

#### Obeticholic Acid for the Treatment of Primary Biliary Cholangitis and Nonalcoholic Steatohepatitis

Public Meeting - July 15, 2016

## Welcome and Introduction

- Why are we here today?
  - Unmet medical need
  - Potential for substantial innovation in treatment
  - Innovation often expensive and needed for many other conditions as well
  - Health care not our only social goal



#### The Increasing Costs of Health Care Squeeze Out Other Public Spending Priorities, Too

#### STATE BUDGET, FY2001 VS. FY2011 (BILLIONS OF DOLLARS)



NOTE: Dollar figures are inflation adjusted using a measure specific to government spending as developed by the U.S. Bureau of Labor and Statistics. SOURCE: Massachusetts Budget and Policy Center <u>Budget Browser</u>.



# Welcome and Introduction

- How do we create access to affordable health care?
  - Get smarter
  - Get wiser
  - Get together
- What are the Institute for Clinical and Economic Review (ICER) and the New England Comparative Effectiveness Public Advisory Council (CEPAC)?



# Sources of Funding (%)





### Welcome and Introduction

- How was the ICER report on OCA developed?
- How does the CEPAC consider evidence for voting?



#### ICER Value Assessment Framework





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### Welcome and Introduction

• What is the agenda for the day?



### Agenda

- Public Meeting Convened, Topic Overview | 10:00 am
- Presentation of the Evidence, and Economic Analyses | 10:30 11:45 am (Dr. Reiner Banken, Dr. Jagpreet Chhatwal, Dr. Rick Chapman)
- Public Comments | 11:45 12:30 pm
- Lunch | 12:30 1:00 pm
- New England CEPAC Deliberation and Vote | 1:00 2:00 pm
- Policy Roundtable Discussion | 2:00 3:00 pm
- Summary, Closing Remarks | 3:00 3:30 pm
  - Download meeting materials: https://icerreview.org/meeting/obeticholic-acid/





#### **Evidence Review for PBC**

#### Reiner Banken, MD, MSc Senior Fellow Institute for Clinical and Economic Review

#### *Disclosures:* Consulting work for Hoffman La Roche, Merck and Otsuka

*Key review team members:* Anne Loos, MA Dan Ollendorf, PhD Elizabeth Russo, MD



# **Topic in Context**

- PBC is a rare, autoimmune liver disease with variable progression to cirrhosis and liver failure
- Until recently, UDCA was the only FDA-approved treatment
  - UDCA has been shown to slow disease progression\*
- UDCA is well tolerated with beneficial biochemical effects within weeks or months, sometimes years
  - Around 40% of patients may have an inadequate response to treatment\*
- Treatment with UDCA does not improve fatigue and pruritus affecting patients' quality of life



\*Carey EJ, et al. *Lancet.* 2015;386(10003):1565-1575.

## Natural History of PBC





Figure from Selmi C, et al. *Lancet.* 377(9777):1600-1609.

# Obeticholic Acid (Ocaliva™)

- OCA is an oral bile acid analogue that has shown positive effects on liver biomarkers in PBC patients
- Approved by the FDA on May 27, 2016 for the treatment of PBC
  - in combination with UDCA for patients with an inadequate response after at least 1 year of UDCA treatment;
  - or as monotherapy for patients unable to tolerate UDCA
- Starting dose of 5 mg orally 1x/daily and titrate to 10mg based on response after 3 months



# Methods (PICO)

- Target population
  - Adults with PBC who have had an inadequate response to or are unable to tolerate UDCA
- Intervention
  - OCA+UDCA for patients with inadequate response to UDCA, or as a monotherapy for patients unable to tolerate UDCA
- Comparator
  - Continued use of UDCA in patients able to tolerate such therapy, and usual care for patients intolerant to UDCA
- Outcomes
  - Biochemical response (ALP, bilirubin, other markers of liver function )
  - Liver fibrosis, cirrhosis, transplantation and carcinoma
  - Treatment-related adverse events



# Sources of Evidence

3 industry-sponsored double-blind RCTs (1 Phase III and 2 Phase II)

- Study 301-POISE (Phase III; unpublished)
  - Evaluated OCA+UDCA vs. UDCA for patients with inadequate response to UDCA, and OCA vs. placebo as monotherapy for patients intolerant to UDCA (7%)
- Study 202 (Phase II; published; good quality rating)
  - Evaluated OCA+UDCA vs. UDCA for patients with inadequate response to UDCA
- Study 201 (Phase II; unpublished)
  - Evaluated OCA vs. placebo as monotherapy



# Benefits

- Significant reduction in ALP from baseline for the OCAtreated groups compared to controls (i.e., placebo plus UDCA or placebo alone)
  - Sustained improvement during open-label long-term safety extension period up to 18 months (POISE)
- 45% of trial patients on OCA 10mg reached POISE composite endpoint of ALP<1.67xULN, ≥15% decrease in ALP, and normal bilirubin compared to 8% on placebo/UDCA
- Other markers of liver function (AST, ALT, GGT) consistently favored OCA





- Although pruritus is a symptom of PBC, there is increased frequency and severity of pruritus due to OCA treatment
  - Mitigated by titrating dose (5-10mg)
- Reductions in beneficial HDL of unknown clinical significance
- Other serious adverse events are rare
  - Treatment-related vs. disease-related?



#### Effectiveness: Controversies and Uncertainties

- ALP reduction accepted by the FDA as a surrogate endpoint reasonably likely to predict clinical outcomes
  - Results of Phase IIIb trial on clinical outcomes expected in 2023
- Very limited evidence on effectiveness for patients with moderate to advanced disease, or OCA as monotherapy
- No universally-accepted criteria for defining inadequate response to UDCA



# **Effectiveness: Summary**

- Moderate certainty of a comparable or better net health benefit for patients with early disease taking OCA plus UDCA ("B+" rating)
  - Insufficient evidence of effectiveness in patients with moderate and advanced disease ("I" rating)
- Promising but inconclusive evidence for OCA as monotherapy ("P/I" rating)
- Other benefits or disadvantages
  - OCA has the potential to improve clinically-relevant outcomes in patients with no other treatment option



# **Public Comments Received**

# No comments concerning the comparative effectiveness review

- Timing of the review was questioned, as results of the Phase III trial of OCA in PBC (POISE) have not yet been published
- Criticism of lack of engagement with clinical experts and patient advocates





#### Value of OCA for PBC Treatment Jagpreet Chhatwal, PhD Assistant Professor, Harvard Medical School Senior Scientist, Massachusetts General Hospital

#### **Disclosures:**

I have received research grant and consulting fees from Gilead Sciences on unrelated projects. Other team members have nothing to disclose.

Key Review Team Members: Jagpreet Chhatwal, PhD Chin Hur, MD, MPH Matthew J. Klebanoff, BA Sumeyye Samur, PhD



# Objective

- To evaluate the cost-effectiveness of obeticholic acid (OCA) treatment for patients with PBC who have an inadequate response to ursodeoxycholic acid (UDCA) treatment
  - Developed a mathematical model
  - Compared long-term outcomes of OCA+UDCA vs UDCA



#### **Model Schematic**





# **Model Inputs**

#### **Target Population**

	Value	Primary Source
Mean age (years)	55.8	POISE study
PBC stage distribution		POISE study
Stage 1-3	90%	
Stage 4 (cirrhosis)	10%	
Sex: Female / Male	91% / 9%	POISE study

- **Efficacy**: primary end point in Phase III POISE study
  - ALP <1.67xULN, ≥15% reduction in ALP, and normal bilirubin</li>
- Adverse events: pruritus as in Phase III POISE study



#### Model Validation: Transplant-Free Survival



#### **Model Results**



# Cumulative Incidence of Decompensated Cirrhosis





# Cumulative Incidence of HCC





#### Cumulative Number of Liver Transplants





# Cumulative Number of Liver-Related Deaths





#### **Transplant Free Survival**





# Cost-Effectiveness of OCA Added to UDCA

#### Annual Cost of OCA = \$69,350

	UDCA*	OCA + UDCA	Increment
QALYs	10.7	11.8	1.1
Total Cost (\$)	142,000	634,000	492,000
ICER (\$/QALY)			473,000

\*Results correspond to inadequate response to UDCA, as observed in POISE study

Abbreviations: QALYs: Quality-adjusted life years ICER: Incremental cost-effectiveness ratio



#### Which Variables Affect Cost-effectiveness Results?





### Limitations

- Limited data on the natural history of PBC
  - Calibrated missing transition probabilities such that transplant-free survival of the model matched available evidence
  - Sensitivity analyses specifically focusing on uncertain aspects of natural history
- Limited long-term efficacy data of OCA
  - Assumed efficacy did not change after 12 months
- Data on quality of life (QoL) of PBC patients is lacking
  - No published QoL utility assessments
    - Therefore used hepatitis C utility data
    - Particularly in advanced cirrhosis states, the QoL is likely similar in PBC and hepatitis C patients


### Summary

- In patients who had an inadequate response to UDCA, treatment with OCA improves long-term clinical outcomes
  - Increases transplant-free survival and life expectancy
  - **Decreases** the incidence of HCC and need for liver transplantation
- Using the list price of OCA (\$69,350/year), the estimated cost-effectiveness of OCA plus UDCA is above commonly used cost-effectiveness thresholds in the U.S.
- Sensitivity analyses showed that the cost of OCA was the most important variable



## **Public Comments Received**

- Requested specific analysis of OCA monotherapy among patients intolerant to UDCA, as the subgroup with greatest unmet need
- Analysis does not reflect number of liver transplantations for PBC patients in the US, and does not account for increased risk of progressing to liver transplant or death among patients with total bilirubin >1.6xULN
- Patients in POISE trial are at higher risk than those in the model
- Certain costs are under-estimated, and QoL parameters do not accurately reflect well-being of PBC patients
- WTP thresholds ranging from \$150,000 to \$300,000 would be more appropriate for an orphan drug





#### Potential Budget Impact Analysis for PBC

#### **Rick Chapman, PhD, MS** Director of Health Economics Institute for Clinical and Economic Review

## *Disclosures:* I have no conflicts of interest.

*Key review team members:* Dan Ollendorf, PhD



#### Potential Budget Impact: Methods

- Explored the potential health system budget impact of OCA for PBC over 5-year time horizon
- Total net cost: incremental health care costs for OCA treatment of PBC minus any offsets in costs from averted disease progression
  - Used modeled results for treatment costs and cost offsets per patient
- Potential population eligible for treatment derived from published estimates



#### Potential Budget Impact: Population

- Estimated entire candidate population for treatment
  - Adults with PBC who have either inadequate response to UDCA or are unable to tolerate UDCA
  - Prevalence of 40.2/100,000
  - 43.5% treated with UDCA
    - 40% inadequate response
    - 3% unable to tolerate UDCA
  - N ≈ 24,350
- Assumed uptake: 50% over 5 years
  - 10% per year
- Year 5 treated estimate ≈ 12,175



#### Potential Budget Impact for PBC Treatment at 5 Years

	Eligible	Number	Weighted BI	Average BI
	Population	Treated	per Patient	per year
				(millions)
OCA	24,350	12,175	\$128,500	\$312.9





#### **Evidence Review of OCA for NASH**

#### Reiner Banken, MD, MSc Senior Fellow Institute for Clinical and Economic Review

#### *Disclosures:* Consulting work for Hoffman La Roche, Merck and Otsuka

*Key review team members:* Anne Loos, MA Dan Ollendorf, PhD Elizabeth Russo, MD



## **Topic in Context**

- Nonalcoholic steatohepatitis (NASH) is a form of nonalcoholic fatty liver disease (NAFLD) that can progress to cirrhosis, liver failure, and cancer, but also regress without treatment
- NASH affects 3.5% to 5% of the US population, especially with type 2 DM. Its rising incidence is related to a rise in obesity
- NASH is an undertreated silent disease with a large percentage of individuals unaware of being afflicted
- Lifestyle interventions, especially weight loss, are first-line treatment. Vitamin E is a first-line treatment of NASH, but with long term safety concerns. Pioglitazone is also used in some patients
- NASH is expected to become the most common indication for liver transplantation in the United States between 2020 and 2025
  New ENGLAND CEPAC COMPARATIVE EFFECTIVENESS

## Obeticholic Acid (Ocaliva™)

- OCA is an oral bile acid analogue influencing lipid and glucose metabolism and hepatic inflammation
- A US-based Phase II trial of treatment of NASH with OCA (FLINT) has shown an improvement in liver histology
- Interim findings from a Phase III trial are expected to be available around March 2017
- Clinical interest in its potential off-label use for NASH is likely to be great given the unmet medical need and the lack of other approved treatments



## Methods (PICO)

- Target population
  - Adults with biopsy-confirmed NASH and fibrosis
- Intervention
  - Treatment with OCA
- Comparator
  - Usual care, including lifestyle interventions and treatment with vitamin E
- Outcomes
  - Impact on NASH, liver fibrosis, cirrhosis, carcinoma and transplantation, and markers of liver function
  - Adverse events (e.g., pruritus, effects on blood lipids)



#### Sources of evidence

Two industry-sponsored double-blind RCTs (Phase II trials)

- 1. NCT00501592 trial (published-Mudaliar 2013)
  - Phase IIa proof-of-concept study
  - Fair quality according to USPSTF criteria
  - 64 patients with type 2 diabetes and NAFLD
  - OCA compared to placebo over 6 weeks
  - Outcome insulin resistance



## Sources of evidence (2)

#### FLINT trial (published-Neuschwander-Tetri 2015)

- Good quality according to USPSTF criteria
- 283 patients with NASH with 53% diabetics
- OCA compared to placebo over 72 weeks
- Both groups received recommendations on healthy lifestyle behaviors and appropriate management of hypertension, hyperlipidemia, and diabetes
- Liver biopsies baseline and after 72 weeks,
- NAFLD activity score (NAS) as primary outcome



## Results of effectiveness in included studies

#### 1. NCT00501592 trial:

- Lowered insulin resistance.
- Liver enzymes improved.

#### **2.** FLINT trial:

- NAS decrease without worsening fibrosis (*primary outcome*) for OCA (45% vs. 21%; RR 1.9; 95% CI 1.3-2.8)
- Resolution or improvement in fibrosis (secondary outcome) with an improvement for OCA (35% vs. 19%; RR 1.8; 95% Cl 1.1-2.7) and less fibrosis progression (16% vs. 29%; p=0.047).
- Histological improvements only statistically significant in patients with diabetes
- Liver enzymes improved
- Increase in insulin resistance





- Reductions in beneficial HDL and increase in harmful LDL
  - Unknown clinical significance of these changes for NASH patients who already have an overall increased mortality from heart disease
- OCA treatment is associated with increased pruritus



#### Effectiveness: Controversies and Uncertainties

- FDA breakthrough designation for treatment of NASH with concomitant liver fibrosis
- Ongoing 5-year Phase III trial with interim findings expected to be available around March 2017
- Side effect of pruritus for largely asymptomatic patient with NASH raises the question of long-term adherence to treatment



#### **Effectiveness: Summary**

- Insufficient evidence for the use of OCA as an offlabel treatment for adults with nonalcoholic steatohepatitis with fibrosis.
- Additional trials are underway (REGENERATE and CONTROL) and should be examined carefully to further characterize the effectiveness of OCA activity on NASH.
- Great unmet medical need for a widespread silent disease with serious consequences.



## **Public Comments Received**

No comments concerning the comparative effectiveness review

- Report is premature considering the ongoing Phase III trial (REGENERATE) and the lack of a current labeled indication for OCA in NASH
- Patients with advanced fibrosis might be dissuaded from enrolling in this trial based on the findings of our report





#### Value of OCA for NASH Treatment Jagpreet Chhatwal, PhD Assistant Professor, Harvard Medical School Senior Scientist, Massachusetts General Hospital

#### Disclosures:

I have received research grant and consulting fees from Gilead Sciences on unrelated projects.

Other team members have nothing to disclose.

*Key Review Team Members:* Jagpreet Chhatwal, PhD Chin Hur, MD, MPH Matthew J. Klebanoff, BA Sumeyye Samur, PhD



### Objective

- To evaluate the cost-effectiveness of obeticholic acid (OCA) treatment for patients with NASH
- Comparator: standard or usual care (placebo arm of FLINT study)

Neuschwander-Tetri BA, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, nonalcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet*. 2015;385(9972):956-65.



#### **Model Schematic**



## **Key Modeling Assumptions**

- Used FLINT study for efficacy of OCA in NASH patients
- Primary endpoint based on the phase III REGENERATE trial, instead of that used in the FLINT trial
  - Percentage of patients who achieved NASH resolution without worsening of fibrosis
  - No data to inform the model beyond week 72; therefore, assumed treatment efficacy did not change after week 72
- Used 25 mg OCA drug dose, as dosage used in the FLINT trial



### Model Inputs

- Patient characteristics (NASH CRN Brunt et al.)
  - Mean age: 49 years
  - Female gender: 66%
  - Histology (NASH fibrosis): Stage 1: 39%, Stage 2: 27%, Stage 3: 34%
- Efficacy: Subgroup analysis of Phase II FLINT study (source: post hoc analysis)
- Adverse events: Pruritus and dyslipidemia (FLINT study)

Brunt EM, et al. Nonalcoholic fatty liver disease (NAFLD) activity score and the histopathologic diagnosis in NAFLD: distinct clinicopathologic meanings. *Hepatology*. 2011;53(3):810-20.



#### Model Validation: Survival in NASH Patients



NASH fibrosis: F0: 36%, F1: 18%, F2: 15%, F3: 18%, F4: 13%; Age: 50; Female: 58%

Adams LA, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. 62 *Gastroenterology*. 2005;129(1):113-21.



#### **Modeling Results**



# Cumulative Incidence of Decompensated Cirrhosis





### **Cumulative Incidence of HCC**





#### Cumulative Number of Liver Transplants



ICER

PUBLIC ADVISORY COUNCIL

PROGRAM

#### Cumulative Number of Liver-Related Deaths





#### **Transplant-Free Survival**





#### **Cost-Effectiveness of OCA**

#### Annual Cost of OCA = \$69,350

	Placebo	OCA	Increment
QALYs	10.9	11.0	0.1
Total Cost (\$)	70,000	371,000	301,000
ICER (\$/QALY)			2.75 million

Abbreviations: QALYs: Quality-adjusted life years ICER: Incremental cost-effectiveness ratio



#### Limitations

- No data from Phase III trial on the the efficacy of OCA in NASH patients
- Limited data on the long-term effectiveness of OCA in NASH patients
- We did not consider other treatment options for NASH such as pioglitazone, vitamin E and lifestyle interventions
- Limited data on NASH-associated quality of life and costs
  - We used data from hepatitis C to inform our model and tested the sensitivity of results to these inputs



### Summary

- In comparison with placebo, treatment with OCA would marginally improve long-term outcomes
  - Treatment with OCA would increase 15-year transplant-free survival from 68.6% to 69.9%
- Using the list price of OCA (\$69,350/year), the estimated cost-effectiveness of OCA for NASH treatment is above commonly used costeffectiveness thresholds in the U.S.
- Data from Phase III trial will inform more reliable long-term effectiveness and cost-effectiveness analyses



#### **Public Comments Received**

 No public comments were received for the modeling in NASH




# Potential Budget Impact Analysis for NASH

#### **Rick Chapman, PhD, MS** Director of Health Economics Institute for Clinical and Economic Review

# *Disclosures:* I have no conflicts of interest.

*Key review team members:* **Dan Ollendorf, PhD** 



## Potential Budget Impact: Methods

- Explored the potential health system budget impact of OCA for NASH over 5-year time horizon
- Total net cost: incremental health care costs for OCA treatment of NASH minus any offsets in costs from averted disease progression
  - Used modeled results for treatment costs and cost offsets per patient
- Potential population eligible for treatment derived from published estimates



# Potential Budget Impact: Population

- Estimated entire candidate population for treatment
  - Adult NASH patients with fibrosis stages F1–F3
  - NASH prevalence in US estimated as 3.5% to 5%
    - Used lower estimate of 3.5%
  - Assumed only 5% of patients diagnosed
    - Difficulty of definitive diagnosis (requires liver biopsy)
    - Lack of effective medical treatments
  - N ≈ 567,000
- Assumed uptake: 10% over 5 years
  - 2% per year
- Year 5 treated estimate ≈ 56,700



## Potential Budget Impact for NASH Treatment at 5 Years

	Eligible	Number	Weighted BI	Average BI per
	Population	Treated	per Patient	year (billions)
OCA	567,000	56,700	\$95,400	\$1.08





# **Public Comments**

Members of the public pre-registered to make oral comments.

## Lunch Meeting will resume at 1:00PM





# **Questions for Deliberation**

**Obeticholic Acid for PBC and NASH** 

# Comparative *Clinical Effectiveness* Example Question

Is the evidence "adequate" to demonstrate that "intervention A" is superior to "comparator B" for patients with "condition X"?

- Yes
- No



## Care Value Example Question

# What is the care value of "intervention A" vs "comparator B"?

- A. Low
- **B.** Intermediate
- C. High



# **Practice Question**

How long can lobsters live?

A. 25 years

B. 40 years

C. Up to 100 years



#### PBC



## Comparative Clinical Effectiveness: PBC

For patients with PBC (primary biliary cholangitis or primary biliary cirrhosis), who fail to achieve an adequate reduction in alkaline phosphatase on ursodeoxycholic acid (UDCA) monotherapy, is the evidence adequate to demonstrate a net health benefit with the addition of obeticholic acid to continuing therapy with UDCA?

- Yes
- No



## Care Value: PBC

Given the available evidence for patients with PBC, what is the care value of adding obeticholic acid to UDCA alone?

#### A. Low

- **B.** Intermediate
- C. High



### NASH



### **Comparative Clinical Effectiveness: NASH**

For patients with nonalcoholic steatohepatitis (NASH) and fibrosis, is the evidence adequate to demonstrate a net health benefit with the addition of obeticholic acid to usual care (e.g., lifestyle interventions, treatment with vitamin E, etc.)?

- Yes
- No



## Care Value: NASH

Given the available evidence for patients with NASH, what is the care value of adding obeticholic acid to usual care vs. usual care alone?

A. LowB. IntermediateC. High



## **Policy Roundtable**



# **Policy Roundtable Participants**

Policy Roundtable				
Kathleen Corey, MD, MPH, MMSc	Juan Carlos Lopez-Talavera, MD, PhD			
Director, MGH Fatty Liver Clinic	Senior Vice President, Global Medical			
Massachusetts General Hospital	Affairs			
Gastrointestinal Unit	Intercept Pharmaceuticals			
Judith Donovan Patient with PBC	Daniel Pratt, MD Clinical Director, Liver Transplantation; Director of the Autoimmune Cholestatic Liver Center Massachusetts General Hospital			
<b>Barbara Henry, RPh</b>	Thomas Simpatico, MD			
Lead Clinical Pharmacy Specialist	Chief Medical Officer			
Harvard Pilgrim Health Care	Vermont Department of Health Access			



# **Meeting Adjourned**



## **Next Steps**

- Final Report and accompanying materials expected in late July.
- Meeting materials and outputs: <u>https://icer-review.org/meeting/obeticholic-acid/</u>

### For more information please visit icer-review.org/programs/new-england-cepac

