4] It is unclear if this is the primary reason for the increased discontinuation rate in the 100 mg dose arm. None of the resmetirom trials reported patients complaining of pruritus. See table 3.4 and Supplement Table D14.

Table 3.4. Resmetirom Adverse Events and Discontinuation

	MAESTRO-NASH[4]			Phase 2[12]	
	Placebo (N=318)	Resmetirom 80 mg (N=316)	Resmetirom 100 mg (N=321)	Placebo (N=41)	Resmetirom (N=84)
Serious Adverse Events	12.1%	11.8%	12.7%	4.9%	6%
Diarrhea	16%	28%	34%	2%	4%
Overall Discontinuation	NR	NR	NR	17%	12%
Discontinuation due to Adverse Events	3.7%	2.8%	7.7%	2.4%	3.6%

mg: milligram, N: total number, NR: not reported

Obeticholic Acid

The topline results from a new analysis of the REGENERATE trial reported that approximately 1,000 participants with NASH received OCA for at least four years.[6] The discontinuation rate because of adverse events was almost double in the OCA 25 mg group (21.6%) than placebo (11.3%).[6] The frequency of serious adverse events was similar across both arms of the REGENERATE trial (26% in the OCA 25 mg, and 22% in the placebo group).[6] Gallbladder disease was most common among the reported serious adverse events.[6] More participants developed gallbladder disease in the OCA 25 mg group (2.5%) compared to the placebo (0.7%).[6] In addition, more participants were diagnosed with severe hyperglycemia or diabetes in the OCA 25 mg group (1.1%) compared to placebo (0.1%).[6] The REGENERATE trial also reported 10 deaths in the OCA 25 mg, and eight in the placebo group but majority of them were not related to cardiovascular reasons.[6] Approximately 1% of participants in each arm experienced a major adverse cardiac event (MACE), defined as a combination of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for unstable angina.[6] The FLINT trial reported observing 18 cardiovascular related adverse events in the OCA 25 mg group compared to 16 events in the placebo.[23] In the REGENERATE trial, there were seven cases of liver injury adjudicated as highly likely or probably related to treatment in the OCA 25 mg group compared to only 1 case in the placebo group.[6] See Table D21.

Pruritus was a common adverse event with OCA. A total of 55% of the participants experienced pruritus in the OCA 25 mg group compared to 24% participants in the placebo group (table 3.5).[6] Most importantly, pruritus was the main adverse event leading to treatment discontinuation in the OCA 25 mg group.[6] More than half of the adverse events related discontinuations in the OCA 25 mg were because of pruritus compared to only 9% in the placebo group.[6]

Table 3.5. Obeticholic Acid Adverse Events and Discontinuation

	REGENERATE[6]	
Arm	Placebo (N=825)	OCA 25 mg (N=827)
Serious AEs, n (%)	21.9%	26.1%
Death, n (%)	1.0%	1.2%
Overall Discontinuation	NR	NR
Discontinuation due to AEs, n (%)	11.3%	21.6%
Pruritus, n (%)	24.4%	54.8%

mg: milligram, N: total number, NR: not reported, OCA: obeticholic acid

Subgroup Analyses and Heterogeneity

The MAESTRO-NASH trial reported that the key primary outcomes were achieved regardless of baseline fibrosis stage or diabetes status but no subgroup data were presented.[4]

The REGENERATE revised analyses found a higher response rate among the participants with F3 fibrosis stage at baseline compared to participants with F2 stage (Table 3.6).[6] It is worth noting that data on both primary endpoints stratified by fibrosis stages were only available for the preplanned interim analyses population (N=931). Approximately one in four OCA 25 mg participants with F3 at baseline achieved ≥ 1 stage improvement in fibrosis without worsening of NASH and the difference in responder percentage was statistically significant when compared to placebo (p<0.0001).[6] Although statistically significant difference was found comparing to placebo (p=0.04), only 19% OCA 25 mg participants with F2 at baseline achieved this endpoint.[6]

Table 3.6. Updated Results Stratified by Fibrosis Stage: REGENERATE trial[6]

	Fibrosis Stage 3 (F3)		Fibrosis Stage 2 (F2)	
	Placebo (N=169)	OCA 25 mg (N=169)	Placebo (N=142)	OCA 25 mg (N=139)
≥1 stage improvement in fibrosis with no worsening of NASH at 18 months	9.5%	25.4%*	9.9%	18.7%†

mg: milligram, N: total number, OCA: obeticholic acid

*p=0.0001 versus placebo

†p=0.0396 versus placebo

Uncertainty and Controversies

NASH is typically asymptomatic for most of its clinical course, and that course can be long. As such, the therapies that are intended to alter the progression of liver fibrosis over many years, but have only been studied in trials lasting several years. Thus, there are important uncertainties about their actual long-term 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 OCA. OCA initially raised LDL-C levels in patients who are at high risk for CV disease, though the differences between the OCA and placebo groups disappeared with time. When used for primary biliary cirrhosis at doses lower than those for NASH, OCA had reports of hepatic decompensation and death.

Trials of resmetirom 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 resmetirom and OCA via network meta-analysis (NMA) were not possible.

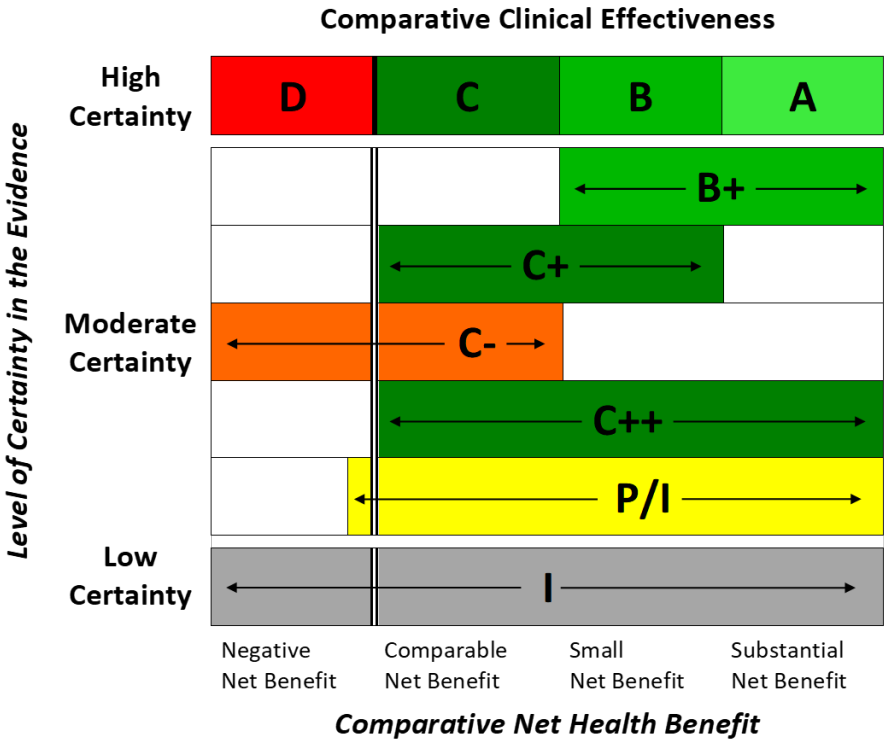
For both drugs, it remains unclear whether the changes in the primary outcomes will translate into a reduction in cirrhosis, decompensated liver failure, HCC, liver transplantation and death or into improvements in quality of life. Long term follow-up of the randomized trials should be able to answer these questions.

For resmetirom, whether the LDL lowering will persist and result in a reduction in cardiovascular outcomes remains unclear. Similarly, for OCA it is uncertain whether the LDL increase is truly transient or will result in an increase in cardiovascular events.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. 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, resmetirom appears to reduce progression, promote regression of fibrosis, and lead to resolutions of NASH compared with placebo. There is uncertainty about the long-term importance and benefit of these changes, but we assess that it is likely that resmetirom will reduce progression to cirrhosis, and thus improve certain patient-important outcomes, over the long-term. The magnitude of this benefit, however, is uncertain. The harms appear small, though diarrhea is common and there were more discontinuations due to adverse events in the high dose resmetirom group. Reassuringly, LDL-cholesterol levels were reduced with resmetirom compared with placebo, which may translate into a reduction in CVD events and death over time, though this remains to be demonstrated. Given the uncertainties, we conclude that there is moderate certainty of comparable to substantial net health benefits with high certainty of at least comparable benefits compared with standard of care (C++).

In patients with NASH and fibrosis, OCA appears to reduce progression and promote regression of fibrosis compared with placebo, although less than half of the randomized patients were assessed with biopsy at 18 months. 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 increase in LDL-cholesterol seen initially with OCA is particularly concerning because CVD is the primary cause of death in patients with NASH. 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").

Table 3.7. Evidence Ratings

Population	Evidence Rating
Resmetirom	
NASH patients of any fibrosis stage	C++
Obeticholic acid	
NASH patients with Stage 2 fibrosis	I
NASH patients with Stage 3 fibrosis	P/I

4.Long-Term Cost Effectiveness

4.1 Methods Overview

The primary aim of this analysis was to estimate the cost-effectiveness of resmetirom and OCA for NASH using a decision analytic model. The model compares both treatments to standard care. The base-case analysis takes a health care sector perspective (i.e., focuses on direct medical care costs only), and a lifetime horizon. Productivity changes and other indirect costs and effects are considered in a scenario analysis using a modified societal perspective. The model was developed in Microsoft Excel.

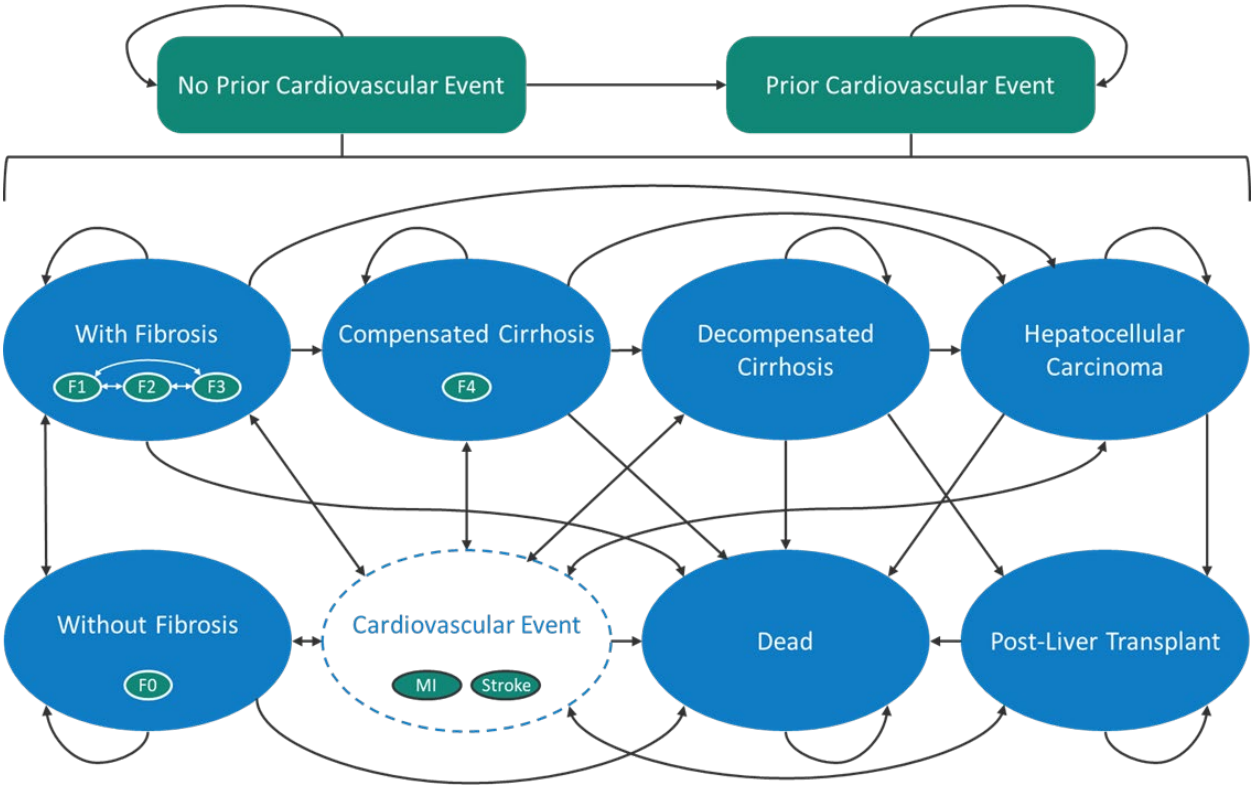
We adapted the 2020 ICER decision analytic model for patients with NASH with fibrosis for this evaluation.[8] Clinical and economic model inputs were updated from key clinical trials, the prior ICER model, prior relevant economic models, and published literature. [8,27]Costs and outcomes were discounted at 3% per year.

The model simulates a hypothetical cohort of patients with NASH being treated with resmetirom, obeticholic acid, or standard care. Model cycle length was annual.

The Markov model structure was composed of two cardiovascular (CV) event history submodels with equivalent liver disease-specific state transition probabilities (Figure 4.1). Each submodel allows 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 remained in the model until they died. 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. Patients with NASH who enter the prior CV event submodel experienced the same liver-related transition probabilities after experiencing a CV event but an increased risk for recurrent CV events and mortality. Diabetes was not explicitly modeled due to lack of data on differential effects by diabetes status. We note that it was included as a component in the Framingham risk score that determined CV risk.

Figure 4.1. Model Schematic



In response to public comments and internal model validation processes, changes to the economic evaluation between the draft Evidence Report and the Evidence Report included:

- Updating cost estimates for early and advanced fibrosis health states using estimates from the GAIN study[28]
- Correcting the discontinuation rate for OCA
- Correcting health state costs used for HCC
- Presenting advanced liver disease outcomes
- Adding additional scenario analyses:
    - Fibrosis progression based on Phase II results for Resmetirom
    - Including the cost of biopsy in the first cycle
    - Discontinuation due to adverse events only
    - Discontinuation for resmetirom based on phase II data that assessed discontinuation by early (up to 12 weeks) versus late (week 13-36)[28]

4.2 Key Model Assumptions and Inputs

Our model includes several assumptions stated below.

Table 4.1. Key Model Choices and Assumptions

Assumption	Rationale
Treatment effects for "improvement" and "worsening" were used as the basis for deriving transition probabilities among fibrosis stages and applied uniformly regardless of starting stage.	Stage-level outcome achievement is not reported in the available clinical trial data. Specific stage transitions for both OCA and Resmetirom were weighted by the results of a meta-analysis of fibrosis progression in NAFLD vs. NASH.[29]
Pending detailed data from the resmetirom phase III trial, we assumed that the absolute difference in the improvement in fibrosis without worsening of NAS between treatment groups was comparable to the absolute difference between improvement in fibrosis alone between treatment groups.	Only top line data from the phase III are currently available. We further note that data from the OCA phase III trial support the comparability of these two estimates.
Patients who transition to F4 were assumed to discontinue OCA treatment.	The New Drug Application (NDA) for approval of OCA therapy stipulates that OCA treatment must be discontinued in patients with symptoms of cirrhosis. We considered a scenario analysis of treating 50% of F4 patients with OCA based on clinical expert opinion that OCA may slow or reverse deterioration in patients with compensated cirrhosis
Patients continued OCA or resmetirom treatment as they continued to respond to treatment and remained in F4 lower.	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 were 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 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.	Input from clinical experts indicated that increased LDL-C puts patients at an increased risk of CV events.
All patients receive treatment for systolic blood pressure and no patients were smokers. Patient systolic blood pressure (132 mm Hg) was based on the FLINT trial.	These demographic characteristics were not reported in the REGENERATE or MAESTRO-NASH trials but were required for the Framingham Heart Study calculations which were used to calculate CV event risk in the model.

CV: cardiovascular, LDL: low density lipoprotein, mmol/L: Millomoles per liter, NAFLD: non-alcoholic fatty liver disease, NASH: Non-Alcoholic Steatohepatitis, OCA: obeticholic acid

The population comprised a hypothetical cohort of patients with NASH fibrosis stages 2 and 3 being treated with either OCA, resmetirom, or standard care. The baseline patient characteristics for the model are outlined in Table 4.2 and are based on pooled estimates from the REGENERATE trials.[30]

Table 4.2. Baseline Population Characteristics

Baseline Characteristics	REGENERATE Pooled Population
Mean age (SD)	55
Female (%)	58.5
Fibrosis stage F0 (%)	0
Fibrosis stage F1 (%)	0
Fibrosis stage F2 (%)	45.4
Fibrosis stage F3 (%)	54.6
NAS ≥6 (%)	68.6
Type 2 diabetes (%)	55.9
Dyslipidemia (%)	67.2
Hypertension (%)	66.4
LDL cholesterol, mg/dL (SD)	114.1

LDL: low density lipoprotein, mg/dL: Milligrams per deciliter,
NAS: non-alcoholic fatty liver disease activity score,
SD: standard deviation, TBD: to be determined
Source: Younossi et al., 2019[30]

Clinical Inputs

For transitions with resmetirom, we used available top line results from the Phase III trial, coupled with data from the Phase II trial. We used the 12% absolute risk difference seen for ≥1-stage improvement in fibrosis with no worsening of NAS as a proxy for ≥1-stage improvement in fibrosis alone and applied it to the placebo rates used in resmetirom's prior early economic model. The remaining distributions for patients staying the same or having worsened fibrosis on resmetirom were proportionally weighted by the Phase II MAESTRO-NASH trial that approximated the clinical effect using MRI-PDFF treatment responses. These probabilities were held constant throughout the model lifetime.

We utilized results of the REGENERATE trial as the basis for modeling transitions among fibrosis health states for OCA. Specifically, the absolute risk differences between OCA and placebo in the per-protocol probabilities for worsening and improvement in fibrosis were applied to the probability of worsening and improvement fibrosis health states for standard care to obtain the probabilities for OCA. These probabilities were held constant throughout the model lifetime. The outcome for no change in fibrosis was calculated as the remainder of improvement and worsening outcomes.

These data are shown in Table 4.3.

Table 4.3. Efficacy Endpoints for Improvement and Worsening of Fibrosis

Parameter	Base Case	Lower Value	Upper Value	Source
Resmetirom Absolute Risk Difference vs. Standard Care*				
Improvement of Fibrosis	0.12	0.11	0.13	Madrigal Pharmaceuticals, 2023[4]
Worsening of Fibrosis	-0.12	-0.11	-0.14	
Obeticholic Acid Absolute Risk Difference vs. Standard Care*				
Improvement of Fibrosis	0.15	0.14	0.17	Younossi et al., 2019[30]
Worsening of Fibrosis	-0.08	-0.07	-0.09	
Standard Care Probabilities*				
Improvement of Fibrosis	0.23	0.21	0.26	Younossi et al., 2019 (placebo group)[30]
Worsening of fibrosis	0.21	0.19	0.23	

*Per-protocol estimates

Transition Probabilities

The MAESTRO-NASH and REGENERATE trials did not report specific fibrosis stage transitions, and it is not known if they will be available in the final analyses. Therefore, we use the distributions of transitions of NASH patients between fibrosis stages from Singh et al.[29] to calculate transition weights (Table E.2.) to apply to the improvement/worsening/no change treatment effects to estimate stage-specific transition probabilities for standard care, resmetirom, and OCA (Tables E.3.-E.5.).

Discontinuation

For OCA, we derived an annual discontinuation rate from the REGENERATE trial based on all-cause discontinuation at 18 months (25.0%; annual probability of discontinuation = 17.45%). For resmetirom, we derived an annual discontinuation rate from the MAESTRO-NASH trial based on all-cause discontinuation at 36 weeks (11.9%, annual probability of discontinuation = 16.76%). We included a scenario analysis in which we used discontinuation rates due to adverse events only as observed in the clinical trials. These were 3.6% in 36 weeks for resmetirom and 13.6% in 18 months for OCA.

All patients were assumed to discontinue upon reaching F4. We ran a scenario analysis in which 50% of patients in the F4 health state could still improve their fibrosis stage and thus continue treatment after 2 years, while the remaining 50% could not improve and discontinued treatment. All patients who transition to either the decompensated cirrhosis or HCC health states were assumed to discontinue treatment.

Health State Utilities

Health state utilities were derived from the Global Assessment of the Impact of NASH (GAIN) study,[28] 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 (Table 4.4.). Cirrhosis and HCC utilities were obtained from patients with hepatitis C and the liver transplantation utility was obtained from a systematic literature review of liver transplant patients with varying advanced liver etiology. Additionally, we included disutilities for CV events as well as living with CV disease. Disutilities for CV events were assumed to last one year.

Table 4.4. Health State Utilities

Health State	Base Case	Lower Value	Upper Value
NASH Fibrosis Stage 0-2[28]	0.76	0.61	0.91
NASH Fibrosis Stage 3[28]	0.73	0.64	0.82
Compensated Cirrhosis[31]	0.66	0.49	0.83
Decompensated Cirrhosis[31,32]	0.57	0.46	0.68
Hepatocellular Carcinoma [31,33]	0.50	0.40	0.60
Liver Transplantation (Year of) [34]	0.66	0.49	0.83
Post-Liver Transplantation [34]	0.73	0.64	0.82
Disutility: Myocardial Infarction Event[35]	-0.041	-0.041	-0.041
Disutility: Stroke Event[35]	-0.052	-0.053	-0.052
Disutility: Prior Cardiovascular Event[35]	-0.034	-0.034	-0.033

Cost Inputs

All costs used in the model were updated to 2022 US dollars.

Drug Costs

In the absence of known prices for resmetirom and OCA for the treatment of NASH, we used placeholder prices based on Javanbakht et al 2022[27] and currently available strengths of OCA, respectively as outlined in Table 4.5.

Table 4.5. Drug Costs

Drug	WAC per Dose	Discount from WAC	Net Price per Dose	Net Price per Year
Resmetirom*	NA	NA	$52.05	$19,000
Obeticholic Acid, 25 mg[†]	$268.15	13.1%	$233.02	$85,000

WAC: wholesale acquisition cost, NA: not available

*Placeholder price based on Javanbakht et al 2022[27]
†Placeholder price for obeticholic acid was based on the discounted WAC price for the 5 and 10 mg tablets from Redbook assuming that a 25mg tablet will be available. The discount from WAC was based on an average of the most recent four quarters available from SSR health (2021 Q4 to 2022 Q3).

Non-Drug Costs

We used NASH-specific costs for early and advanced fibrosis based on the US estimates from the GAIN study where direct medical resource utilization information was collected on web-based case record forms by specialists. These estimates were then adjusted to an annual time period.[28]. CV disease costs were obtained from a published cost-effectiveness analysis of PCSK9 inhibitor therapy by Kazi et al.,[36] and a cost estimation of CV disease study by O'Sullivan et al.[37]

Table 4.6. Annual Non-Drug Costs

Annual Cost	Base Case	Lower Value	Upper Value
F0-F2[28]	$7,063	$5,650	$8,475
F3[28]	$8,423	$6,738	$10,108
Compensated Cirrhosis[38]	$34,275	$27,420	$41,131
Decompensated Cirrhosis[38]	$158,480	$126,784	$190,176
Hepatocellular Carcinoma[38]	$115,002	$92,001	$138,002
Liver Transplant Procedure[38]	$232,674	$186,140	$279,209
Post Liver Transplant Procedure[38]	$43,358	$34,686	$52,030
MI Event[36]	$60,425	$48,340	$72,510
Stroke Event[36]	$64,375	$51,500	$77,250
Post-MI[36]	$2,980	$2,384	$3,576
Post-Stroke[36]	$6,273	$5,018	$7,527
CV Death Event[37]	$20,035	$16,028	$24,041

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

4.3 Results

Base-Case Results

The total discounted costs, life years (LYs) gained, quality-adjusted life years (QALYs) gained, equal-value life years (evLYs) gained are detailed in Table 4.7 for resmetirom versus SC. Over a lifetime

horizon, treatment with resmetirom resulted in incremental cost savings of approximately $22,400, and incremental QALYs and evLYs of approximately 0.60 and 0.68, respectively, compared to SC alone from the health care sector perspective. The modest survival benefit from the base-case analysis with resmetirom compared to SC was a result of delayed disease progression. More detailed summaries of the relevant clinical event(s) avoided (e.g., liver transplant, decompensated cirrhosis) are in Supplement E.

Table 4.7 Results for the Base-Case for Resmetirom Compared to Standard Care, Health Care Sector Perspective

Treatment	Drug Cost*	Total Cost	QALYs	evLYs	Life Years
Resmetirom	$76,000	$416,000	10.66	10.74	15.05
Standard Care	$0	$439,000	10.05	10.05	14.56

evLY: equal value of life-year, LY: life-year, QALY: quality-adjusted life-year
*Placeholder price based on Javanbakht et al 2022[27]

The total discounted costs, LYs gained, QALYs gained, evLYs gained are detailed in Table 4.8 for OCA versus SC. Over a lifetime horizon, treatment with OCA resulted in higher incremental costs of approximately $237,000, and incremental QALYs and evLYs gains of approximately 0.43 and 0.48, respectively, compared to SC alone from the health care sector perspective. The modest survival benefit from the base-case analysis with OCA compared to SC was a result of delayed disease progression. More detailed summaries of the relevant clinical event(s) avoided (e.g., liver transplant, decompensated cirrhosis) are in Supplement E.

Table 4.8 Results for the Base-Case for Obeticholic Acid Compared to Standard Care, Health Care Sector Perspective

Treatment	Drug Cost*	Total Cost	QALYs	evLYs	Life Years
Obeticholic Acid	$317,000	$676,000	10.48	10.53	14.88
Standard Care	$0	$439,000	10.05	10.05	14.56

evLY: equal value of life-year, LY: life-year, QALY: quality-adjusted life-year

*Placeholder price for obeticholic acid was based on the discounted WAC price for the 5 and 10 mg tablets from Redbook assuming that a 25mg tablet will be available. The discount from WAC was based on an average of the most recent four quarters available from SSR health (2021 Q4 to 2022 Q3).

Table 4.9. presents the incremental cost-effectiveness ratios from the base-case analysis, which includes estimates from the incremental cost per QALY gained, incremental cost per evLY gained, and incremental cost per LYG. For resmetirom compared to SC alone, the incremental cost per QALY gained resulted with resmetirom as the less costly, more effective treatment choice from the health care system perspective, with the incremental cost per evLY gained resulting in a similar conclusion. For OCA compared to SC alone, the incremental cost per QALY gained was approximately $558,000 from the health care system perspective, and the incremental cost per evLY gained was approximately $496,000.

Table 4.9. Incremental Cost-Effectiveness Ratios for the Base Case, Health Care Sector Perspective

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained
Resmetirom*	Standard Care	Less costly, more effective	Less costly, more effective	Less costly, more effective
Obeticholic Acid†	Standard Care	$558,000	$496,000	$754,000

evLY: equal value of life-year, LY: life-year, QALY: quality-adjusted life-year

*Placeholder price based on Javanbakht et al 2022[27]

†Placeholder price for obeticholic acid was based on the discounted WAC price for the 5 and 10 mg tablets from Redbook assuming that a 25mg tablet will be available. The discount from WAC was based on an average of the most recent four quarters available from SSR health (2021 Q4 to 2022 Q3).

Sensitivity Analyses

Results from one-way sensitivity analyses and probabilistic sensitivity analyses for both resmetirom and OCA can be found in Supplemental Section E4.

Scenario Analyses

We conducted numerous scenario analyses to examine uncertainty and potential variation in the findings. A list of these scenarios and the results can be found in Supplemental Section E5.

Threshold Analyses

Threshold analyses were conducted to calculate the annual price needed to meet commonly accepted cost-effectiveness thresholds for QALY gained (Table 4.10) and evLY gained (Table 4.11).

Table 4.10. QALY-Based Threshold Analysis Results

Drug/Treatment	Annual Price to Achieve $50,000 per QALY Gained	Annual Price to Achieve $100,000 per QALY Gained	Annual Price to Achieve $150,000 per QALY Gained	Annual Price to Achieve $200,000 per QALY gained
Resmetirom	$32,100	$39,600	$47,100	$54,600
Obeticholic Acid	$27,100	$32,800	$38,500	$44,300

QALY: quality-adjusted life-year

Table 4.11. evLY-Based Threshold Analysis Results

Drug/Treatment	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Resmetirom	$33,100	$41,600	$50,100	$58,600
Obeticholic Acid	$27,800	$34,200	$40,700	$47,100

evLY: equal value of life-year

Uncertainty and Controversies

There were important uncertainties relevant to generating model outcomes, related to the effectiveness on fibrosis progression and drug costs for both resmetirom and OCA. The lack of detailed data on stage specific changes in fibrosis stage required a number of assumptions regarding these estimates in the model. These included assumptions about the relationship between the treatment effect across different fibrosis metrics, the distribution of those effects across fibrosis change categories, and the stage-specific distribution of fibrosis changes."

For OCA, given the ITT results were not available from the Phase III trial, we used per-protocol estimates for both OCA and placebo for improvement or worsening of fibrosis. Similar to resmetirom, in the absence of data to inform stage-specific transition probabilities, we applied an absolute risk difference uniformly across different starting fibrosis stages, and these were also weighted by stage-specific transitions from the literature and not from the REGENERATE trial.

In our analyses, treatment with resmetirom or OCA resulted in additional life-years gained compared to their respective standard care comparators. Neither drug has demonstrated a direct survival benefit in a clinical trial or observational study to date. This reduction in mortality seen in the model was an indirect result of slowing disease progression with both drugs.

We also assumed the underlying risk of CV events could be accurately predicted by the Framingham equation, along with the adjustment for the LDL-C changes associated with resmetirom and OCA. However, we did not model changes in HDL-C that were observed, as we did not want to simultaneously model two uncertainties related to cholesterol. Additionally, the impact of LDL on mortality for both treatment options were based on short term assessments from the clinical trials. We held the effect constant (i.e., LDL reduction for RES, LDL increase for OCA) for the lifetime of the model, but the actual long-term trends seen in clinical practice or future studies may be different. Finally, 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. There were uncertainties with the placeholder prices that were used as well. With resmetirom, we used an annual placeholder price of $19,000 based on a prior early economic model developed by the manufacturer. However, no rationale was given to the placeholder price and the manufacturer did not provide additional data on the price upon request. With OCA, in the absence of data provided by the manufacturer, we used an annual placeholder price of $85,000 based on the current 5 mg and 10 mg OCA formulations used for the treatment of primary biliary cholangitis.

4.4 Summary and Comment

In our lifetime model, treatment of patients with NASH with fibrosis with either resmetirom or OCA resulted in small gains in QALYs, evLYs, and life years and reductions in lifetime disease-related costs compared to their respective standard of care. As discussed above, the model needed to extrapolate from limited data for resmetirom, including published phase 2 data and topline phase 3 data from a press release. For OCA, the lack of data from the ITT population required the use of data from the per protocol analysis and the clinical team also noted substantial uncertainties about the balance of benefits and harms. The cost-effectiveness of both drugs will depend on their price though, notably, at our placeholder price, resmetirom would appear to be cost saving. If the price of OCA is not substantially reduced from the price of the approved (lower) doses used for PBC, it will not meet typical cost-effectiveness thresholds.

5. Contextual Considerations and Potential Other Benefits

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 was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	Most patients with NASH are asymptomatic and will not progress. Those at high short term risk of death are those with cirrhosis and the new therapies are not intended to treat them.
Magnitude of the lifetime impact on individual patients of the condition being treated	The majority of patients with NASH do not progress to cirrhosis and its associated complications. For those who do, the lifetime impact can be significant.

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	The majority of patients with NASH are not impacted by their disease, but those who progress to advanced liver disease are severely impacted.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	Similarly, this applies to the caregivers of those patients who progress to advanced liver disease.
Patients' ability to manage and sustain treatment given the complexity of regimen	NA
Society's goal of reducing health inequities	The health inequities landscape for NASH is complex. A recent (2022) analysis of US data found that Caucasians had a significant 42% higher overall prevalence of NASH, but all non-Caucasians were combined.[39] In other analyses Hispanic populations have a higher prevalence of NASH, while Black populations have a lower prevalence of NASH. A separate analysis published in 2022 found no association between income and NASH in the US, but a significant decrease in NASH with higher levels of education. No data were available on the prevalence of NASH with stage 2 or 3 fibrosis (population of interest) by race/ethnicity. There are other disparities that arise in the care of patients with NASH. In particular, it is more challenging for low-income patients to access needed liver transplantations due to the need for time off

Potential Other Benefit or Disadvantage	Relevant Information
	of work, travel to transplant centers, and the support required to qualify for the transplant list. An oral therapy that prevents the need for transplant and is available to all patients may decrease disparities in long term outcomes. However, these new therapies must be priced at a level to allow for access to all patients.
Other	A reduction in the need for liver transplantation for patients with NASH would increase the supply of livers available for transplantation in patients with other diseases.

ICER did not calculate the Health Improvement Distribution Index (HIDI) because of sparse and conflicting data on the relative prevalence of NASH with stage 2 or 3 fibrosis in subgroups of interest.

6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for the annual cost of treatment with the resmetirom and OCA are presented in Table 6.1 below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLY gained. The HBPB for resmetirom ranged from $39,600 to $50,100 and the HBPB for OCA ranged from $32,800 to $40,700.

Table 6.1. Annual Cost-Effectiveness Threshold Prices for Resmetirom and OCA

	Annual Price*	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices*
Resmetirom				
QALYs Gained	$19,011	$39,600	$47,100	No discount needed
evLYs Gained	$19,011	$41,600	$50,100	No discount needed
OCA				
QALYs Gained	$85,111	$32,800	$38,500	39%-45%
evLYs Gained	$85,111	$34,200	$40,700	40%-48%

OCA: obeticholic acid, WAC: wholesale acquisition cost, evLY: equal value life year, QALY: quality-adjusted life year
*Based on placeholder prices

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the total potential budget impact of resmetirom compared to SOC, and separately for the impact of OCA compared to SOC for adults with NASH with significant fibrosis and not cirrhosis. For resmetirom and OCA, we used placeholder annual prices of $19,000 and $85,111, respectively, and for both resmetirom and OCA we used threshold prices (at $50,000, $100,000, and $150,000 per QALY) for each drug in our estimates of budget impact. Potential budget impact is defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs minus any offsets in these costs from averted health care events. All costs will be undiscounted and estimated over a five-year time horizon.

This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment. To estimate the size of the potential candidate populations for treatment, we applied a prevalence estimate of 1.4% to the 2023-2027 projected US population aged 18 years of age and older. Our estimate was based on a 4% prevalence of NASH in the overall US population [based on a reported average of 1.5% to 6.5%][31] and the proportion of patients with NASH who have moderate to severe fibrosis which was reported to be 35%.[29] For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 762,119 patients per year. Given we are assessing two new market entrants, we assumed that 50% of patients each year (N=381,059) will initiate resmetirom and the remaining 50% of patients each year (N=381,059) will initiate OCA.

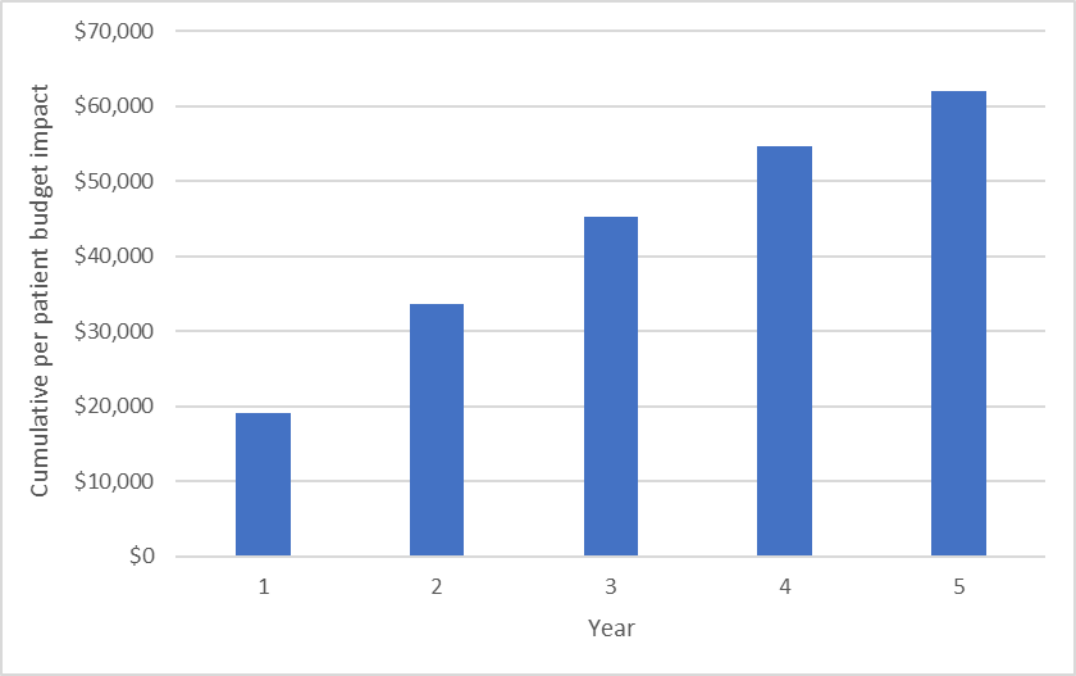
The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. The five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $777 million per year for new drugs. ICER's methods for estimating potential budget impact are described in detail in the Supplemental Section F.

7.2 Results

Figure 7.1. illustrates the cumulative per patient potential budget impact for resmetirom compared to SOC. At resmetirom's placeholder price, the average annual budget impact per patient was $19,011 in Year one with cumulative net annual costs increasing to $61,918 in Year five. Annual net costs decreased in years two through five due to treatment discontinuation. Although the cost-effectiveness analysis found that resmetirom at its placeholder price was cost-saving over the

lifetime time horizon of the model, our time horizon for the potential budget impact is limited to the first 5 years of the model where there were net increases in costs.

Figure 7.1. Cumulative Net Cost per Patient Treated with Resmetirom



Assuming a 20% uptake of resmetirom each year (for 50% of eligible patients given that we are assessing two new market entrants), 5.2% of patients could be treated over five years at the placeholder price before reaching the ICER potential budget impact threshold of $777 million per year. Fewer percentages of eligible patients could be treated at the $50,000, $100,000 and $150,000 per QALY threshold prices (2.8%, 2.2% and 1.8%, respectively) as illustrated in Figure 7.2.

Figure 7.2. Percent Uptake Each Year Before Reaching Budget Impact Threshold (Resmetirom)

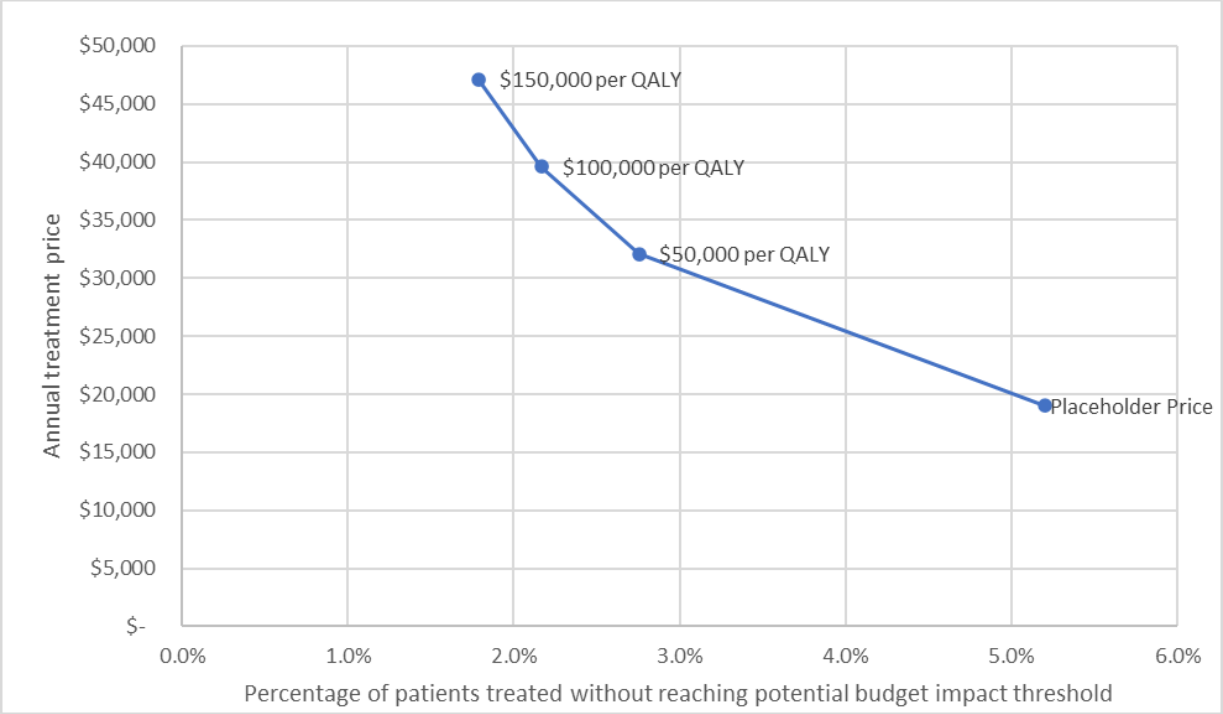
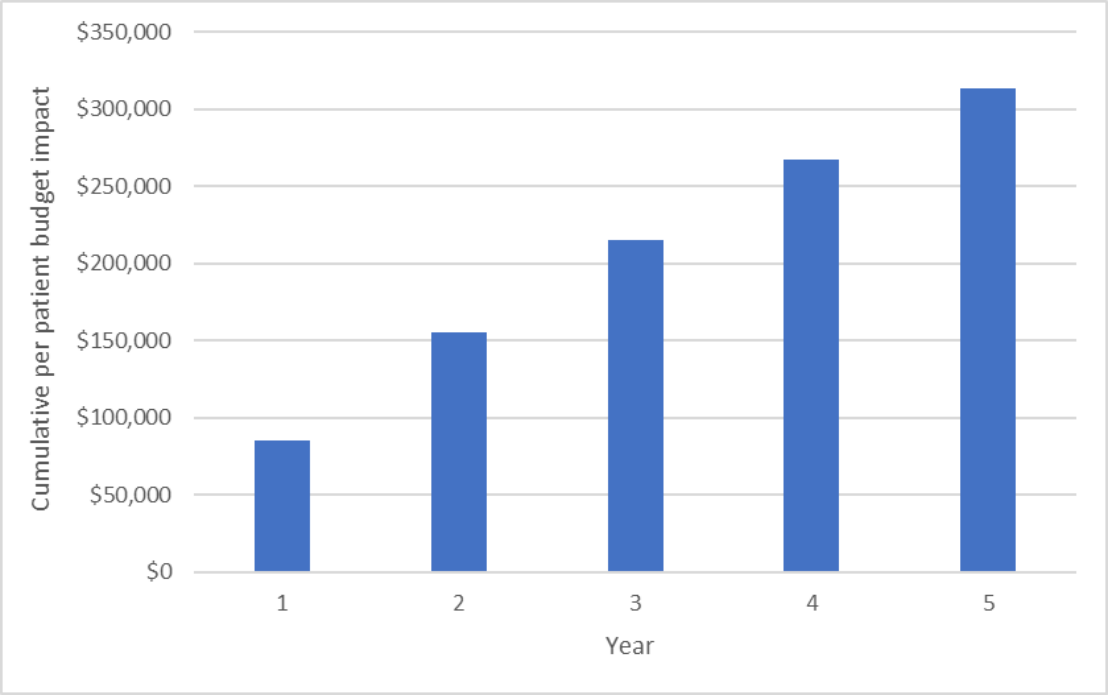


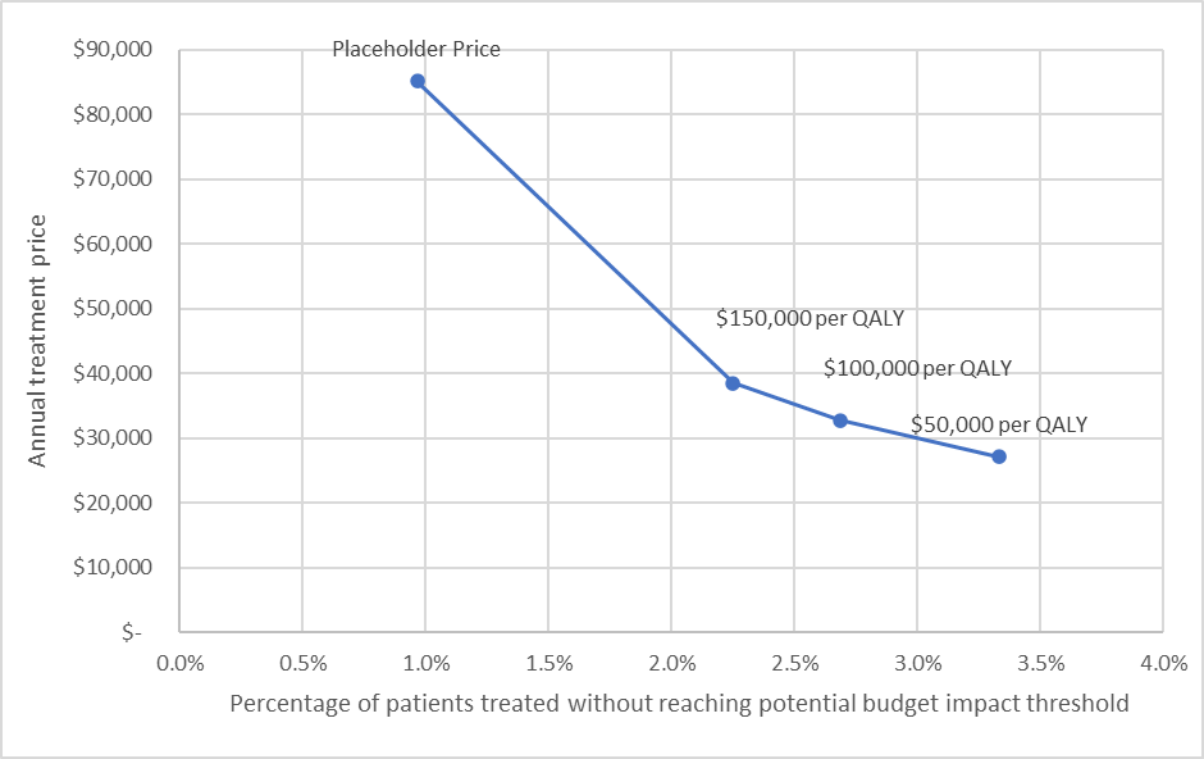
Figure 7.3. illustrates the cumulative per patient potential budget impact for OCA compared to SOC. At OCA's placeholder price, the average annual budget impact per patient was $85,111 in Year one with cumulative net annual costs increasing to $313,601 in Year five. Annual net costs decreased in years two through five due to treatment discontinuation.

Figure 7.3. Cumulative Net Cost per Patient Treated with OCA



Assuming a 20% uptake of OCA each year (for 50% of eligible patients given that we are assessing two new market entrants), 0.97% of patients could be treated over five years at its placeholder price before reaching the ICER potential budget impact threshold of $777 million per year. A higher percentage of eligible patients could be treated at the $50,000, $100,000 and $150,000 per QALY threshold prices (3.3%, 2.7% and 2.2%, respectively) as illustrated in Figure 7.4.

Figure 7.4. Percent Uptake Each Year Before Reaching Budget Impact Threshold (OCA)



Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Nonalcoholic Fatty Liver Disease (NAFLD): Hepatic steatosis without another explanation such as alcohol consumption or use of medications that cause hepatic steatosis.

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.

NASH Resolution: ≥2-point reduction in NAS with a ballooning score of 0, inflammation score of 0 or 1.[12]

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).

36-Item Short Form Survey Health Survey (SF-36): A generic instrument assessing eight domains of quality of life: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Scores range from 0-100 with a higher score indicating better HRQoL.[13]

Chronic Liver Disease Questionnaire-NASH (CLDQ-NASH): A disease specific instrument assessing six domains of quality of life: Abdominal, Activity/Energy, Emotional, Fatigue, Worry, and Systemic. Scores range from 1-7, with lower scores corresponding with worse or more frequent symptoms.[25]

Other Relevant Definitions

Health Improvement Distribution Index: The Health Improvement Distribution Index identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an

opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The Health Improvement Distribution Index is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if the disease prevalence was 10% in poor Americans whereas the disease prevalence across all Americans was 4%, then the Health Improvement Distribution Index would be 10%/4% = 2.5. For interventions known to increase health in this disease and that accomplish equal access across the entire population, poor Americans would receive 2.5 times the health improvements as compared to the same sized group of Americans without regard to economic status. Health Improvement Distribution Indexes above 1 suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. This statistic may be helpful in characterizing a treatment's contextual considerations and potential other benefits (Section 5). ICER did not calculate the Health Improvement Distribution Index (HIDI) in this review because of sparse and conflicting data on the relative prevalence of NASH with stage 2 or 3 fibrosis in subgroups of interest.

A2. 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.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by OCA or resmetirom (e.g., hospitalization for decompensated cirrhosis), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of NASH beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

B. Patient Perspectives: Supplemental Information

B1. Methods

To inform our understanding of the patient perspective, we had one focus group with four patients, and we spoke with representatives from the Fatty Liver Foundation and Global Liver Institute. We also reviewed and summarized the patient perspective from prior ICER reports on NASH.

C. Clinical Guidelines

American Association for the Study of Liver Diseases (AASLD): The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease[2]

The AASLD's 2018 practice guidance indicate that any pharmacological treatments should be aimed at patients with biopsy-proven NASH with fibrosis. 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. Bariatric surgery may also be considered for eligible individuals with obesity on a case-by-case basis; however, its safety and efficacy in NASH with cirrhosis patients has not been established.

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 NASH patients with diabetes 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.

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)[40]

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. Due to lack of 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 Organisation (WGO) Global Guidelines: Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis[41]

The WGO 201 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). If interventions are ineffective for patients after a 6-month period, pharmacotherapies can then be considered. Bariatric surgery can also be considered for individuals with morbid obesity but is 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. 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)[42]

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.[42] NICE also recommends lifestyle interventions as described by previous clinical societies above.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population of focus for the review was adults age ≥ 18 with NASH with significant fibrosis and not cirrhosis. We looked at subgroups of interest including fibrosis stage, presence of diabetes, and race/ethnicity.

Interventions

The full list of interventions is as follows:

- Resmetirom
- Obeticholic Acid (Ocaliva)

Comparators

We compared all the agents to each other and to usual care alone (as estimated by the placebo arms of the clinical trials).

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - All-cause mortality
    - Cirrhosis
    - Decompensated cirrhosis
    - Health related quality of life
    - Hepatocellular carcinoma
    - Liver-related mortality
    - Liver transplantation
    - Cardiac and cardiovascular events (heart attacks, strokes, etc.)
    - NASH symptoms (abdominal pain, fatigue)

    - Adverse events including
        - Adverse events leading to drug discontinuation
        - Serious adverse events
        - Pruritis
        - Weight gain or loss
        - Diarrhea
        - Nausea
- Other Outcomes
    - Changes in lipid levels
    - Changes in blood pressure
    - Changes in NAFLD Activity Score (NAS)
    - Fibrosis stage
    - Liver markers of inflammation
    - Quantitative measures of liver fat content
    - Resolution of NASH

Timing

Evidence on intervention efficacy, safety, and effectiveness was collected from studies of any duration.

Setting

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

Study design

Randomized controlled trials, non-randomized controlled trials, and comparative observational studies with any sample size were included.

Table D1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		

Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.

	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study characteristics	17	Cite each included study and present its characteristics.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing interests	26	Declare any competing interests of review authors.
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on resmetirom and obeticholic acid for NASH followed established best research methods.[43,44] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[45] The PRISMA guidelines include a checklist of 27 items.

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.

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 https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/.

Table D2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

#	Search Terms
1	exp fatty liver, nonalcoholic/
2	("NASH" or "non-alcoholic fatty liver disease" or "non alcoholic fatty liver disease" or "nafld" or "nonalcoholic fatty liver disease" or "fatty liver, nonalcoholic" or "fatty livers, nonalcoholic" or "liver, nonalcoholic fatty" or "livers, nonalcoholic fatty" or "nonalcoholic fatty liver" or "nonalcoholic fatty livers" or "nonalcoholic steatohepatiti*" or "steatohepatiti*, nonalcoholic" or "non-alcoholic steatohepatitis").ti,ab.
3	1 or 2
4	("ocaliva" or "obeticholic acid" or "OCA" or "6ECDCA" or "6-ECDCA" or "INT747" or "INT 747" or "INT-747" or "DSP1747" or "DSP-1747" or "DSP 1747" or "Zektayos-Hepjuvo").ti,ab.
5	limit 4 to ed=20200115-20221103
6	("resmetirom" or "VIA-3196" or "VIA3196" or "VIA 3196" or "MGL3196" or "MGL 3196" or "MGL-3196").ti,ab.
7	3 and (5 or 6)
8	7 not ("address" or "autobiography" or "bibliography" or "biography" or "comment" or "congress" or "consensus development conference" or "corrected and republished article" or "duplicate publication" or "editorial" or "guideline" or "interview" or "lecture" or "legal case" or "legislation" or "letter" or "news" or

	"newspaper article" or "patient education handout" or "periodical index" or "personal narrative" or "portrait" or "practice guideline" or "published erratum" or "review" or "video-audio media").pt.
9	8 not (animals not (humans and animals)).sh.
10	limit 9 to English
11	Remove duplicates from 10

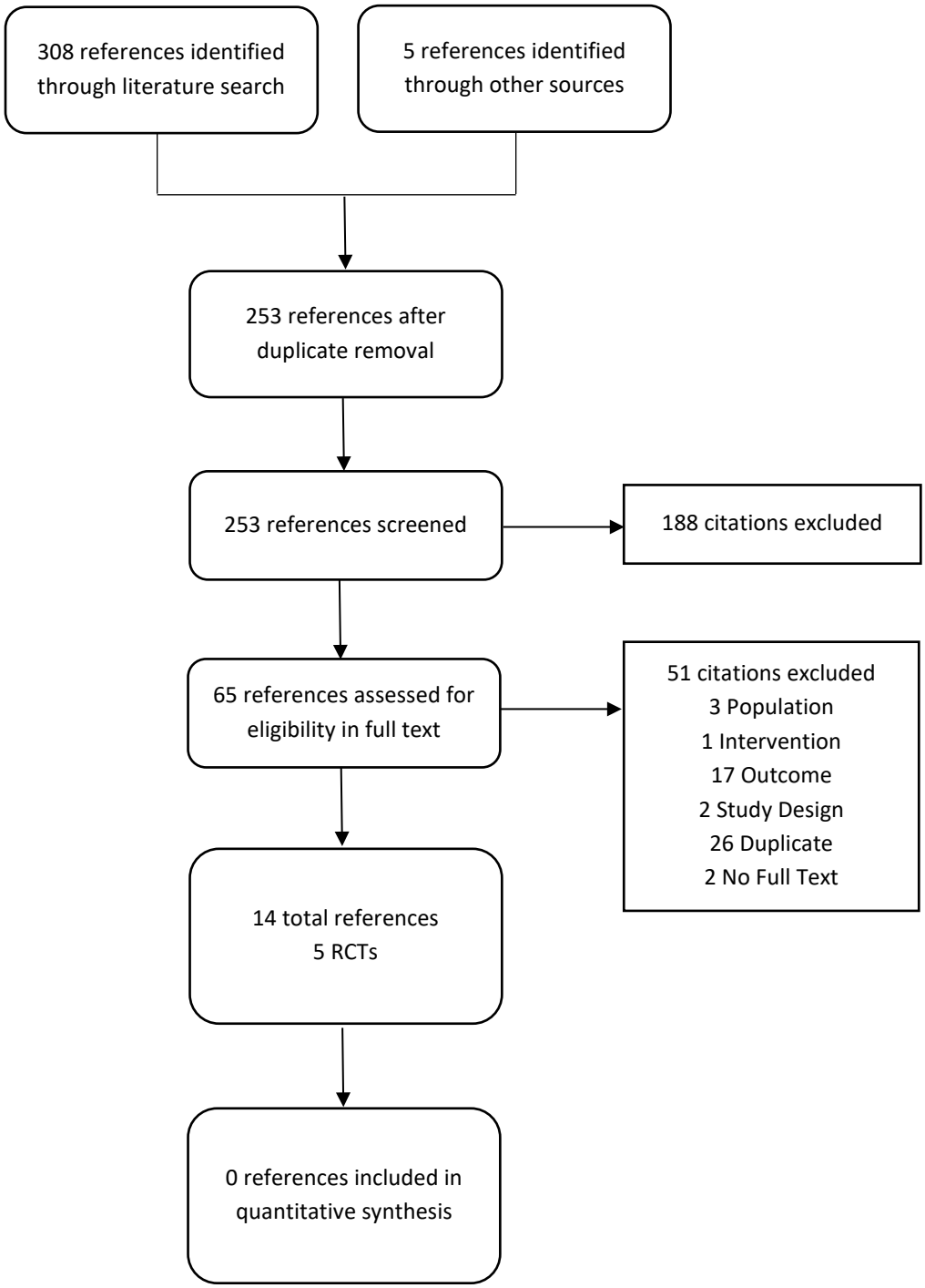
Search last ran on March 06, 2023.

Table D3. Search Strategy of EMBASE

#	Search Terms
1	'nonalcoholic steatohepatitis'/exp
2	('nash':ti,ab OR 'nash (nonalcoholic steatohepatitis)':ti,ab OR 'non alcohol steato-hepatitis':ti,ab OR 'non alcohol steatohepatitis':ti,ab OR 'non alcoholic steato-hepatitis':ti,ab OR 'non-alcohol steato-hepatitis':ti,ab OR 'non-alcohol steatohepatitis':ti,ab OR 'non-alcoholic steatohepatitis':ti,ab OR 'non-alcoholic steatosis hepatitis':ti,ab OR 'non-alcoholic steatotic hepatitis':ti,ab OR 'nonalcohol steato-hepatitis':ti,ab OR 'nonalcohol* steatohepatitis':ti,ab OR 'nonalcoholic fatty liver inflammation':ti,ab OR 'nonalcoholic steato-hepatitis':ti,ab OR 'nonalcoholic steatosis hepatitis':ti,ab OR 'nonalcoholic steatotic hepatitis'):ti,ab
3	#1 OR #2
4	('ocaliva' OR 'obeticholic acid' OR 'OCA' OR '6ECDCA' OR '6-ECDCA' OR 'INT747' OR 'INT 747' OR 'INT-747' OR 'DSP1747' OR 'DSP-1747' OR 'DSP 1747' OR 'Zektayos-Hepjuvo'):ti,ab AND [15/01/2020]/sd
5	('resmetirom' OR 'VIA-3196' OR 'VIA3196' OR 'VIA 3196' OR 'MGL3196' OR 'MGL 3196' OR 'MGL-3196'):ti,ab
6	#3 AND (#4 OR #5)
7	#6 NOT ('addresses' OR 'autobiography' OR 'bibliography' OR 'biography' 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')/it
8	#7 NOT ((‘animal’/exp OR ‘nonhuman’/exp OR ‘animal experiment’/exp) NOT ‘human’/exp)
9	#8 AND [English]/lim
10	#9 NOT [medline]/lim

Search last ran on March 06, 2023.

Figure D1. PRISMA Flow Chart Showing Results of Literature Search for Resmetirom and Obeticholic Acid



Study Selection

We performed screening at both the abstract and full-text level. Two investigators 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. Two investigators reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to resmetirom and obeticholic acid. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

Data Extraction and Quality Assessment

We examined the risk of bias for the two primary outcomes of the phase 3 trials: ≥ 1 point improvement in fibrosis stage with no worsening of NASH and NASH resolution with ≥ 2 point reduction in NAS without worsening of fibrosis using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2)[46] and guidance criteria published by Higgins et al (2019).[47] See Tables D4 and D5 below. Risk of bias was assessed for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. To assess the risk of bias in trials in the report, we rated the categories as: "low risk of bias", "some concerns", or "high risk of bias". Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias: The study is judged to be at low risk of bias for all domains for this result.
Some concerns: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
High risk of bias: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

Although no peer reviewed full-text publication was available for the MAESTRO-NASH trial, we still assessed the risk of bias. While performing the assessment, there was an assumption that the trial followed the standard guidelines such as appropriate randomization and allocation concealment. We did not assess the risk of bias in MAESTRO-NAFLD-1 trial because we only analyzed the incidence of adverse events from this trial.

Table D4. Risk of Bias Assessment: ≥ 1 Point Improvement in Fibrosis Stage With no Worsening of NASH

Studies	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Resmetirom						
MAESTRO-NASH	Low	Low	Low	Some concern	Low	Some concern
Obeticholic Acid						
REGENERATE	Low	Low	High	Low	Low	High

*The direction of the bias was unpredictable for missing outcome data, measurement of the outcome, and overall risk of bias.
Phase 2 trial did not assess the fibrosis primary outcome

Table D5. Risk of Bias Assessment: NASH Resolution With ≥ 2 Points Reduction in NAS Without Worsening of Fibrosis

Studies	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Resmetirom						
MAESTRO-NASH	Low	Low	Low	Some concern	Low	Some concern
Phase 2 trial	Low	Low	Some concern	Low	Low	Some concern
Obeticholic Acid						
REGENERATE	Low	Low	High	Low	Low	High

*The direction of the bias was unpredictable for missing outcome data, measurement of the outcome, and overall risk of bias.
NAS: NAFLD (Non-Alcoholic Fatty Liver Disease) Activity Score

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).[48,49]

Assessment of Bias

We evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias using ClinicalTrials.gov. Search terms included “resmetirom,” “obeticholic acid", and "nonalcoholic steatohepatitis". We selected studies which would have met our inclusion criteria and for which no findings have been published. We provided qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Data Synthesis and Statistical Analyses

Relevant data on key outcomes of the main studies were summarized qualitatively in the body of the review and in evidence tables (see Supplement Section D3). Key differences between the studies in terms of the study design, patient characteristics, outcomes, and study quality were explored in the text of the report. The feasibility of conducting a quantitative synthesis was evaluated by looking at trial design, populations, analytic methods, and outcome assessments across outcomes of interest in the resmetirom and obeticholic acid trials. Based on the differences in study population, study design, and outcomes assessed we were unable to conduct quantitative syntheses.

D2. Additional Clinical Evidence

The main report discusses primary sources of data to inform our review of resmetirom and obeticholic acid for the treatment of NASH. In this supplement, we describe evidence from resmetirom phase 2 trial including the open label extension and OCA 10 mg dose that are not presented in the main report.

Evidence Base

Resmetirom

This phase 2 resmetirom trial had a total of 125 patients randomized 2:1 to receive once-daily resmetirom 80 mg or placebo for 12 weeks.[12] The resmetirom arm allowed for dose adjustment by 20 mg up or down after four weeks of treatment based on unblinded measurements of resmetirom levels at two weeks. Patients were included if they had biopsy proven NASH and the inclusion criteria described above for MAESTRO-NASH, plus at least 10% fat content based on MRI-PDFF. Both MAESTRO-NASH and the phase 2 trial excluded patients if they had cirrhosis, hepatic decompensation, chronic liver disease other than NASH, or serum ALT and AST levels more than five times the upper limit of normal. The primary outcome was percent relative change from baseline in MRI-PDFF hepatic fat fraction at 12 weeks. This phase 2 trial continued for 36 weeks before being continued as an open label extension phase (N = 31) for an additional 36 weeks.[14] Patients were eligible for this extension phase only if they completed the main trial, had a liver biopsy, a MRI-PDFF assessment at week 36, and uncontrolled ALT or AST levels during weeks 16 to 30. All patients in the extension phase received resmetirom, although the dose slightly varied based on previous allocation, post-dose pharmacokinetic assessment, and blinding status.

The phase 3 MAESTRO-NAFLD-1 trial randomized 1,143 patients 1:1:1:1 to receive resmetirom 80 mg, 100 mg, placebo, or open label resmetirom 100 mg. MAESTRO-NAFLD-1 included both suspected or confirmed diagnoses of NASH or NAFLD.[15] Since this trial did not include NASH patients exclusively, we primarily focused on the incidence of adverse events and LDL cholesterol data.

Obeticholic Acid

Details about the REGENERATE and FLINT trial characteristics are described both in the main report and ICER's previous review in 2020.[22] It is important to note that the REGENERATE trial used different subsets of the efficacy population to analyze the primary endpoints. As mentioned in the main report, after conducting the preplanned interim analysis in 2019 with a total of 931 F2-F3 participants, the FDA requested the manufacturer reread the liver biopsies using a consensus panel of pathologists. The manufacturer revised the primary endpoint results for those 931 participants and provided data on an additional 676 participants for a total of 1607 with histology results.[6]

Clinical Benefits

Resmetirom

The relative change from baseline in hepatic fat fraction by MRI-PDFF at 12 weeks was a primary endpoint in this phase 2 trial.[12] The reduction in hepatic fat was greater with resmetirom than placebo at week 12 (-32.9% vs. -10.4%; mean difference -22.5%, 95% CI -32.9% to -12.2%) and at week 36 (-37.3% vs. -8.5%, mean difference -28.4%, 95% CI -41.3 to -15.4).[12] This reduction from baseline was also evident later in the open label extension phase, overall and by specific dose.[14] For example, patients receiving resmetirom in the phase 2 trial had a 45.8% reduction in fat at week 36 of the OLE compared with baseline in the phase 2 trial and patients receiving placebo in the phase 2 trial had a 52.0% reduction in fat at week 36 of the OLE compared with week 36 of the phase 2 trial.[14] Resmetirom 100 mg produced a greater statistically significant absolute reduction (-59%, $p < 0.001$) from baseline than resmetirom 80 mg (-45%, $p < 0.001$), suggesting a dose-dependent relationship.[14] At 36 weeks in the phase 2 trial, at least a 2 point reduction in NAFLD activity score was achieved by more patients receiving resmetirom than placebo (56% vs. 32%; OR 2.7; 95% CI 1.1 to 6.3).[12] More patients receiving resmetirom had at least a 30% reduction in fat (60% vs. 18%, OR 6.8, 95% CI 2.6 to 17.6).[12]

In the phase 2 trial, LDL cholesterol was reduced with resmetirom compared with placebo (-17.3%; 95% CI -24.8 to -9.9, $p < 0.001$).[12] Reductions in LDL were maintained or perhaps reduced further during the OLE.[14] Similarly, both resmetirom 80 mg and 100 mg doses had significantly greater ($p < 0.0001$) reductions in LDL-cholesterol compared to placebo at 24 weeks in the MAESTRO-NAFLD-1 trial.[15,50] See Supplement Table D11 below.

Serum markers that can reflect liver injury include ALT, AST, GGT, and total bilirubin. At 36 weeks, reductions in ALT, AST, and GGT were larger with resmetirom than placebo, but there was no statistically significant difference between groups in total bilirubin.[12]

Obeticholic Acid

The results for the 25 mg arm of the REGENERTE trial are presented in the main report. For context, we are summarizing the results for the 10 mg arm of the trial. In the revised preplanned interim analysis (N=931), more patients treated with OCA 10 mg than placebo had improvement at month 18 in the fibrosis primary outcome (14% vs. 10%).[6] The proportions were higher for both groups when an additional 676 participants were introduced into the analysis (N=1,607; 16% in the OCA 10 mg and 12% in the placebo group).[6] However, the differences between OCA 10 mg and placebo in both cases were not statistically significant.[6]

The reduction in ALT was greater with OCA 10 mg than placebo at 18 months (change from baseline: -25% for OCA 10 mg, and -12% for placebo) and the reduction appeared similar with OCA

10 mg at 48 months (change from baseline: -26% for OCA 10 mg).[24] The mean differences between the OCA 10 mg and placebo were statistically significant at both timepoints (p<0.0001 and p=0.01, respectively).[24] The OCA 10 mg group had a marginal reduction from baseline in the liver stiffness value at 18 months (change from baseline: -1.2% for OCA 10 mg) and reduced further at 48 months (change from baseline: -1.9% for OCA 10 mg).[24] Of note, OCA 10 mg only reached statistical significance at 18 months but not at 48 months (p=0.001 and p=0.078, respectively).[24] See Supplement Table D18.

Harms

Resmetirom

The MAESTRO-NAFLD-1 trial included presumed NASH patients based on non-invasive tests and the primary endpoint was the incidence of adverse events at 52 weeks. Overall, the adverse events profile of 969 patients included in this trial was similar to those observed in the MAESTRO-NASH study. Specifically, diarrhea and nausea were more common among the resmetirom groups compared to placebo and no new AEs were identified.[15] See Supplement Table D14.

Obeticholic Acid

Discontinuation rates due to adverse events were similar between OCA 10 mg and placebo groups (12.4% vs 11.3%).[6] One in 4 participants receiving OCA 10 mg experienced serious adverse events in the REGENERATE trial.[6] The REGENERATE trial also reported nine deaths in the OCA 10 mg of which one was felt to be cardiovascular death.[6] MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for unstable angina) occurred in 1% of patients receiving OCA 10 mg.[6] One-third of the participants receiving OCA 10 mg experienced pruritus and approximately 14% of discontinuations due to adverse events were related to pruritus.[6]

D3. Evidence Tables

Table D6. Study Design

Study	Study Design and Treatment Arms	Inclusion Criteria	Primary Outcomes
Resmetirom			

MAESTRO-NASH[17]	**Study Design**
	Double-blind, randomized, placebo-controlled study
	
	Treatment Arms
	Placebo (N=318)
	Resmetirom 80 mg (N=316)
	Resmetirom 100 mg (N=321)
		Inclusion Criteria
		- Adults with suspected/confirmed diagnosis of NASH:
		  - Metabolic risk factors & AST > 20 IU/L
		  - Liver fibrosis defined as biochemical test; fibroscan test; or liver biopsy with diagnosis of NASH with fibrosis Stage 2 or 3
		  - MRI-PDFF with ≥ 8% fat fraction
		  - Biopsy-proven NASH with fibrosis stage ≥1 to <4 and NAS ≥4
		Exclusion Criteria
		- History of significant alcohol consumption (3 months in prior 1 year)
		- History of bariatric surgery/intestinal bypass surgery (prior 5 years)
		- HbA1c >9.0%
		- GLP-1 agonist therapy; high dose vitamin E (>400 IU/day); pioglitazone unless stable 24 weeks prior to biopsy
		- Cirrhosis on liver biopsy (stage 4 fibrosis)
		- Diagnosis of HCC, chronic liver diseases, any other condition that would impede study
			- ≥1 point improvement in fibrosis with no NAS worsening [52 weeks]
			- NASH resolution with ≥2 point reduction in NAS without worsening of fibrosis [52 weeks]

Phase 2[18]	**Study Design** Double-blind, randomized, placebo-controlled study enrolled patients in 25 medical centers across the United States.	**Inclusion Criteria** - Adults with biopsy-proven NASH - Fibrosis stage 1 to 3; NAS ≥4 - BMI <45 kg/m^2 - MRI-PFDD fat fraction ≥10% **Exclusion Criteria**	- Percent relative change from baseline in hepatic fat fraction by MRI-PDFF at 12 weeks for resmetirom vs. placebo

	Treatment Arms - Placebo (N=41) - Resmetirom (N=84): 80 mg for the first 4 weeks, then the dose was adjusted by 20 mg up or down or remained 80 mg based on the week 2 estimated AUC	- History of significant alcohol consumption (3 months in prior 1 year) - Prior or planned bariatric surgery - Use of OCA, ursodeoxycholic acid, high dose vitamin E (>400 IU/day), pioglitazone in prior 90 days - Stage 4 cirrhosis Hyperthyroidism; type 1 diabetes, uncontrolled type 2 diabetes (HbA1c ≥9.5), chronic liver diseases, any condition likely to impede study	
Phase 2 Open-Label Extension (OLE)[14]	**Study Design** Open-label extension study **Treatment Arms** - Placebo/Resmetirom (N=14) - Resmetirom/Resmetirom (N=17)	Inclusion Criteria - Patients who had 36-week MRI-PDFF and 36-week liver-biopsy were eligible to continue the extension study. - ALT or AST levels that had not fully normalized during weeks 16 to 30 of the main study.	- Relative and absolute change in MRI-PDFF at OLE week 36

MAESTRO-NAFLD1[19]	**Study Design**
	Double-blind, Placebo-controlled study, 80 medical centers across the United States
	
	Treatment Arms
	- Placebo (N=320)
	- Resmetirom 80 mg (N=327)
	- Resmetirom 100 mg (N=325)
	- Resmetirom 100 mg open-label (N=171)
		Inclusion Criteria
		- Adults with suspected/confirmed NASH or NAFLD:
		  - Fibroscan with kPa ≥5.5 and <8.5; CAP ≥280 dB.m-1 OR
		  - MRE ≥2 and <4.0; MRI-PDFF ≥8% liver fat consistent with steatosis and fibrosis stage ≥1 and <4. OR
		  - Recent liver biopsy (within past 2 years) documenting NASH/NAFLD with steatosis ≥1 showing one of the following:
		  ○ NAS ≥4, with fibrosis stage 0/1A/1C with PRO-C3 <14
		  ○ NAS <4, with fibrosis stage ≤3
		  ○ NAS ≥4, with fibrosis stage ≤3 without ballooning
		- Compensated NASH cirrhosis at screening
		  - Child Pugh-A score 5-6
		  - MELD < 12
		  - Albumin ≥3.2
			- Adverse events at 52 weeks

		- Bilirubin < 2 - MRI-PDFF fat fraction ≥8% **Exclusion Criteria** - History of significant alcohol consumption (3 months in prior 1 year) - History of bariatric surgery/intestinal bypass surgery (prior 5 years) - HbA1c >9.0% - GLP-1 agonist therapy or high dose vitamin E (>400 IU/day) unless stable 24 weeks prior to biopsy - Cirrhosis on liver biopsy (stage 4 fibrosis) Diagnosis of HCC, chronic liver diseases, uncontrolled hypertension, any other condition that would impede study	
Obeticholic Acid			
REGENERATE[20]	**Study Design** Phase 3, Multicenter, Double-blind, Randomized Controlled Trial **Treatment Arms** - Placebo (N=825) - Obeticholic acid 10 mg (N=825) Obeticholic acid 25 mg (N=827)	**Inclusion Criteria** - Adults with NASH and stage 2-3 fibrosis or stage 1 with additional risk factors (obesity, type 2 diabetes, ALT >1.5x ULN) defined by NASH CRN scoring - Patient with biopsy: not taking or stable on TZDs/glitazones or vitamin E in prior 6 months **Exclusion Criteria** - MELD score >12 - ALT ≥10x ULN - HbA1c > 9.5% - Bilirubin >1.5 mg/dL - History liver transplant, significant alcohol consumption, chronic liver diseases, biliary diversion Histological presence of cirrhosis	- Patients with ≥1 stage improvement liver fibrosis with no NASH worsening - Patients with NASH resolution with no liver fibrosis worsening [18 months]
FLINT[21]	**Study Design** Multicenter, double-blind, placebo controlled, parallel group, randomized clinical trial **Treatment Arms**	**Inclusion Criteria** - Adults with defined or probable NASH - NAS score ≥4 with at least 1 in each NAS component **Exclusion Criteria** - Current/history of significant alcohol consumption	- Improvement in liver histology, defined as a decrease in NAFLD activity score(NAS) of at least 2 points without a worsening of fibrosis from

	- Placebo (N=97) - Obeticholic acid 25 mg (N=99)	- Prior/planned bariatric surgery - HbA1c ≥9.5% in prior 60 days - Liver biopsy showing cirrhosis - Hepatic decompensation; chronic liver disease Use of ursodeoxycholic acid	baseline to end-of-treatment (EOT).

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, CAP: Controlled Attenuation Parameter, dL: deciliter, HBA1c: hemoglobin A1C, HCC: hepatocellular carcinoma, IU: international units, kg: kilogram, kPa: kilopascal, L: liter, m^2: meter squared, mg: milligram, MRE: magnetic resonance elastography, MRI-PDFF: magnetic resonance imaging proton density fat fraction, N: total number, NALFD: nonalcoholic fatty liver disease, MELD: model for end-stage liver disease, NAS: NAFLD (nonalcoholic fatty liver disease) activity score, NASH: nonalcoholic steatohepatitis, OLE: open-label extension, ULN: upper limit of normal

Table D7. Resmetirom Baseline Characteristics: Demographics

Study	Arm	N	Age (Mean, SD)	Male, n (%)	Race, n (%)				Ethnicity, Hispanic, n (%)	BMI, kg/m2 (Mean, SD)
					Asian	Other	Black/ African American	White		
MAESTRO-NASH[16]	Placebo	321	57, 11	143 (44)	NR	NR	NR	281 (88)	52 (16)	35, 7
	Resmetirom 80 mg	322	56, 12	140 (43)	NR	NR	NR	291 (90)	71 (22)	36, 6
	Resmetirom 100 mg	323	57, 11	141 (44)	NR	NR	NR	291 (90)	81 25)	36, 7
Phase 2[12]	Placebo	41	47.3, 11.7	24 (58.5)	3 (7.3)	0 (0.0)	1 (2.4)	37 (90.2)	22 (53.7)	33.6, 5.8
	Resmetirom	84	51.8, 10.4	38 (45.2)	2 (2.4)	1 (1.2)	1 (1.2)	80 (95.2)	37 (44.0)	35.8, 6.2
Phase 2 OLE[14]	Placebo/ Resmetirom	14	42.4, 10.5	8 (57.1)	0 (0)	0 (0)	0 (0)	14 (100.0)	9 (64.3)	35.1, 5.2
	Resmetirom/ Resmetirom	17	53.1, 11.8	8 (47.1)	2 (11.8)	1 (5.9)	1 (5.9)	13 (76.5)	7 (41.2)	34.5, 5.2
	Overall Resmetirom	31	48.2, 12.3	16 (51.6)	2 (6.5)	1 (3.2)	1 (3.2)	27 (87.1)	16 (51.6)	35.3, 5.2
MAESTRO-NAFLD1[15]	Placebo	309	55.7, 12.2	146 (47.2)	NR	NR	NR	276 (89.3)	118 (38.2)	35.2, 5.8
	Resmetirom 80 mg	320	56.2, 11.7	141 (44.1)	NR	NR	NR	284 (88.8)	105 (32.8)	35.4, 6
	Resmetirom 100 mg	314	56.2, 11.5	142 (45.2)	NR	NR	NR	278 (88.5)	103 (32.8)	35.4, 6.4

BMI: Body Mass Index, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, SD: standard deviation

Table D8. Resmetirom Baseline Characteristics II

	Arm	N	Comorbid Conditions		Concomitant Drugs		Fibrosis Stage				
			T2D, n (%)	Hypertension, n (%)	Antidiabetics, n (%)	Cholesterol Lowering, n (%)	Stage 0, n (%)	Stage 1, n (%)	Stage 2, n (%)	Stage 3, n (%)	Mean Stage, SD
MAESTRO-NASH[16]	Placebo	321	210 (65)	257 (80)	270 (28)	473 (49)	0	18 (6) †	112 (35)	191 (60)	NR
	Resmetirom 80 mg	322	224 (70)	243 (76)			0	16 (5) †	107 (33)	199 (62)	NR
	Resmetirom 100 mg	323	213 (66)	254 (79)			0	15 (5) †	100 (31)	208 (64)	NR
Phase 2[12]	Placebo	41	13 (31.7) *	18 (43.9)	13 (31)	4 (10)	2 (5)	19 (46)	13 (32)	7 (17)	NR
	Resmetirom	84	36 (42.9) *	45 (53.6)	35 (41)	19 (23)	1 (1)	47 (56)	18 (21)	18 (21)	NR
Phase 2 OLE[14]	Placebo/ Resmetirom	14	5 (35.7)	6 (42.9)	4 / 7 (57.1)	3 / 7 (42.9)	0	NR	7 (50)		1.8, 1
	Resmetirom/ Resmetirom	17	9 (52.9)	10 (58.8)	7 / 13 (53.8)	6 / 13 (46.2)	3 (17.6)	NR	13 (76.5)		2, 0.8
	Overall Resmetirom	31	NR	NR	NR	NR	3 (9.7)	NR	20 (64.6)		1.8, 1
MAESTRO-NAFLD1[15]	Placebo	309	156 (50.5)	238 (77.0)	NR	NR	NR	NR	NR	NR	NR
	Resmetirom 80 mg	320	156 (48.8)	243 (75.9)	NR	NR	NR	NR	NR	NR	NR
	Resmetirom 100 mg	314	152 (48.4)	237 (75.5)	NR	NR	NR	NR	NR	NR	NR

mg: milligram, n: number, N: total number, NR: not reported, SD: standard deviation, T2D: type 2 diabetes

*Any diabetes, type 2 diabetes not specified

† Stage 1b specified

Table D9. Resmetirom Efficacy Outcomes

Study	Timepoint	Arm	N	≥1 fibrosis stage improvement with no worsening of NASH, n (%)	NAS (Mean, SD)	NASH resolution* with no worsening in fibrosis, n (%)	NAS ≥2 point reduction, n (%)	NAS ≥2 point reduction with ≥1 point reduction in Inflammation or Ballooning, n (%)
MAESTRO-NASH[16]	52 weeks	Placebo	318	NR (14)	NR	32 (10)	NR	NR
		Resmetirom 80 mg	316	NR (24); p = 0.0002	NR	82 (26); p<0.0001	NR	NR
		Resmetirom 100 mg	321	NR (26); p < 0.0001	NR	96 (30); p<0.0001	NR	NR
Phase 2[12]	Baseline	Placebo	41	NR	4.8, 1.1	NR	NR	NR
		Resmetirom	84	NR	4.9, 1.0	NR	NR	NR
	36 weeks	Placebo	41	NR	NR	6/31 (6.5)	11/34 (32.4)	11/34 (32.4)
		Resmetirom	73	NR	NR	18 (24.7); OR 4.75 (95%CI 1.03-21.9); p=0.032	41 (56.2); OR 2.7 (95%CI 1.1 to 6.3); p=0.024	37 (50.7); LSMD: 2.2 (95%CI 0.9-5.0); p=0.096
Phase 2 OLE[14]	Baseline (week 36 of main study)	Placebo/ Resmetirom	14	NR	4.2, 1.5	NR	2/14 (14.3)	NR
		Resmetirom/ Resmetirom	17	NR	3.9, 1.4	NR	9/17 (52.9)	NR
		Overall Resmetirom	31	NR	4.1, 1.4	NR	11/31 (35.5)	NR

95%CI: 95 percent confidence interval, LSMD: least squares mean difference, mg: milligram, n: number, N: total number, NAS: NAFLD (nonalcoholic fatty liver disease) activity score, NR: not reported, OLE: open-label extension, OR: odds ratio, SD: standard deviation

* NASH resolution is ballooning score of 0 and inflammation score of 0 or 1, with at least a 2-point reduction in NAS and no worsening of fibrosis

Table D10. Resmetirom Fat Fraction Outcomes (MRI-PDFF)

Study	Timepoint	Arm	N	Baseline MRI-PDFF (Mean, SD)	Change from Baseline MRI-PDFF, (Mean, SD)	MRI-PDFF LSMD (95% CI), P value	≥5% MRI-PDFF reduction (n/N)	≥30% MRI-PDFF Reduction, n/N (%)	≥30% MRI-PDFF treatment difference, Odds Ratio (95%CI)
Phase 2[12]	12 weeks	Placebo	41	19.6, 8.2	-10.4, 4.3	NR	NR	7/38 (18.4)	NR
		Resmetirom	84	20.2, 6.8	-32.9, 3.0	-22.5 (-32.9, -12.20; p<0.0001	NR	47/78 (60.3)	OR 6.8 (2.6, 17.6), P < 0.0001
	36 weeks	Placebo	41	19.6, 8.2	-8.9, 5.4	NR	NR	10/34 (29.4)	NR
		Resmetirom	84	20.2, 6.8	-37.3, 3.7	-28.4 (-41.3, -15.4); p<0.0001	NR	50/74 (67.6)	OR 4.9 (2, 11.9), P = 0.0006
Phase 2 OLE[14]	12 weeks	Placebo/ Resmetirom	14	18, 7	-39.9, 4.2, P < 0.001	NR	8/12 (66.7)	8/12 (66.7)	NR
		Resmetirom/ Resmetirom	17	14.2, 6.1	-33.5, 5.6, P < 0.001	NR	12/15 (80.0)	9/15 (60.0)	NR
		Overall Resmetirom	31	15.9, 6.7	-36.4, 3.6, P < 0.001	NR	20/27 (74.1)	17/27 (63.0)	NR
	36 weeks	Placebo/ Resmetirom	14	18, 7	-52.0, 7.1, P < 0.001	NR	8/10 (80.0)	7/10 (70.0)	NR
		Resmetirom/ Resmetirom	17	14.2, 6.1	-45.8, 5.1, P < 0.001	NR	14/15 (93.3)	13/15 (86.7)	NR
		Overall Resmetirom	31	15.9, 6.7	-48.4, 4.2, P < 0.001	NR	22/25 (88.0)	20/25 (80.0)	NR
		Resmetirom 80 mg	18	NR	-44.6, 4.9, P < 0.001	NR	15 (83.3)	14 (77.8)	NR
		Resmetirom 100 mg	7	NR	-58.8, 6.8, P < 0.001	NR	7 (100.0)	6 (85.7)	NR

MRI-PDFF: magnetic resonance imaging-proton density fat fraction, N: number, N: total number, NR: not reported, OLE: open-label extension, SD: standard deviation

Table D11. Resmetirom Lipid Outcomes

Study (Timepoint)	Arm	N	Total Cholesterol	HDL Cholesterol			LDL Cholesterol			Triglycerides		
			Baseline Mean, SD	Baseline Mean, SD	CFB, SE, P value	LSMD (95% CI), P value	Baseline Mean, SD	CFB, SE, P value	LSMD (95% CI), P value	Mean, SD	CFB, SE, P value	LSMD (95% CI), P value
MAESTRO-NASH[16] (52 weeks)	Placebo	318	NR	NR	NR	NR	Overall: 99, 40	1	NR	Overall: 188, 132	NR	NR
	Resmetirom 80 mg	316	NR	NR	NR	NR		-12; p<0.0001	NR		NR	NR
	Resmetirom 100 mg	321	NR	NR	NR	NR		-16; p<0.0001	NR		NR	NR
Phase 2[12] (36 weeks)	Placebo	41	198.4, 37.3	45.2, 13.4	2.2, 3.4; NR	NR	111.3, 30.4	6.2, 3.1	NR	NR	-20.5, 5.5	NR
	Resmetirom	84	193, 39.3	43.8, 12.5	6.0, 2.3; NR	3.8 (-4.4, 12.0), p=0·36	116.9, 30	-11.2, 2.1	-17.3 (-24.8, -9.9), p<0·001	NR	-15.4, 3.8	-36.0 (-49.2. -22.7), p<0·001
Phase 2 OLE[14] (12 weeks)	Resmetirom	31	NR	NR	-1.2, 1.1, p=0.25	NR	NR	-31.6, 5.2, p<0.001	NR	NR	-33.0, 11.2, p=0.014	NR
Phase 2 OLE[14] (36 weeks)	Resmetirom	31	NR	NR	-1.7, 1.2, p=0.15	NR	NR	-39.8, 8.4, p<0.001	NR	NR	-23.3, 6.7, p=0.002	NR
	Resmetirom 80 mg	21	NR	NR	NR	NR	NR	-33.1, 5.7, p<0.001	NR	NR	-44.2, 11.7, p=0.023	NR
	Resmetirom 100 mg	7	NR	NR	NR	NR	NR	-30.1, 9.8, p=0.005	NR	NR	-51.7, 22.2, p=0.028	NR
MAESTRO-NAFLD-1[15,50]	Placebo	309	NR	NR	NR	NR	105.9, 36.9	-1.7, 2.0	NR	NR	NR	NR
	Resmetirom 80 mg	320	NR	NR	NR	NR	111.3, 37.8	-12.7, 2.1; p <0.0001	NR	NR	NR	NR
	Resmetirom 100 mg	314	NR	NR	NR	NR	109.1, 36.4	-14.4, 2.1; p <0.0001	NR	NR	NR	NR

95%CI: 95 percent confidence interval, CFB: Change from baseline, HDL: high-density lipoprotein, LDL: low-density lipoprotein, LSMD: least squares mean difference, mg: milligram, MRI-PDFF: magnetic resonance imaging proton density fat fraction, n: number, N: total number, NR: not reported, OLE: open-label extension, SD: standard deviation, SE: standard error

Table D12. Resmetirom Liver Enzyme Levels

Study (Timepoint)	Arm	N	ALT			AST			Total Bilirubin		
			Baseline Mean, SD	CFB, SE, P value	LSMD (95% CI); P value	Baseline Mean, SD	CFB, SE, P value	LSMD (95% CI), P value	Baseline Mean, SD	CFB, SE, P value	LSMD (95% CI), P value
MAESTRO-NASH[4]	Overall	966	55, 32	NR	NR	41, 23	NR	NR	NR	NR	NR
Phase 2[12] (12 weeks)	Placebo	41	50.0, 29.2	-5.2 (3.9)	NR	38.0, 20.7	-1.1, 2.5	NR	0.57, 0.25	NR	NR
	Resmetirom	84	60.1, 32.2	-8.2 (2.7)	-3.0 (-12.4 to 6.4), P = 0.53	35.1, 17.7	-5.8, 1.8	-4.8 (-10.9 to 1.4), P = 0·13	0.55, 0.23	NR	NR
Phase 2[12] (36 weeks)	Placebo	41	50.0, 29.2	11.0, 6.8	NR	38.0, 20.7	3.6, 2.8	NR	0.57, 0.25	-0.033, 0.026	NR
	Resmetirom	84	60.1, 32.2	-15.4, 4.7	-26.4 (-42.8 to -9.9), P = 0.0019	35.1, 17.7	-7.4, 1.9	-11.1 (-17.8 to -4.3), P = 0·0016	0.55, 0.23	0.013, 0.018	0·046 (-0.017 to 0.11), P = 0.15
Phase 2 OLE[14] (12 weeks)	Placebo/ Resmetirom	14	70.6, 51.7	-16.8, 4.7, P = 0.001	NR	40.9, 24.8	-5.7, 4.2, P = 0.19	NR	0.51, 0.17	NR	NR
	Resmetirom/ Resmetirom	17	58.5, 35.6	-14.4, 4.4, P = 0.003	NR	43.8, 16.4	-4.1, 3.9, P = 0.30	NR	0.57, 0.20	NR	NR
	Overall Resmetirom	31	64, 43.2	-15.5, 4.8, P = 0.003	NR	42.5, 20.3	-4.9, 3.5, P = 0.17	NR	0.54, 0.19	NR	NR
Phase 2 OLE[14] (36 weeks)	Placebo/ Resmetirom	14	70.6, 51.7	-31.7, 4.6, P < 0.001	NR	40.9, 24.8	-16.6, 3.1, P < 0.001	NR	0.51, 0.17	NR	NR
	Resmetirom/ Resmetirom	17	58.5, 35.6	-16.4, 4.1, P = 0.001	NR	43.8, 16.4	-1.2, 2.8, P = 0.68	NR	0.57, 0.20	NR	NR
	Overall Resmetirom	31	64, 43.2	-23.3, 6.7, P = 0.002	NR	42.5, 20.3	-8.1, 4.1, P = 0.061	NR	0.54, 0.19	NR	NR
	Resmetirom 80 mg	21	NR	-24.4, 4.1, P < 0.001	NR	NR	-7.2, 3.0, P = 0.025	NR	NR	NR	NR

	Resmetirom 100 mg	7	NR	-20.3, 7.4, P = 0.01	NR	NR	-10.2, 5.4, P = 0.068	NR	NR	NR	NR

95%CI: 95 percent confidence interval, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CFB: Change from baseline, LSMD: least squares mean difference, mg: milligram, n: number, N: total number, NR: not reported, OLE: open-label extension, SD: standard deviation, SE: standard error

Table D13. Resmetirom Phase 2 HRQoL: 36-Item Short Form Survey (SF-36)[13]

	Week 12			Week 36		
	Placebo (N=38)	Resmetirom (N=78)	Placebo vs. Resmetirom	Placebo (N=34)	Resmetirom (N=72)	Placebo vs. Resmetirom
	Mean CFB, SE; p-value	Mean CFB, SE; p-value		Mean CFB, SE; p-value	Mean CFB, SE; p-value	
Physical functioning	5.26, 3.82; p=0.25	0.19, 1.76; p=0.86	p=0.33	6.01, 3.18; p=0.11	1.60, 1.86; p=0.64	p=0.38
Social functioning	–3.29, 3.55; p=0.35	2.40, 2.13; p=0.34	p=0.34	0.37, 3.75; p=0.94	1.04, 2.69; p=0.72	p=1.00
Physical component	0.25, 0.90; p=0.92	1.05, 0.62; p=0.12	p=0.39	0.96, 1.03; p= 0.38	1.40, 0.70; p=0.030	p=0.61
Mental component	0.32, 1.38; p=0.34	0.34, 0.76; p=0.18	p=0.81	0.01, 1.49; p=0.71	0.31, 0.93; p=0.67	p=0.98
Bodily Pain	–0.39, 3.23; p=0.97	6.31, 2.67; p=0.022	p=0.18	–1.06, 3.53; p=0.90	4.99, 2.93; p=0.071	p=0.16
General health	–1.76, 2.38; p=0.35	0.95, 1.62; p=0.80	p=0.41	-0.56, 2.32; p=0.61	3.68, 1.85; p=0.16	p=0.27
Mental health	3.16, 3.36; p=0.16	1.96, 1.54; p=0.16	P =0.38	1.47, 3.37; p=0.55	2.05, 1.8; p=0.22	p=0.76
Role physical	0.82, 3.19; p=0.69	1.84, 2.14; p=0.37	p=0.96	2.57, 3.36; p=0.43	1.04, 2.32; p=0.71	p=1.00
Role emotional	2.85, 3.40; p=0.11	–1.60, 2.24; p=0.83	p=0.23	0.74, 3.52; p=0.96	-1.50, 2.58; p=0.54	p=0.41
Vitality	0.16, 2.65; p=0.99	0.80, 1.93; p=0.48	p=0.74	1.10, 3.22; p=0.72	2.34, 1.94; p=0.19	p=0.78

CFB: change from baseline, HRQoL: health-related quality of life, N: number, SE: standard error
Scores range from 0-100, positive mean change indicated improvement in HRQoL.
* Statistical significance above a 0.05 level achieved

Table D14. Resmetirom Adverse Events and Discontinuation

Study	MAESTRO-NASH[16]			Phase 2[12]		Phase 2 OLE[14]	MAESTRO-NAFLD1[15]		
Timepoint	52 weeks			Week 12 to 36					
Arm	Placebo	Resmetirom 80 mg	Resmetirom 100 mg	Placebo	Resmetirom	Overall Res	Placebo	Resmetirom 80 mg	Resmetirom 100 mg
N	318	316	321	41	84	31	318	327	324
Any adverse event(s), n (%)	NR	NR	NR	28 (68.3)	73 (86.9)	18 (58.1)	260 (81.8)	289 (88.4)	279 (86.1)
Serious AEs, n (%)	NR (12.1)	NR (11.8)	NR (12.7)	2 (4.9)	5 (6.0)	0 (0.0)	20 (6.3)	20 (6.1)	24 (7.4)
TRAEs, n (%)	NR	NR	NR	NR	NR	NR	253/309 (81.8)	283/320 (88.4)	270/314 (86.1)
Serious TRAEs, n (%)	NR	NR	NR	0 (0.0)	0 (0.0)	NR	NR (9.1)	NR (7.6)	NR (9.0)
Death, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nausea, n (%)	NR (13)	NR (22)	NR (19)	1 (2)	5 (6)	1 (3.2)	25 (7.9)	38 (11.6)	59 (18.2)
Diarrhea, n (%)	NR (16)	NR (28)	NR (34)	1 (2)	3 (4)	3 (9.7)	44 (13.8)	76 (23.2)	101 (31.2)
Headache, n (%)	NR	NR	NR	6 (14.6)	11 (13.1)	0 (0)	NR	NR	NR
UTI, n (%)	NR	NR	NR	4 (9.8)	9 (10.7)	1 (3.2)	NR	NR	NR
Fatigue, n (%)	NR	NR	NR	4 (9.8)	4 (4.8)	NR	NR	NR	NR
Discontinuation due to AEs, n (%)	NR (3.7)	NR (2.8)	NR (7.7)	1 (2.4)	3 (3.6)	NR	4 (1.3)	8 (2.4)	9 (2.8)
Discontinuation, lost to follow-up, n (%)	NR	NR	NR	4 (9.8)	5 (6.0)	NR	16/320 (5.0)	24 (7.3)	22/325 (6.8)
Discontinuation for other reasons, n (%)	NR	NR	NR	2 (4.9)	2 (2.4)	NR	39/320 (12.2)	49 (15)	32/325 (9.8)

AE: adverse event, mg: milligram, n: number, N: total number, NR: not reported, TRAE: treatment-related adverse event, OLE: open-label extension, UTI: urinary tract infection

Table D15. Obeticholic Acid Baseline Characteristics: Demographics

Study	Arm	N	Age (Mean, SD)	Male, n (%)	Race, n (%)				Ethnicity, Hispanic, n (%)	BMI, kg/m2 (Mean, SD)
					Asian	Other	Black/African American	White		
FLINT[23]	Placebo	97	50, 12	35 (36.1)	NR	NR	NR	77 (79.4)	NR	34, 6
	OCA 25 mg	99	52, 11	30 (30.3)	NR	NR	NR	84 (84.8)	NR	35, 6
REGENERATE[6]	Placebo	825	54.4, 11.2	347 (42.1)	NR	NR	NR	685 (83.0)	233 (28.2)	34.1, 5.5
	OCA 10 mg	825	55.3, 10.8	350 (42.4)	NR	NR	NR	679 (82.3)	205 (24.8)	33.7, 5.6
	OCA 25 mg	827	55.3, 11.7	333 (40.3)	NR	NR	NR	674 (81.5)	233 (28.2)	33.7, 5.5
REGENERATE HRQoL[25]	Placebo	407	53.6, 11.7	176 (43.2)	NR	NR	NR	338 (92)	NR	34.3, 5.9
	OCA 10 mg	407	54.4, 11	177 (43.5)	NR	NR	NR	343 (91)	NR	33.9, 5.6
	OCA 25 mg	404	54.2, 11.8	171 (42.3)	NR	NR	NR	325 (87)	NR	33.8, 5.5

kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, OCA: obeticholic acid, SD: standard deviation

Table D16. Obeticholic Acid Baseline Characteristics II

	Arm	N	Comorbid Conditions		Concomitant Drugs		Fibrosis Stage			
			T2D, n (%)	Hypertension, n (%)	Antidiabetics, n (%)	Cholesterol Lowering, n (%)	Stage 1, n (%)	Stage 2, n (%)	Stage 3, n (%)	Mean Stage, SD
FLINT[23]	OCA 25 mg	99	52 (52.5)	64 (64.6)	NR	51 (51.5)	NR	NR	NR	1.8, 1
	Placebo	97	52 (53.6)	57 (58.8)	NR	43 (44.3)	NR	NR	NR	1.8, 1
REGENERATE[6]	OCA 25 mg	827	479 (57.9)	NR	NR	NR	0	300/730 (41.1)	430/730 (58.9)	NR
	OCA 10 mg	825	476 (57.7)	NR	NR	NR	0	289/729 (39.6)	440/729 (60.4)	NR
	Placebo	825	470 (57.0)	NR	NR	NR	0	290/728 (39.8)	438/728 (60.2)	NR
REGENERATE HRQoL[25]	OCA 10 mg	407	219 (53.8)	NR	221/399 (55.4)	178/399 (44.6)	96 (24)	142 (35)	169 (42)	NR
	Placebo	407	220 (54.1)	NR	212/398 (53.3)	186/398 (46.7)	95 (23)	130 (32)	182 (45)	NR
	OCA 25 mg	404	224 (55.4)	NR	211/381 (55.4)	170/381 (44.6)	96 (24)	139 (34)	169 (42)	NR
Baseline Characteristics not reported: Stage 0 and stage 4 fibrosis										

mg: milligram, n: number, N: total number, NR: not reported, OCA: obeticholic acid, SD; standard deviation, T2D: type 2 diabetes

Table D17. Obeticholic Acid REGENERATE Primary Efficacy Results

Study	REGENERATE (18 months)					
	2022 Consensus Panel Read[6]			2019 Central Pathologist Read[30]		
Arm	Placebo	10 mg OCA	25 mg OCA	Placebo	10 mg OCA	25 mg OCA
N	311	312	308	311	312	308
>=1 fibrosis stage improvement with no worsening of NASH, n (%)	30 (9.6)	44 (14.1); p = NS	69 (22.4); p<0.0001	37 (12)	55 (18); RR 1.5 (95%CI 1 0, 2.20; p=0.045	71 (23); RR 1.9 (95%CI 1.4, 2.8); p=0.0002
NASH resolution with no worsening in fibrosis, n (%)	NR (3.5)	NR (6.1); p =NS	NR (6.5); p=NS	25 (8)	35 (11), RR 1·4 (95%CI 0·9, 2·3); p=NS	36 (12) 1·5 (0·9–2·4); p=NS

95%CI: 95 percent confidence interval, LSMD: least squares mean difference, mg: milligram, n: number, N: total number, NAS: NAFLD (nonalcoholic fatty liver disease) activity score, NS: not significant, NR: not reported, OCA: obeticholic acid, OLE: open-label extension, RR: risk ratio, SD: standard deviation

Table D18. Obeticholic Acid REGENERATE Liver Biomarker Outcomes[6]

Timepoints	Arms	N	ALT			AST	Liver Stiffness by VCTE	
			Mean, SD	CFB, SE, P value	LSMD (95% CI); P value	Mean, SD	Mean, SD	LSMD (95% CI), P value
Baseline	25 mg OCA	827	72.6 (52.7)	NA	NA	NR	11.74, 6.37	NA
	10 mg OCA	825	71.4 (46.3)	NA	NA	NR	12.07, 6.19	NA
	Placebo	825	77.1 (51.7)	NA	NA	NR	12.19, 6.69	NA
18 months	25 mg OCA	827	NR	NR	N=608: -30.1 (NR); p<0.0001	NR	NR	N=433: -1.07 (NR); p=0.0015
	10 mg OCA	825	NR	NR	N=634: -25.2 (NR); P<0.0001	NR	NR	N=469: -1.15 (NR); p=0.0006
	Placebo	825	NR	NR	N=635: -12.1	NR	NR	N=465 : 0.41 [0.01 to 0.80] (NR)
24 months	25 mg OCA	1	59, (56, 63)	NR	NR	66, [62, 70]	NR	NR
	Placebo	1	43, (41, 45)	NR	NR	48, [45, 50]	NR	NR
48 months	25 mg OCA	NR	NR	NR	N=293: -31.0 (NR); p<0.0001	NR	NR	N=191: -2.32 (NR); p=0.0172

	10 mg OCA	NR	NR	NR	N=304: -26.4 (NR); p=0.0104	NR	NR	N=201: -1.86 (NR); p=0.0784
	Placebo	NR	NR	NR	N=305: -19.9	NR	NR	N=186: -0.64 (NR)

95%CI: 95 percent confidence interval, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LSMD: least squares mean difference, mg: milligram, n: number, N: total number, NA: not applicable, NAS: NAFLD (nonalcoholic fatty liver disease) activity score, NS: not significant, NR: not reported, OCA: obeticholic acid, OLE: open-label extension, RR: risk ratio, SD: standard deviation, VCTE: vibration-controlled transient elastography

Table D19. Obeticholic Acid REGENERATE HRQoL: Chronic Liver Disease Questionnaire (CLDQ)[25]

	Baseline: Mean Score, SD			Month 18: Mean Score, SD		
	Placebo (N=407)	**OCA 10 mg** (N=407)	**OCA 25 mg** (N=404)	**Placebo** (N=407)	**OCA 10 mg** (N=407)	**OCA 25 mg** (N=404)
Abdominal	5.34, 1.53	5.3, 1.51	5.26, 1.5	5.67, 1.41	5.55, 1.49	5.7, 1.4
Activity	5.49, 1.37	5.44, 1.36	5.49, 1.33	5.7, 1.34	5.44, 1.41*	5.66, 1.38
Emotional	5.37, 1.21	5.31, 1.23	5.35, 1.25	5.58, 1.22	5.38, 1.20*	5.49, 1.23
Fatigue	4.57, 1.49	4.61, 1.49	4.62, 1.4	4.89, 1.5	4.67, 1.46*	4.91, 1.46
Systemic	5.08, 1.25	4.99, 1.24	5.07, 1.22	5.27, 1.25	5.05, 1.31*	5.19, 1.26
Worry	5.26, 1.41	5.15, 1.4	5.24, 1.56	5.63, 1.45	5.68, 1.34	5.69, 1.49
Itch	5.82, 1.46	5.72, 1.55	5.71, 1.57	5.7, 1.59	5.55, 1.72	5.34, 1.82*
Total	5.18, 1.14	5.13, 1.12	5.17, 1.12	5.46, 1.14	5.3, 1.13*	5.44, 1.14

HRQoL: health-related quality of life, mg: milligram, N: total number, OCA: obeticholic acid, SD: standard deviation

Scores range from 1-7, with lower scores corresponding with worse or more frequent symptoms

* P<0.05 compared with placebo

Table D20. Obeticholic Acid REGENERATE HRQoL: EuroQol-5D (EQ-5D)[25]

	Overall Population at Baseline Mean Score, SD
Mobility	1.52, 0.82
Self-care	1.14, 0.46
Activities	1.49, 0.84
Pain/Discomfort	2.09, 0.98
Anxiety/Depression	1.63, 0.91
VAS	73.7, 18.0
Utility score	0.814, 0.173

HRQoL: health-related quality of life, SD: standard deviation, VAS: visual analogue scale

Table D21. Obeticholic Acid Adverse Events and Discontinuation[6]

Study	REGENERATE	
Arm	Placebo	25 mg OCA
N	825	827
Any adverse event(s), n (%)	766 (92.8)	807 (97.6)
Serious AEs, n (%)	181 (21.9)	216 (26.1)
TRAEs, n (%)	NR	NR
Serious TRAEs, n (%)	NR	NR
Death, n (%)	8 (1.0)	10 (1.2)
Discontinuation due to AEs, n (%)	93 (11.3)	179 (21.6)
Neoplasms, n (%)	84 (10.2)	76 (9.2)
Pruritus, n (%)	200 (24.2)	453 (54.8)
Cardiovascular AEs (Extended MACE), n (%)	26 (3.2)	37 (4.5)
Cardiovascular AEs (4-point MACE), n (%)	12 (1.5)	13 (1.6)
Gallbladder disease, n (%)	33 (4.0)	63 (7.6)
Serious Gallbladder disease, n (%)	6 (0.7)	21 (2.5)
Hyperglycemia/Diabetes, n (%)	190 (23.0)	201 (24.3)
Potential liver injury (highly likely or probably related), n (%)	1 (0.1)	7 (0.8)
Acute Kidney Injury, n (%)	3 / 33 (9.1)	3 / 33 (9.1)

AE: adverse event, MACE: major adverse cardiac events, mg: milligram, n: number, N: total number, NR: not reported, TRAE: treatment-related adverse event

D4. Ongoing Studies

Figure D22. Ongoing Studies

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Est. Completion Date
Resmetirom					
A Study to Evaluate the Effect of Resmetirom on Clinical Outcomes in Patients With Well-compensated NASH Cirrhosis (MAESTRO-NASH OUTCOMES) *Madrigal Pharmaceuticals, Inc.* NCT05500222	Multi-national, multicenter, double-blind, placebo-controlled randomized trial	- Resmetirom 80mg once daily - Matching placebo once daily	Adult patients with well-compensated NASH cirrhosis	Composite Clinical Outcome event* [up to 36 months]	November 2025
A Phase 3 Study to Evaluate Safety and Biomarkers of Resmetirom (MGL-3196) in Patients with Non-alcoholic Fatty Liver Disease (NAFLD), MAESTRO-NAFLD-OLE *Madrigal Pharmaceuticals, Inc.* NCT04951219	Multi-center, open-label active treatment extension study	Single-blind - Resmetirom 80mg daily - Resmetirom 100mg daily Open-label - Resmetirom 100mg daily	Adult patients who completed 52 weeks of the MAESRO-NALFD-1 trial	Incidence of adverse events [52 weeks]	April 2024
Obeticholic Acid					
Comparative Study Between Obeticholic Acid vs. Vitamin E in Patients With Non-alcoholic Steatohepatitis *Tanta University* NCT05573204	Randomized controlled, parallel, prospective 6-month trial, open-label trial	- Obeticholic acid 10mg oral tablet - Vitamin E 400 mg twice daily	Adults aged ≥18 years with NASH without cirrhosis	Fibrosis improvement (≥1 stage) with no worsening of NASH [6 months]	September 2024

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)Resmetirom trials MAESTRO-NASH and MAESTRO-NAFLD1 trials are still ongoing but are described in Supplement Table D6.
mg: milligram, NASH: nonalcoholic steatohepatiti
* Composite Clinical Outcome event consists of any event of all-cause mortality, liver transplant, ascites, hepatic encephalopathy, gastroesophageal variceal hemorrhage, and confirmed increase of MELD score from <12 to .>/= 15 due to liver disease

D5. Previous Systematic Reviews and Technology Assessments

We identified three previously conducted systematic reviews which are summarized below. They compared pharmacological interventions for non-alcoholic steatohepatitis by means of a network meta-analysis. 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 were unable to identify any HTAs of resmetirom for the treatment of NASH.

Previous Systematic Reviews

Aishwarya TS, Mounika N, Vishwakarma G, Adela R. Effect of obeticholic acid in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) patients: a systematic review and meta-analysis. RPS Pharmacy and Pharmacology Reports. 2022; 1:1-12.

A systematic literature review and meta-analysis was conducted to describe the efficacy and safety of obeticholic acid (OCA) in patients with NAFLD/NASH. Four randomized controlled trials with a total of 2,399 patients were included. Effects of OCA on liver enzymes, liver histology, lipoproteins, body weight and adverse events were described. OCA showed a statistically significant reduction in ALT, AST, and GGT levels compared to placebo. Patients on OCA had a statistically significant increase in total cholesterol and a statistically significant reduction in HDL-cholesterol with a non-significant increase in LDL-cholesterol. Patients on OCA had improvements in steatosis, hepatocellular ballooning, lobular inflammation, and fibrosis compared those randomized to placebo. Patients on OCA did however experience an increase in adverse events such as pruritis and constipation. Pruritis is the main disadvantage of OCA but can be treated with medication and temporary treatment discontinuation. Outcomes were dose-dependent with the highest dose (25 mg) showing the most therapeutic potential but worse adverse events.

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).

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

Obeticholic acid for treating liver fibrosis in people with steatohepatitis [ID1645]

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).

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E.1. 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	☐	☐	
	Future related medical costs	X	X	
	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 Sector				
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 Sanders et al[51]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[52]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

E2. Model Inputs and Assumptions

Clinical Inputs

The MAESTRO-NASH and REGENERATE trials did not report specific fibrosis stage transitions, and it is not known if they will be available in the final analyses. Therefore, we use the distributions of transitions of NASH patients between fibrosis stages from Singh et al.[5] to calculate transition weights (Table E.2.) to apply to the improvement/worsening/no change treatment effects to estimate stage-specific transition probabilities (Table E.3. and E.4).

Table E.2. Transition Probability Weights

	Base Case	Lower Value (-20%)	Upper Value (+20%)
F0 to F1 (worsening)	0.64	0.51	0.76
F0 to F2 (worsening)	0.18	0.15	0.22
F0 to F3 (worsening)	0.09	0.07	0.11
F0 to F4 (worsening)	0.09	0.07	0.11
F1 to F0 (improvement)	1.00	0.80	1.00
F1 to F2 (worsening)	0.60	0.48	0.72
F1 to F3 (worsening)	0.33	0.27	0.40
F1 to F4 (worsening)	0.07	0.05	0.08
F2 to F0 (improvement)	0.23	0.28	0.18
F2 to F1 (improvement)	0.77	0.62	0.92
F2 to F3 (worsening)	0.50	0.40	0.60
F2 to F4 (worsening)	0.50	0.40	0.60
F3 to F0 (improvement)	0.00	0.00	0.00
F3 to F1 (improvement)	0.50	0.40	0.60

F3 to F2 (improvement)	0.50	0.40	0.60
F3 to F4 (worsening)	1.00	0.80	1.00
F4 to F0 (improvement)	0.00	0.00	0.00
F4 to F1 (improvement)	0.00	0.00	0.00
F4 to F2 (improvement)	0.00	0.00	0.00
F4 to F3 (improvement)*	1.00	0.80	1.00

*Used only in the F4 treatment continuation scenario.

An example of the process used to calculate annual transition probabilities is provided below. In this example, the standard care transition probability from F2 to improved fibrosis (F1 or F0) is 23%, 56% stay in F2, and 21% worsen (move to F3 or F4).[30] The improved fibrosis transition of 23% is distributed across the two possible stage-specific transitions according to the weights derived from Singh et al.[29] Multiplying the standard care probability of improved fibrosis by the respective weights results in 4% transitioning from F2 to F0 and 12% from F2 to F1 at 12 months. Similarly, the worsening of fibrosis transition of 21% is distributed across the two possible stage-specific transitions, which results in an annual probability of 7% for F2 to F3 and 7% for F2 to F4. The treatment effect of OCA (or resmetirom) would then be applied to the change probability, followed by transitioning according to the weights and then calculating a yearly probability. For example, the improvement from F2 to F0 or F1 would be 1.65*0.23=0.39. This would be weighted 23% from F2 to F0 and 77% from F2 to F1 as before, resulting in a 6.1% yearly probability transition from F2 to and F0 and 21.1% for F2 to F1. This example is shown in Table E.3.. The subsequent transitions that reflect the treatment effect of resmetirom and OCA are shown in Tables E.4 and E.5.

Table E.3. Example Application of Transition Probability Weights to Derive Annual Transition Probabilities for Standard of Care

		Change Probability	Weight	Annual Probability*
F2 to F0	Improve	0.23	0.23	0.04
F2 to F1	Improve	0.23	0.77	0.12
F2 to F2	Same	0.56	1.00	0.56
F2 to F3	Worsen	0.21	0.50	0.07
F2 to F4	Worsen	0.21	0.50	0.07
Source		Younossi et al., 2019[30] and Javanbakht et al., 2022[27]	Calculated from Singh et al., 2015[29]	Calculated

*Converted from 18-month probabilities to annual.

Table E.4. Example Application of Treatment Effect to Annual Transition Probabilities for Resmetirom

		Change Probability for Standard of Care	Absolute Risk Fifference	Change Probability for Intervention	Weight	Annual Probability for Resmetirom*
F2 to F0	Improve	0.23	0.12	0.35	0.23	0.06
F2 to F1	Improve	0.23	0.12	0.35	0.77	0.19
F2 to F2	Same	0.56		0.56	1.00	
F2 to F3	Worsen	0.21	-0.12	0.09	0.50	0.03
F2 to F4	Worsen	0.21	-0.12	0.09	0.50	0.03
Source		Younossi et al., 2019[4] and Javanbakht et al., 2022[3]	MAESTRO-NASH	Calculated	Calculated from Singh et al., 2015[5]	Calculated

*Converted from 18-month probabilities to annual.

Table E.5. Example Application of Treatment Effect to Annual Transition Probabilities for OCA

		Change Probability for Standard of Care	Absolute Risk Difference	Change Probability for Intervention	Weight	Annual Probability for OCA*
F2 to F0	Improve	0.23	0.15	0.38	0.23	0.06
F2 to F1	Improve	0.23	0.15	0.38	0.77	0.21
F2 to F2	Same	0.56		0.48	1.00	
F2 to F3	Worsen	0.21	-0.08	0.13	0.50	0.04
F2 to F4	Worsen	0.21	-0.08	0.13	0.50	0.04
Source		Younossi et al., 2019[30] and Javanbakht et al., 2022[27]	REGENERATE trial	Calculated	Calculated from Singh et al., 2015[29]	Calculated

OCA: obeticholic acid

*Converted from 18-month probabilities to annual.

Advanced Liver Disease Events

Liver disease-related transition probabilities (Table E.6.) were based on data from published sources and previous ICER assessments of OCA for NASH. We assumed F0-F2 patients did not transition directly to decompensated cirrhosis or HCC. We derived annualized transition probabilities from the 10-year cumulative incidences of decompensated cirrhosis and HCC for F3 and F4 patients. The annual probability of transitioning to HCC from decompensated cirrhosis was obtained from Ascha

et al.,[53] and assumed to be the same each year. All year 10 transition probabilities were held constant for the remaining time horizon. Treatment with OCA or resmetirom did not have a direct impact on advanced liver disease events. They did, however, have an indirect effect as using these medications slowed the progression to stages F3 and F4, where patients were at risk for experiencing an advanced liver disease event.

Table E.6. Advanced Liver Disease Transitions

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

DCC: decompensated cirrhosis, HCC: hepatocellular carcinoma

Mortality

Mortality

Gender and age-specific background mortality was sourced from the Centers for Disease Control and Prevention US-specific tables (Table E.7.). Mortality for F3 and F4 patients were sourced from Vilar-Gomez et al.,[54] who conducted a multi-national study of 458 patients with biopsy-confirmed NAFLD with bridging fibrosis or compensated cirrhosis followed until death, liver transplantation, or end-of-the-the study; Kaplan-Meier curves were digitized and converted to annual transition probabilities.

Mortality transitions due to complications following liver transplant were calculated at the time of the liver transplant so that the remainder of patients who did not die enter the post-liver transplant

health state (Table E.6.). We also included incremental mortality associated with CV events, linked with changes in LDL cholesterol, as described above.

Table E.7. Mortality Inputs

Parameter	Base case	Lower Value (-20%)	Upper Value (+20%)
Annual Probability: Compensated Cirrhosis to Liver-Related Death[55-57]	0.021	0.0168	0.0252
Annual Probability: Decompensated Cirrhosis to Liver-Related Death[58]	0.130	0.104	0.156
Conditional Probability: Liver Transplant (from DCC) to Liver-Related Death[59,60]	0.094	0.0752	0.1128
Conditional Probability: Liver Transplant (from HCC) to Liver-Related Death[60]	0.101	0.0808	0.1212
Annual Probability: All-Cause Mortality	U.S. Life Tables		

DCC: decompensated cirrhosis, HCC: hepatocellular carcinoma

Liver Transplant and Liver-Related Mortality Events

Liver transplant and liver-related mortality event transition probabilities were based on data from published sources and previous ICER assessments of OCA for NASH (Table E.8.). We derived annualized transition probabilities from the 5-year cumulative incidences of liver transplant and death from HCC[54]. The annual probabilities of transitioning to death from F4 and decompensated cirrhosis were the same each year.[55,56,61] 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.[59] Treatment with OCA or resmetirom did not have a direct impact on liver transplant and liver-related mortality events. They did, however, have an indirect effect as using these medications slowed the progression to decompensated cirrhosis and HCC, where patients were at risk for requiring a liver transplant.

Cardiovascular Events and Non-Liver Mortality

We utilized the pooled REGENERATE trial baseline patient characteristics (Table E.9.), Framingham Heart Study risk calculators, American Heart Association statistics for heart disease and stroke, and risk ratio adjustments based on LDL-C level to derive cycle-level estimates of CV event risk. In each model cycle, an age-updated 10-year risk of CV events was converted to a sex-weighted, cycle-specific risk; we assumed that total and HDL cholesterol at baseline (Table 4.2; used in the Framingham calculator) remained 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 and resmetirom-

treated cohorts. We assumed that the OCA-treated cohorts experienced an elevation in LDL-C of 17.2mg/dL (0.44 mmol/L) in the first cycle and held that difference constant for the remainder of the lifetime horizon. For resmetirom, we assumed all patients experienced a reduction of LDL by 17% based on top-line trial results at 24 weeks and held this for the remainder of the lifetime horizon. Baseline LDL-C is 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. Gender- and age-specific background mortality from the Centers for Disease Control and Prevention U.S.-specific tables were used for background mortality rates. Additionally, once in the prior CV event submodel, the cohort experienced an additional relative risk of CV event recurrence of 1.44.[8]

Table E.8. Liver Transplant and Liver-Related Mortality Transitions

	Liver Transplant Transitions		Liver-Related Mortality Transitions		
Annual Probability:	**DCC to LT***	**HCC to LT†**	**F4 to Death**	**DCC to Death**	**HCC to Death**
Year 1	0.430	0.557	0.021	0.130	0.144
Year 2	0.060	0.136	0.021	0.130	0.044
Year 3	0.030	0.025	0.021	0.130	0.012
Year 4	0.012	0.018	0.021	0.130	0.009
Year 5+	0.008	0.017	0.021	0.130	0.008

DCC: decompensated cirrhosis, HCC: hepatocellular carcinoma, LT: liver transplant, SA: sensitivity analysis
*Conditional probability of death due to complications of liver transplant, from DCC: 0.094 (±20%)
†Conditional probability of death due to complications of liver transplant, from HCC: 0.101 (±20%)

Table E.9. 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[62]	17.2 mg/dL	13.8 mg/dL	20.6 mg/dL	Normal
Resmetirom LDL-C Difference vs. Standard Care at 24 weeks	17%	15%	19%	Beta
Cardiovascular Risk by LDL-C				
On statins: RR per 1 mmol/L increase[63]	1.30	1.04	1.56	Log Normal
Not on statins: RR per 1 mmol/L increase[63]	1.33	1.07	1.60	Log Normal
Cardiovascular Event Parameters				
MI vs. Stroke: Proportion if CV Event[64]	0.79	0.63	0.94	Beta

Proportion of MIs that are fatal[64]	0.24	0.19	0.29	Beta
Proportion of strokes that are fatal[64]	0.21	0.17	0.25	Beta
Recurrent CV Event Relative Risk[65]	1.44	1.40	1.49	Log Normal

RR: relative risk, mg/dL: Milligrams per deciliter, MI: myocardial infarction CV: cardiovascular SA: sensitivity analysis, LDL-C: low-density lipoprotein-cholesterol

Adverse Events

For resmetirom, no serious AEs were reported that occurred in >5% of patients. Additionally, pruritus and increased LDL-C were not reported in the MAESTRO-NASH trials, as seen for OCA. AEs may be included for resmetirom pending phase III results.

Consistent with the prior ICER NASH model, we included costs for Grade three pruritus and increased LDL-C that were observed in the REGENERATE trial (Table E.10). We also applied a disutility for pruritus that lasted for one cycle (i.e., one year). Adverse events 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).

Table E.10. Adverse Events

Parameter	OCA %	Standard Care %	Disutility	Cost/Year
Grade 3 pruritus	3.7%	0.3%	-0.019[25]	$317
Increased LDL-C	12.0%	4.8%	-	$123

LDL-C: low-density lipoprotein-cholesterol, OCA: obeticholic acid

Drug Utilization

The following inputs (Table E.11.) will be used to model drug utilization and associated costs:

- Duration of treatment
- Schedule of doses for each drug in each regimen

Table E.11. Treatment Regimen Recommended Dosage

Generic Name	Resmetirom	Obeticholic Acid
Brand Name	TBD	TBD
Manufacturer	Madrigal	Intercept
Route of Administration	oral	oral

Dosing	100 mg once daily	25 mg once daily

Mg: Milligram, TBD: to be determined

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 (Table E.12).[38] Patients diagnosed by liver biopsy in the GAIN study 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 assessed annual productivity loss costs due to nonfatal CV events based on the societal perspective analysis from a previous ICER report on cardiovascular disease.[33]

Table E.12. Societal Perspective Annual Costs

Annual Societal Cost	Base Case	Lower Value (-20%)	Upper Value (+20%)
NASH Direct Non-Medical Costs			
NASH Fibrosis Stage 0-2	$2,882	$2,306	$3,459
NASH Fibrosis Stage 3	$5,028	$4,023	$6,034
NASH Fibrosis Stage 4	$7,755	$6,204	$9,306
NASH Indirect Costs			
NASH Fibrosis Stage 0-2	$8,236	$6,589	$9,883
NASH Fibrosis Stage 3	$14,368	$11,495	$17,242
NASH Fibrosis Stage 4	$22,159	$17,727	$26,590
Productivity Costs			
CV Event Productivity Loss (Year of Event)[33]	$4,697	$3,758	$5,636

CV: cardiovascular; SA: sensitivity analysis

E3. Results

Table E.13 and E.14 show the results for advanced liver disease outcomes, specifically DCC, HCC, and liver transplant events for resmetirom (Table E.13.) and OCA (Table E.14.).

Table E.13. Advanced Liver Disease Events for Resmetirom Per Patient

	Resmetirom	Standard Care

Decompensated Cirrhosis	0.038	0.134
Hepatocellular Carcinoma	0.038	0.164
Liver Transplant	0.020	0.074

Table E.14. Advanced Liver Disease Events for Obeticholic Acid Per Patient

	Obeticholic Acid	Standard Care
Decompensated Cirrhosis	0.050	0.134
Hepatocellular Carcinoma	0.049	0.164
Liver Transplant	0.025	0.074

E4. Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Figures E.1. and E.2. present the results from the one-way sensitivity analysis from the health care sector perspective for both resmetirom and OCA, respectively. Notably, the most influential inputs on the findings were utility values, drug costs, and transition probabilities. Tables E.15. and E.16. present the lower and upper incremental cost-effectiveness ratios based on the lower and upper limit inputs for the most influential parameters. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1000 simulations, then calculating 95% credible range estimates for each model outcome based on the results, as well as the proportion of simulations that were cost-effective at various commonly used willingness-to-pay thresholds. The results are shown in Tables E.17. and E.18.

Figure E.1. Tornado Diagram for Resmetirom

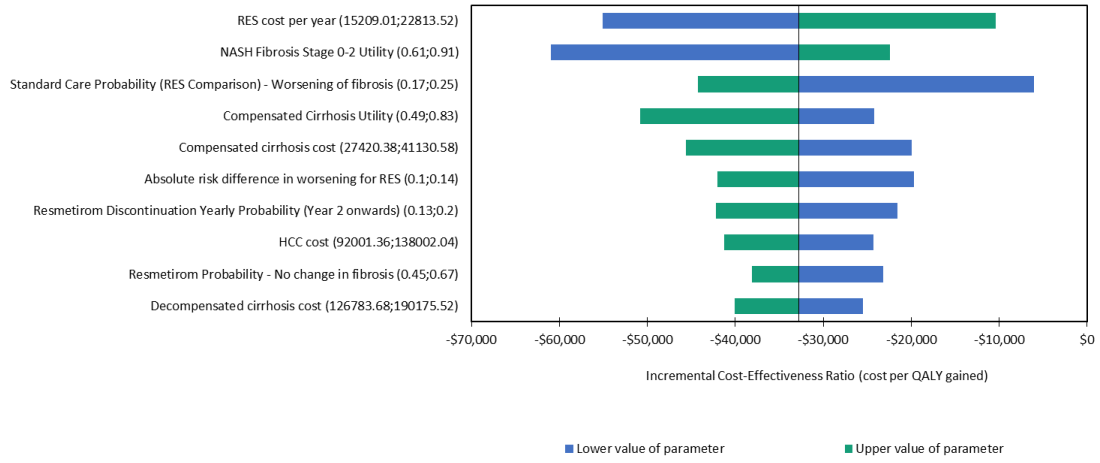


Table E.15. Tornado Diagram Inputs and Results for Resmetirom versus Standard Care

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Resmetirom Cost Per Year	-55,100	-10,400	15,200	22,800
NASH Fibrosis Stage 0-2 Utility	-61,000	-22,400	0.61	0.91
Standard Care Probability – Worsening of Fibrosis	-44,200	-6,000	0.17	0.25
Compensated Cirrhosis Utility	-50,800	-24,200	0.49	0.83
Compensated Cirrhosis Cost	-45,600	-19,900	27,400	41,100
Absolute Risk Difference in Worsening for Resmetirom	-42,000	-19,700	0.10	0.14
Resmetirom Discontinuation Yearly Probability (Year 2 Onwards)	-42,200	-21,600	0.13	0.20
HCC Cost	-41,200	-24,300	92,000	138,000
Resmetirom Probability – No Change in Fibrosis	-38,100	-23,200	0.45	0.67
Decomponsated Cirrhosis Cost	-40,000	-25,500	127,000	190,000

CE: cost-effectiveness, HCC: Hepatocellular Carcinoma

*Note lower input may reflect either upper or lower Incremental Cost-Effectiveness Ratio value depending on the direction that the input has on the Incremental CE Ratio output.

Figure E.2 Tornado Diagram for Obeticholic Acid

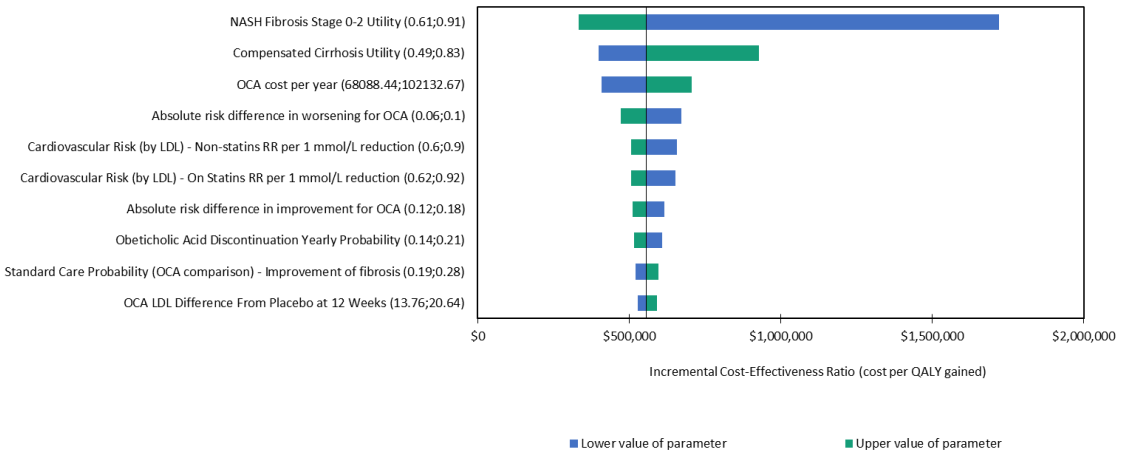


Table E.16. Tornado Diagram Inputs and Results for Obeticholic Acid versus Standard Care

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
NASH Fibrosis Stage 0-2 Utility	333,000	1,721,000	0.61	0.91
Compensated Cirrhosis Utility	398,000	928,000	0.49	0.83
OCA Cost per Year	409,000	707,000	68,100	102,000
Absolute Risk Difference in Worsening for OCA	474,000	672,000	-0.06	-0.10
Cardiovascular Risk (by LDL) – Non-statins RR per 1 mmol/L reduction	507,000	657,000	0.60	0.90
Cardiovascular Risk (by LDL) – On statins RR per 1 mmol/L reduction	508,000	654,000	0.62	0.92
Absolute risk difference in improvement for OCA	510,000	616,000	0.12	0.18
Obeticholic Acid Discontinuation Yearly Probability	517,000	609,000	0.14	0.21
Standard Care Probability – Improvement of fibrosis	521,000	597,000	0.19	0.28
OCA LDL Difference from Placebo at 12 weeks	527,000	591,000	13.76	20.64

CE: cost-effectiveness, LDL: LDL: low density lipoprotein, OCA: obeticholic acid

*Note lower input may reflect either upper or lower Incremental Cost-Effectiveness Ratio value depending on the direction that the input has on the Incremental CE Ratio output.

Table E.17. Probabilistic Sensitivity Analysis Cost per QALY Gained Results

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Resmetirom*	99.40%	99.80%	99.80%	99.80%
Obeticholic Acid†	0.00%	0.00%	0.00%	0.10%

QALY: quality-adjusted life-year

*Placeholder price based on Javanbakht et al 2022[3]

†Placeholder price based on current obeticholic acid price for 5 and 10 mg tablets

Table E.18. Probabilistic Sensitivity Analysis Cost per evLY Gained Results

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Resmetirom*	99.50%	100.0%	100.0%	100.0%
Obeticholic Acid†	0.00%	0.00%	0.00%	0.20%

evLY: equal value life-year

*Placeholder price based on Javanbakht et al 2022[3]

†Placeholder price based on current obeticholic acid price for 5 and 10 mg tablets

E5. Scenario Analyses

We conducted several scenario analyses to examine uncertainty and potential variation in the findings. The scenarios are presented below and the findings are presented in Tables E.19 and E20.

1. Modified societal perspective that includes components such as productivity losses, criminal justice and incarceration, or others as applicable.

2. Fibrosis improvement scenario where 50% of patients in F4 can still improve.

3. No LDL benefit for resmetirom.

4. Fibrosis Progression for resmetirom based on Phase II results.

5. Discontinuation due to adverse events only.

6. Discontinuation for resmetirom based on phase II data that assessed discontinuation by early (up to 12 weeks) versus late (week 13-36). The manufacturer provided Phase II trial data that showed [redacted] patients discontinued from weeks 1-12 and [redacted] patients discontinued from weeks 13-36. We calculated an annual probability of discontinuation from weeks 13-36 and used this as a scenario analysis for Year 2 onwards in the model. We chose to keep the discontinuation probability from the full 36 weeks of data from the Phase II trial as the base case since 36 weeks of data was still a relatively short follow up duration (and our model cycle length was yearly) and the sample size was small.

Table E.19. Selected Scenario Analysis Results (Total Outcomes)

Scenario 1: Modified Societal Perspective					
Treatment	**Drug Cost***	**Total Cost**	**QALYs**	**evLYs**	**LYs**
Resmetirom	$76,400	$643,000	10.66	10.74	15.05
Standard Care (Resmetirom)	$0	$677,000	10.05	10.05	14.56
Obeticholic Acid	$317,000	$903,000	10.48	10.53	14.88
Standard Care (Obeticholic Acid)	$0	$677,000	10.05	10.05	14.56
Scenario 2: F4 Improvement					
Treatment	**Drug Cost***	**Total Cost**	**QALYs**	**evLYs**	**LYs**
Resmetirom	$80,700	$377,000	10.96	11.02	15.30
Standard Care (Resmetirom)	$0	$389,000	10.43	10.43	14.89
Obeticholic Acid	$343,000	$651,000	10.83	10.88	15.18
Standard Care (Obeticholic Acid)	$0	$389,000	10.43	10.43	14.89
Scenario 3: No LDL Benefit for Resmetirom					
Treatment	**Drug Cost***	**Total Cost**	**QALYs**	**evLYs**	**LYs**
Resmetirom	$77,000	$417,000	10.77	10.87	15.19
Standard Care	$0	$439,000	10.05	10.05	14.56
Scenario 4: Fibrosis Progression for Resmetirom Based on Phase II Results					
Treatment	**Drug Cost***	**Total Cost**	**QALYs**	**evLYs**	**LYs**
Resmetirom	$76,100	$420,000	10.62	10.70	15.02
Standard Care	$0	$439,00	10.05	10.05	14.56
Scenario 5: Discontinuation due to Adverse Events Only					
Treatment	**Drug Cost***	**Total Cost**	**QALYs**	**evLYs**	**LYs**
Resmetirom	$152,000	$464,000	10.95	11.06	15.28
Standard Care (Resmetirom)	$0	$439,000	10.05	10.05	14.56

Obeticholic Acid	$476,000	$825,000	10.60	10.67	14.97
Standard Care (Obeticholic Acid)	$0	$439,000	10.05	10.05	14.56
Scenario 6: Early vs. Late Discontinuation for Resmetirom from Phase II					
Treatment	**Drug Cost***	**Total Cost**	**QALYs**	**evLYs**	**LYs**
Resmetirom	$97,000	$430,000	10.74	10.83	15.11
Standard Care	$0	$439,000	10.05	10.05	14.56

evLY: equal value life-year, LDL: low density lipoprotein, QALY: quality-adjusted life-year

Table E20. Selected Scenario Analysis Results (Incremental Cost-Effectiveness Ratios)

Scenario 1: Modified Societal perspective	**Treatment**	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Resmetirom*	SC alone	Less costly, more effective	Less costly, more effective	Less costly, more effective
	Obeticholic Acid†	SC alone	$533,000	$474,000	$720,000
Scenario 2: F4 improvement	**Treatment**	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Resmetirom*	SC alone	Less costly, more effective	Less costly, more effective	Less costly, more effective
	Obeticholic Acid†	SC alone	$645,000	$581,000	$889,000
Scenario 3: No LDL benefit for resmetirom	**Treatment**	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Resmetirom*	SC alone	Less costly, more effective	Less costly, more effective	Less costly, more effective
Scenario 4: Fibrosis Progression for resmetirom based on Phase II results	**Treatment**	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Resmetirom*	SC alone	Less costly, more effective	Less costly, more effective	Less costly, more effective
Scenario 5: Discontinuation due to adverse events only	**Treatment**	**Comparator**	**Cost per QALY Gained**	**Cost per evLY Gained**	**Cost per Life Year Gained**
	Resmetirom*	SC alone	$27,900	$24,900	$35,000
	Obeticholic Acid†	SC alone	$703,000	$625,000	$935,000

Scenario 6: Early vs. late discontinuation for Resmetirom from Phase II	Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained
	Resmetirom*	SC alone	Less costly, more effective	Less costly, more effective	Less costly, more effective

evLY: equal value life-year, LDL: low density lipoprotein, QALY: quality-adjusted life-year, SC: standard care

*Placeholder price based on Javanbakht et al 2022[3]

†Placeholder price based on current obeticholic acid price for 5 and 10 mg tablets

E6. Model Validation

We used several approaches to validate the model. First, we provided preliminary model structure, methods, and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined the data inputs used in the model, as needed. Second, we varied model input parameters to evaluate the face validity of changes in results. We performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we shared the model with the relevant manufacturers for external verification around the time of publishing the draft report for this review. Finally, we compared results to other cost-effectiveness models in this therapy area. The outputs from the model were validated against the trial/study data of the interventions and also any relevant observational datasets.

Prior Economic Models

We identified three recently published studies that examined the cost-effectiveness of pharmacologic treatment for NAFLD or NASH. Tran et al. (2021) considered the cost-effectiveness of OCA daily compared to placebo using a state-transition Markov Model, using one year cycles, for adult patients with definite NASH and fibrosis, with an NAFLD activity score of at least four. Patients could transition through 11 health states, reflecting the natural history of disease. The study estimates OCA treatment decreases the cases of DCC, HCC, LT, and Liver-related deaths (3.58%, 3.95%, 7.88%, and 6.01%, respectively). Base-case analysis reports and incremental cost of CAD$114,172 and incremental QALYs of 0.14 for OCA, yielding an ICER of $815,514 per QALY. This study was from a Canadian payer perspective, with costs and health outcomes discounted at a 1.5% annual rate.

Javanbakht et al. (2022) investigated the cost-effectiveness of resmetirom daily compared to a placebo for the treatment of NASH with fibrosis. Using a Markov model with one year cycles, patients were modeled according to fibrosis stage, and could regress, progress, or not change

during each cycle. The primary endpoint for this study was the relative change in MRIPDFF after 12 weeks for patients located at 25 health centers in the US. The evidence suggests resmetirom treatment reduces the number of DCC, HCC, and LT's incidents (-87, -59, and -30, respectively). Base-case analysis suggests resmetirom provides an additional 1.24 QALYs, and costs US$66,764 more than placebo, resulting in an incremental cost-effectiveness ratio of US$53,929. Costs and outcomes were discounted at a 3% annual rate.

Rustgi et al. (2022) examined the cost-effectiveness of a hypothetical modality compared to standard care (e.g., metabolic syndrome modifications, increased physical activity, weight loss, and dietary changes) for the treatment of NAFLD-fibrosis. Fibrosis stages zero to four (F0-F4), DCC, HCC, LT, and PLT were modeled using a Markov structure for patients in the US. The hypothetical treatment increased mean survival by 6.3 months and QALYS by 0.18. The additional QALYs result in an incremental cost of US$453,926, yielding an incremental cost-effectiveness ratio of greater than US$2.5 million per QALY. Costs and benefits were discounted at 3% annually.

F. Potential Budget Impact: Supplemental Information

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 each 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 one- and five-year time horizons. The five-year timeframe was of primary interest, 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.

The potential budget impact analysis included the candidate populations eligible for treatment. To estimate the size of the potential candidate populations for treatment, we applied a prevalence estimate of 1.4% to the 2023-2027 projected US population aged 18 years of age and older. Our estimate was based on a 4% prevalence of NASH in the overall US population [based on a reported average of 1.5% to 6.5%][31] and the proportion of patients with NASH who have moderate to severe fibrosis which was reported to be 35%.[29] Applying these sources resulted in an average estimated prevalence of 3.81 million eligible patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 762,119 patients per year. Given we are assessing two new market entrants, we assumed that 50% of patients each year (N=381,059) will initiate resmetirom and the remaining 50% of patients each year (N=381,059) will initiate OCA.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[66] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug that would take market share from one or more drugs, and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that resmetirom would be added to SOC and OCA would be added to SOC. In doing so, we assumed that no SOC treatments would be displaced by the entrance of these new treatments within the eligible population.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2022-2023, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $777 million per year for new drugs.

Results

Table F.1 illustrates the per-patient budget impact results for resmetirom and OCA in more detail, based on the placeholder price ($19,011 per year and $85,111 per year, respectively), and the prices to reach $150,000, $100,000, and $50,000 per QALY for both interventions compared to SOC.

Table F1. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon

	Average Annual Per Patient Budget Impact (difference between intervention and SOC)			
	Placeholder price	**$150,000/QALY**	**$100,000/QALY**	**$50,000/QALY**
Resmetirom	$12,360	$34,180	$28,340	$22,560
OCA	$62,720	$27,380	23,060	$18,740

OCA: obeticholic acid, SOC: standard of care, QALY: quality-adjusted life year

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