Obeticholic Acid (OCA) for the Treatment of Patients with Primary Biliary Cholangitis (PBC) in Combination with Ursodeoxycholic Acid (UDCA)

NDA 207999

Gastrointestinal Drugs Advisory Committee
September 13, 2024

Introduction

Sangeeta Sawhney, MD

Senior Vice President,
Head of US Research and Development

Intercept Pharmaceuticals, Inc
AlfaSigmaGroup

Agenda

Introduction	**Sangeeta Sawhney, MD** Senior Vice President, Head of US Research and Development, Intercept Pharmaceuticals, Inc
Disease Background	**Robert Brown, MD, MPH** Vincent Astor Distinguished Professor of Medicine, Chief, Division of Gastroenterology and Hepatology Editor-in-Chief, Liver Transplantation, Weill Cornell Medical College
Methods Used to Assess Clinical Benefit	**Andrew Damokosh, PhD** Senior Vice President, Biostatistics, Intercept Pharmaceuticals, Inc
Study 302 Efficacy and Safety	**Thomas Capozza, MD FACP** Vice President, Clinical Research, Intercept Pharmaceuticals, Inc
Drug-Induced Liver Injury	**Lily Dara, MD** Assistant Professor of Medicine, Department of Medicine, Division of GI/Liver, USC Research Center for Liver Disease, Keck School of Medicine, University of Southern California
Study 405 and Other RWE	**Leona Bessonova, PhD** Executive Director, Medical Affairs Research, Intercept Pharmaceuticals, Inc
Clinical Perspective	**David Jones, OBE** Director, NHIP Academy, Director, Newcastle Center for Rare Disease Professor of Liver Immunology, Newcastle University, Honorary Consultant Hepatologist, Newcastle upon Tyne Hospitals
Conclusions	**Sangeeta Sawhney, MD**

Additional Experts

Nancy A Dreyer, PhD, MPH

Adjunct Professor of Epidemiology, University of North Carolina at Chapel Hill
Chief Scientific Advisor, Picnic Health
Chief Scientific Officer Retired, IQVIA Real-World Solutions

Professor Gideon Hirschfield PhD, MB Bchir

Hepatologist
Lily and Terry Horner Chair in Autoimmune Liver Disease Research
University of Toronto, Canada

PBC is a Serious Rare Disease with Unmet Need

- Rare, serious, progressive disease requiring early intervention
  - 105,000 adults in US[a]
  - More than 80% of PBC patients are women, typically ages 40-60[b]
- Ursodeoxycholic acid (UDCA) was approved in 1997 as a first-line therapy for PBC
- Approximately 40% of PBC patients have inadequate response to UDCA and 5% are intolerant[c]
- Unmet need remains for different mechanisms of action

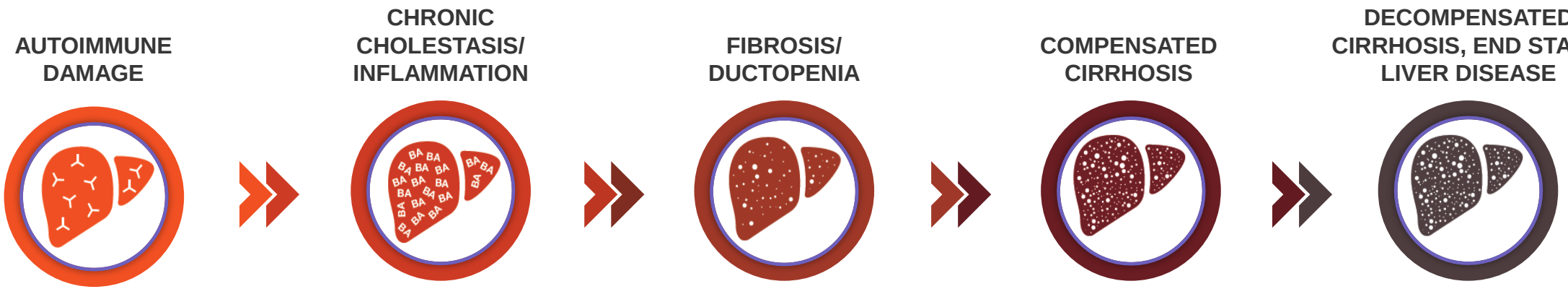
a. Buchanan-Peart et al., AASLD The Liver Meeting; 2023, Nov 10-14; b. Trivella et al., *Hepatol Commun 2023;7(6)*; c. Invernizzi et al., *Dig Liver Dis 2017;49(8)*

Ocaliva (OCA): First Approved Second-Line Therapy for PBC

- Received accelerated approval in 2016 based on Study 301, an RCT
  - Based on reduction in alkaline phosphatase (ALP)
    - Marker of cholestasis, a build-up of toxic bile acid in the liver
    - Recognized as surrogate marker for PBC clinical outcomes

RCT=Randomized controlled trial

OCA Has Been Studied Across the PBC Spectrum



Original USPI (Accelerated Approval 2016)

Registrational Study 301 (POISE) + 5-year LTSE

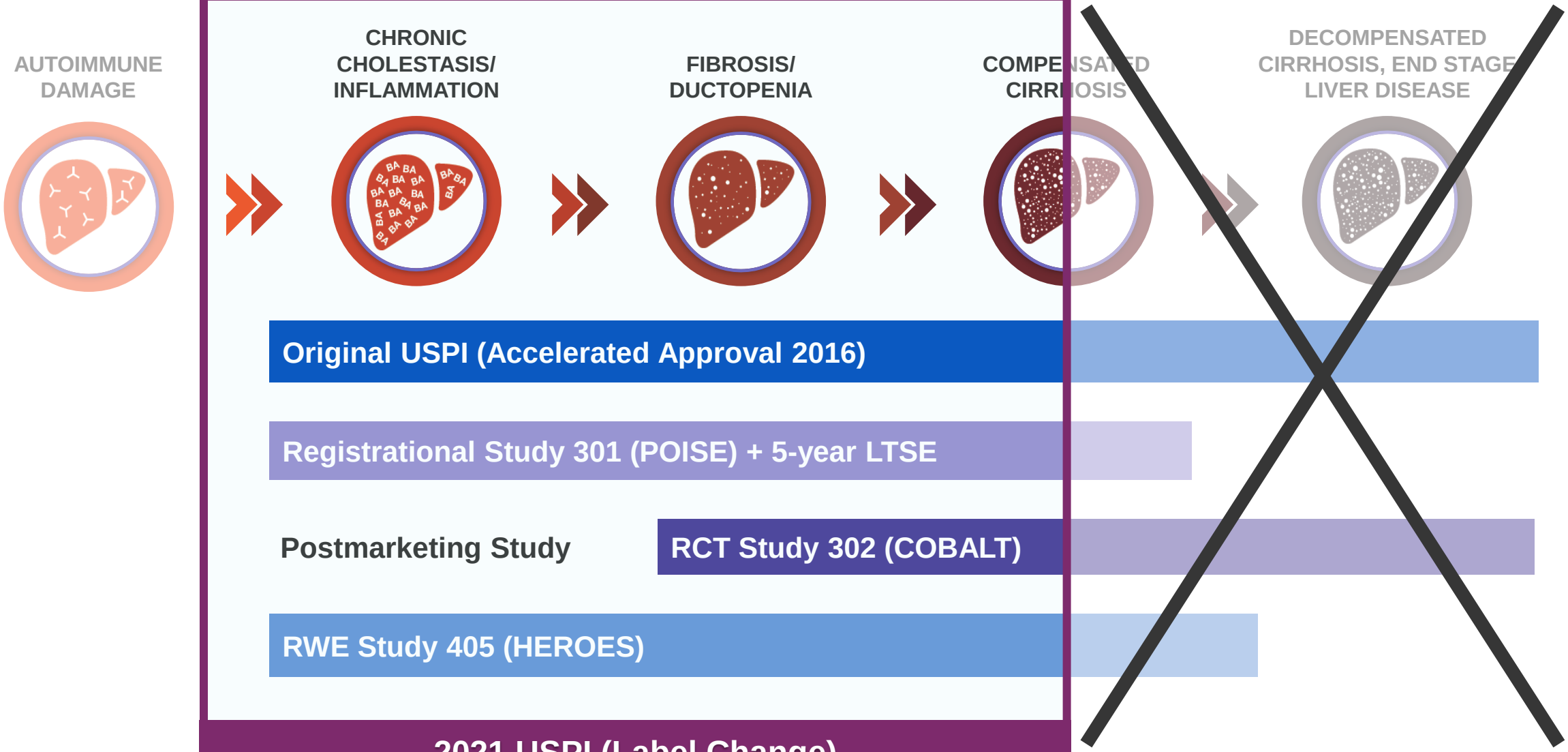
Postmarketing Study

RCT Study 302 (COBALT)

RWE Study 405 (HEROES)

OCA=Obeticholic acid, PBC=Primary biliary cholangitis, USPI=US Prescribing Information, RWE=Real-world evidence

2021 USPI Now Reflects the Appropriate PBC Population



2021 USPI Addresses the Safe Use of Ocaliva

Contraindication

Patients with:

- Decompensated cirrhosis (e.g., CP Class B or C) or a prior decompensation event
- Evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia)
- Complete biliary obstruction

Monitoring and Management

Routinely monitor patients with laboratory and clinical assessments

Temporarily interrupt OCA for severe intercurrent illness:

- After resolution, consider the potential risks and benefits of restarting OCA treatment

Permanently discontinue OCA for new:

- Laboratory or clinical evidence of hepatic decompensation
- Evidence of portal hypertension
- Clinically significant hepatic adverse reactions
- Complete biliary obstruction

CP=Child-Pugh

Key Areas Where FDA and Intercept Are Not Aligned

- Interpretation of:
  - Study 302 for confirmation of benefit
  - Study 302 “USPI” Subgroup liver transplants and deaths
  - Study 405
- Predictability and management of drug-induced liver injury (DILI)

Study 302 ITT Analysis is Flawed

FDA COMMENTS

- ***Study 302 is interpretable*** *and provides informative results regarding the benefit-risk balance of OCA*
- *ITT population (hazard ratio of 0.84 [95% CI: 0.61, 1.16], p-value of 0.304)*

INTERCEPT POSITION

- **ITT analysis in Study 302 is flawed** because of biases due to substantial **functional unblinding**
- Adjustments for treatment crossover and informative censoring show **trend for benefit**

  Hazard ratio of 0.69
  [95% CI: 0.50, 0.96]

ITT=Intention to treat, CI=Confidence interval

Study 302 ITT Analysis: Consider Underlying Reasons for Results

FDA Considerations for Confirmatory Trials:

1. *"When a confirmatory trial does not meet its endpoint, it **does not necessarily mean that the drug is not effective** …"*[1]

2. *"When trials…do not appear to confirm clinical benefit, **FDA must carefully assess each case and consider the underlying reasons**…"*[2]

1. Letter from Patrizia Cavazzoni, Dkt. No. FDA-2021-P-0268 (Oct. 24, 2022), https://www.regulations.gov/document/FDA-2021-P-0268-0005;
2. FDA response to Government Accountability Office (GAO) Report GAO-09-866 (Sep. 2009), https://www.gao.gov/assets/a295766.html

Study 302 "USPI" Subgroup Analysis of Liver Transplants and Deaths Unreliable to Assess Harm

FDA COMMENTS

- ***Signal of harm on liver transplant/death***
- *USPI Population: Hazard ratio of 4.77 [95% CI: 1.03, 22.09]*

- *The USPI-labeled subjects at baseline had early-stage disease and based on the indolent nature of the disease (PBC) progression, these* ***subjects were not expected to progress to a need for liver transplant or die during the clinical trial***

INTERCEPT POSITION

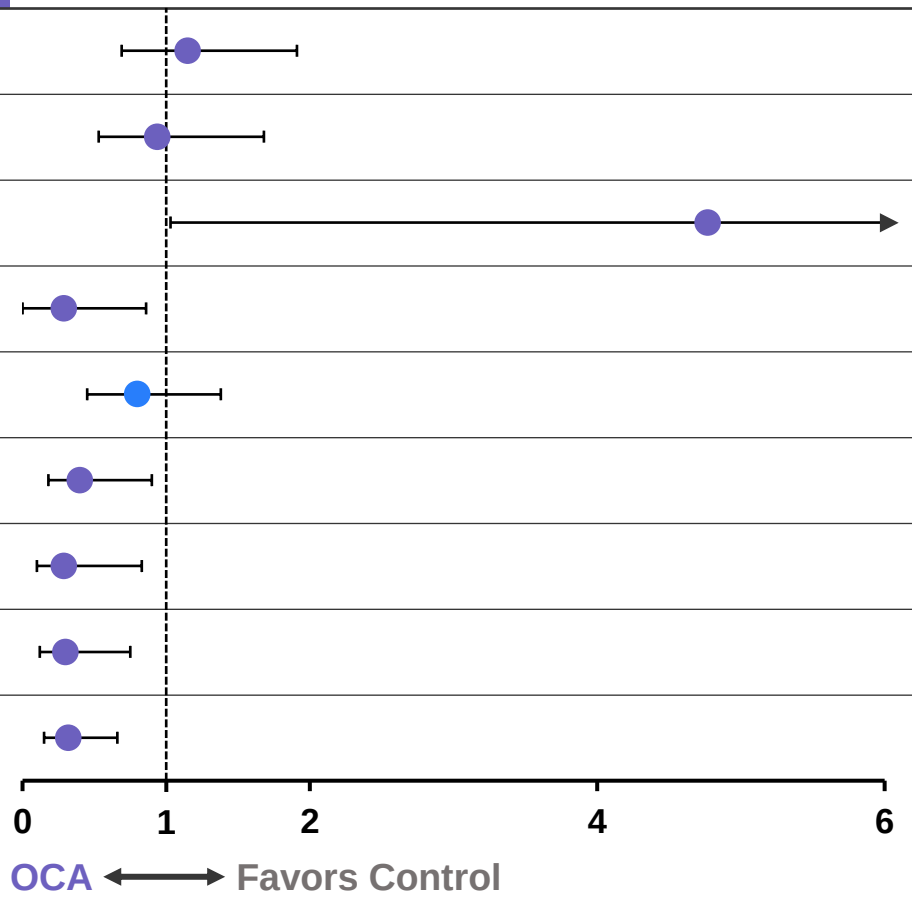
- **Inconsistent with other evidence**
- Not prospectively defined
- Not randomized
- Not managed to 2021 USPI during the study

- **Disease progression does occur in high-risk PBC patients**

Study 302 “USPI” Subgroup Results are Inconsistent With Multiple Other Study Analyses

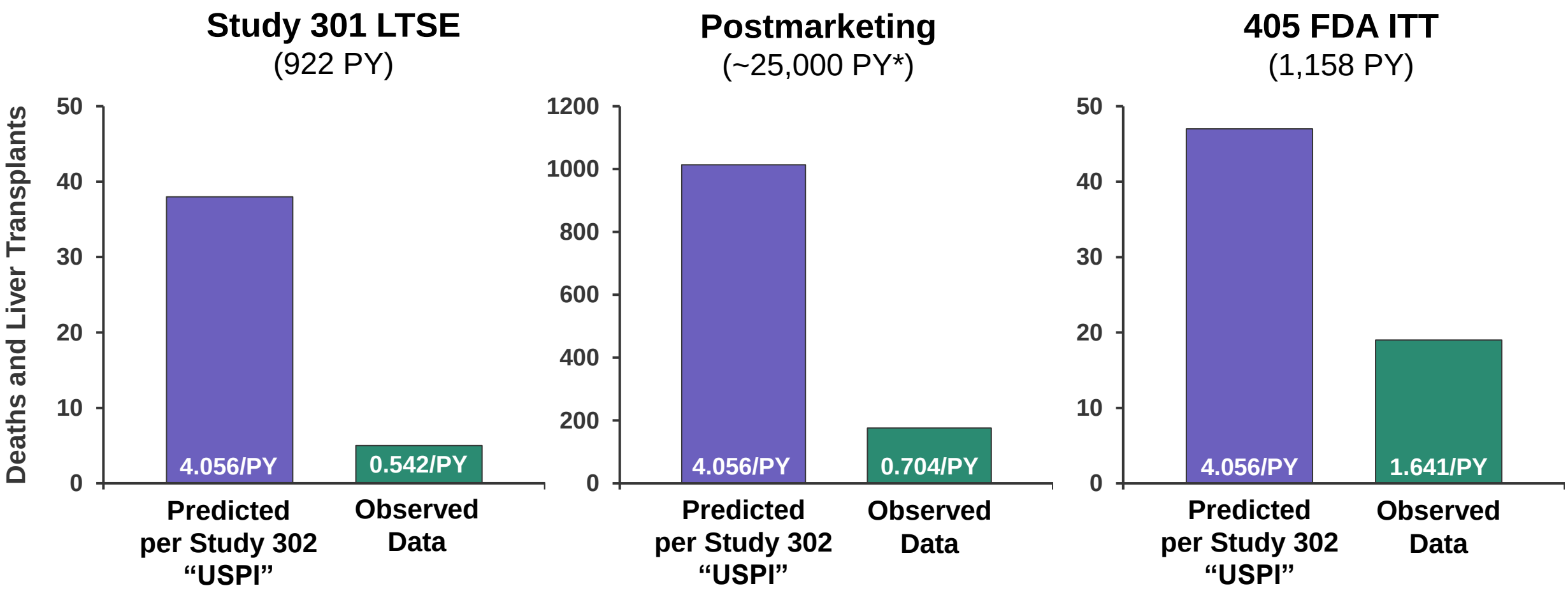
Liver Transplants and Deaths

	Events n (%)		Hazard Ratio (95% CI)
	Controls	OCA-treated	
Study 302 (ITT Overall)	28 (16.9%)	32 (19.0%)	1.15 (0.69, 1.91)
Study 302 (Contraindicated Subgroup)	26 (26.5%)	21 (24.1%)	0.94 (0.53, 1.68)
Study 302 (“USPI” Subgroup)	2 (2.9%)	11 (13.6%)	4.77 (1.03, 22.09)
Study 405 (As-treated)	13 (3.3%)	2 (0.5%)	0.29 (0.00, 0.86)
Study 405 FDA Analysis (ITT-like)	22 (5.5%)	19 (4.7%)	0.80 (0.45, 1.38)
Study 302 EC	18 (10.7%)	9 (5.4%)	0.40 (0.18, 0.90)
Study 301 LTSE EC (Global PBC)	135 (10.0%)	5 (2.4%)	0.29 (0.10, 0.83)
Study 301 LTSE EC (UK PBC)	281 (13.2%)	5 (2.4%)	0.30 (0.12, 0.75)
RECAPITULATE	Not Reported		0.32 (0.15, 0.66)



LTSE=Long term safety extension, EC=External control

Study 302 "USPI" Subgroup HR of 4.77 is Inconsistent with Observed Data



P=patients, PY=patient years
*Conservative estimated exposure, deaths and transplants counted independently

Study 405 is Well Designed and Shows Benefit

FDA COMMENTS

- ***Study 405 did not meet regulatory standards*** *for an adequate and well-controlled clinical investigation because of uncertainty*

- ***Clinical benefit not shown by FDA-ITT*** *analysis of time to death (any cause) or liver transplantation*
- ***ITT-like efficacy*** *for composite outcome of* ***death or liver transplantation has hazard ratio of 0.80 [95% CI: 0.45, 1.38]***

INTERCEPT POSITION

- **Study 405 is well designed**
  - **Consistent with FDA Guidances**
  - Followed best practices for pharmacoepidemiology
- Hazard ratio: 0.37 [95% CI: 014, 0.75]
- Supported by other RWE

- FDA ITT analysis excludes hospitalization for hepatic decompensation
- Not powered for liver transplants and death
- **Shows trend toward benefit**

DILI is Manageable in 2021 USPI Population

FDA COMMENTS

- *Incidence of DILI (3 in OCA arm versus 1 in placebo arm)*
- *Clinical and biochemical markers were not predictive of poor outcomes, i.e., OCA cannot be discontinued in timely manner*
- ***Underscores unpredictable nature of hepatotoxicity due to OCA***
- ***Risk mitigation for these adverse outcomes is not feasible in any subpopulation***

INTERCEPT POSITION

- All 3 cases of DILI in “USPI” Subgroup were manageable:
  - **Early occurrence**
  - **Monitorable with routine labs**
  - **Fully reversible**

PBC and MASH are Distinct Diseases

	PBC	MASH
US Prevalence	• 105,000 adults • Rare disease	• 26 million adults • Majority with metabolic disorder
OCA Dose	• 5 mg QD first 3 months • Then consider 10 mg QD	• 25 mg QD proposed dose
Experience	• >8 years in clinical practice • >42,000 patient-years	• NDA not approved • Development stopped

MASH=Metabolic dysfunction-associated steatohepatitis

OCA Use Is Managed By 2021 USPI and Specialist Prescribers

- Clinicians have experience in using OCA in PBC
- Labeling reflects appropriate patient and appropriate follow-up
- Specialty prescribing and pre-authorization procedures

FDA Framework for Totality of Evidence and Rare Disease

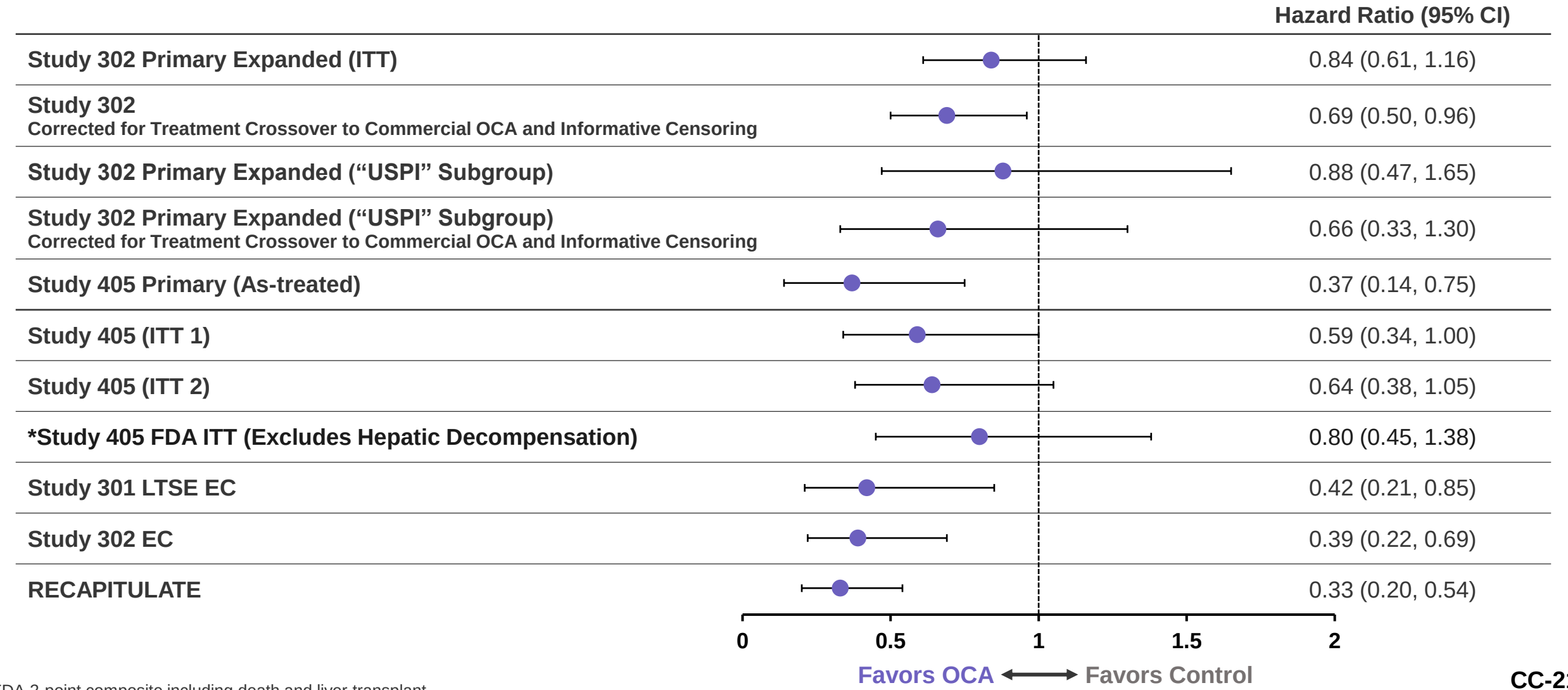
1. **FDA uses a totality of evidence approach** when considering the quantity and quality of evidence to support effectiveness for drugs and biological products[1]

2. **Flexible, patient-focused approach particularly appropriate in the rare disease context**, where clinical trials typically result in a lot more residual uncertainty, and **where there remains unmet medical need**[2]

1. US FDA 1998; Sherman et al., *Nat Rev Drug Discov*. 2017;16(5); 2. Karlin-Smith, *Pink Sheet* 2024 Jul 19; US FDA 2019

Totality of Evidence Verifies Benefit

Hepatic Decompensation, Liver Transplant or Death



*FDA 2-point composite including death and liver transplant

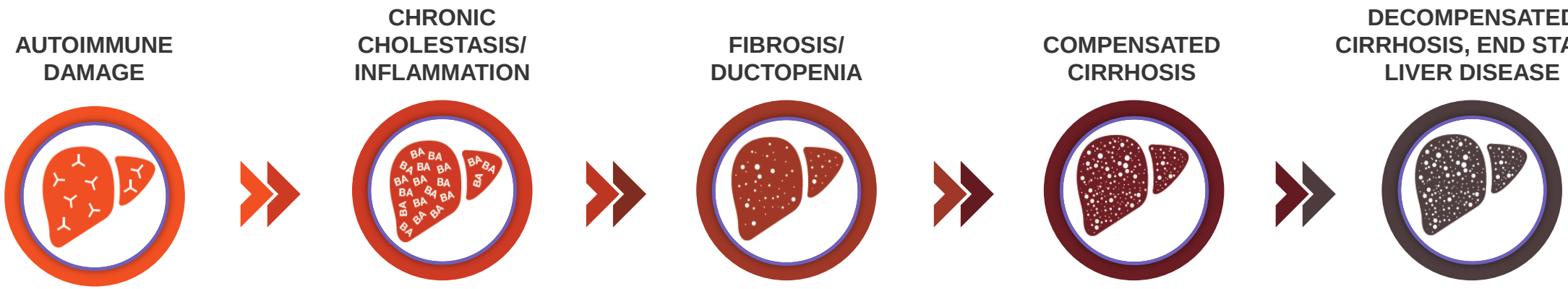
Disease Background

Robert S. Brown, Jr., MD, MPH

Vincent Astor Distinguished Professor of Medicine
Chief, Division of Gastroenterology and Hepatology

PBC is a Rare, Progressive, Serious Disease

MULTI-FACETED DISEASE PATHOPHYSIOLOGY



Elevated ALP, GGT, AST, ALT

Elevated bilirubin

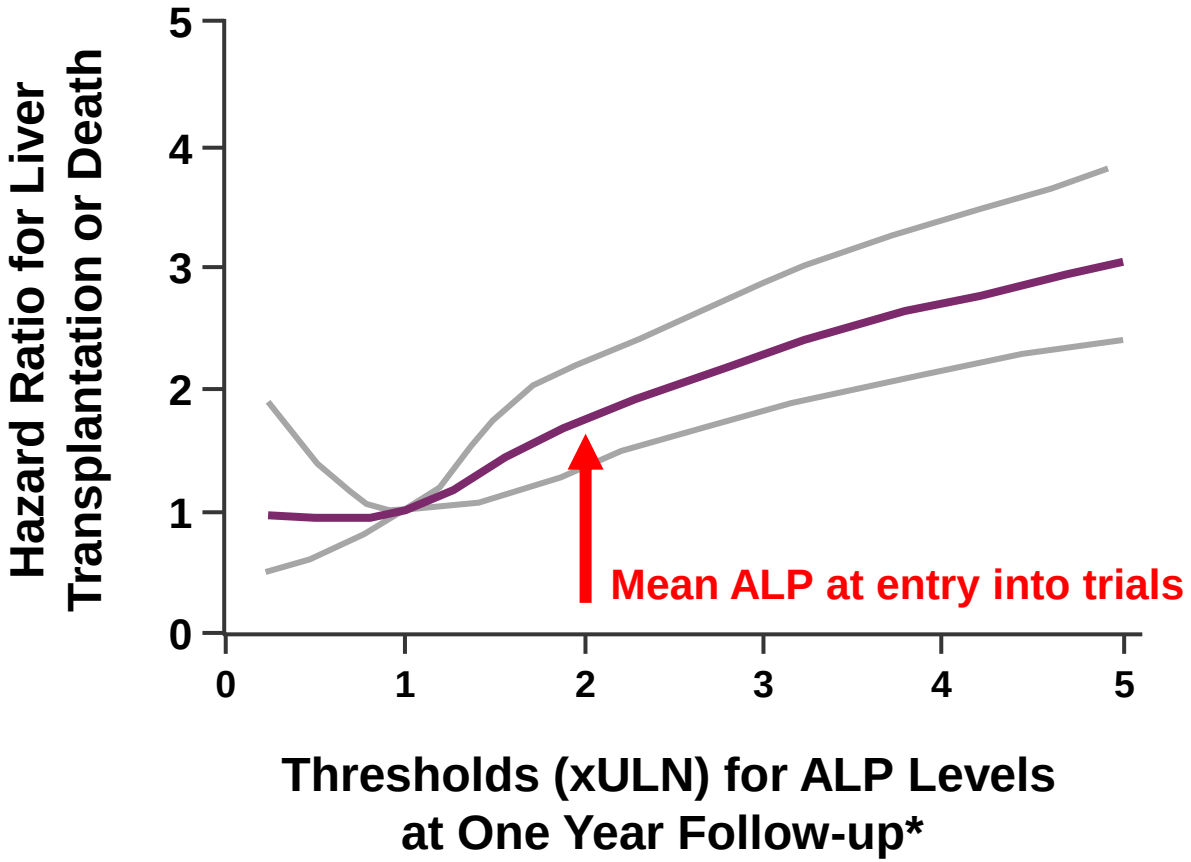
Clinical evidence of portal hypertension

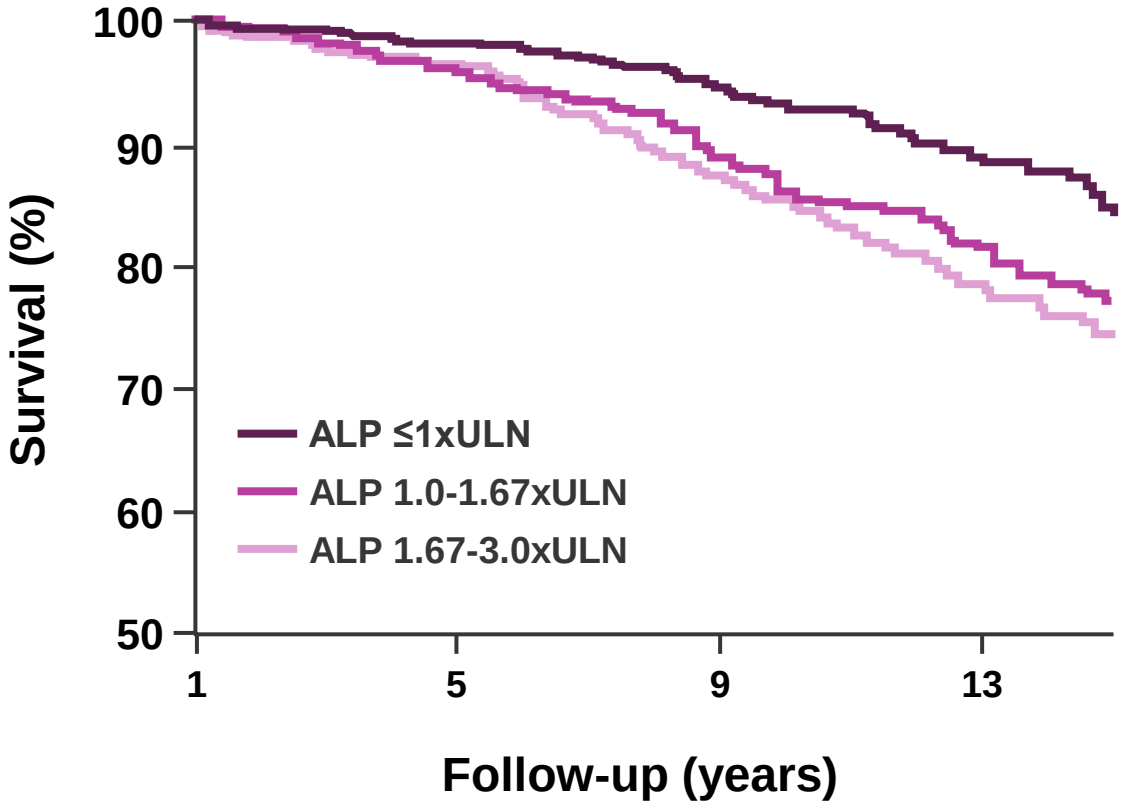
Goal is to intervene early to prevent progression to cirrhosis

ALP=alkaline phosphatase, GGT=gamma-glutamyl transferase, AST=aspartate transaminase, ALT=alanine transaminase

Lower ALP is Associated with Improved Outcomes

Clinicians and Patients Have Been Educated on the Importance of Lowering ALP

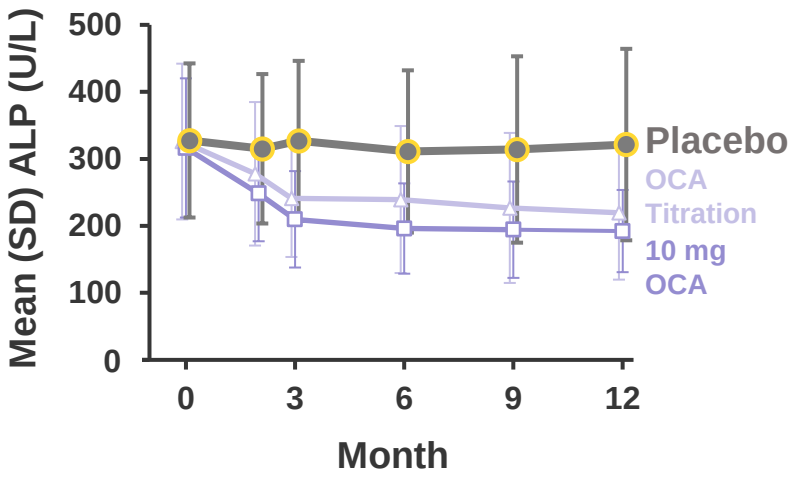




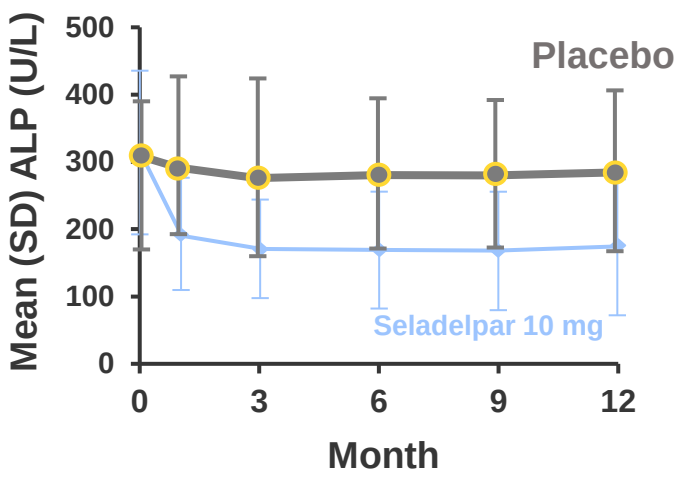
*3710/4635 patients were included for this analysis
xULN=times upper limit of normal
Lammers et al., *Gastroenterology* 2014;147(6); Murillo Perez et al., *Am J Gastroenterol* 2020;115(7) (Supplemental Material)

ALP Remains Stable Without Intervention

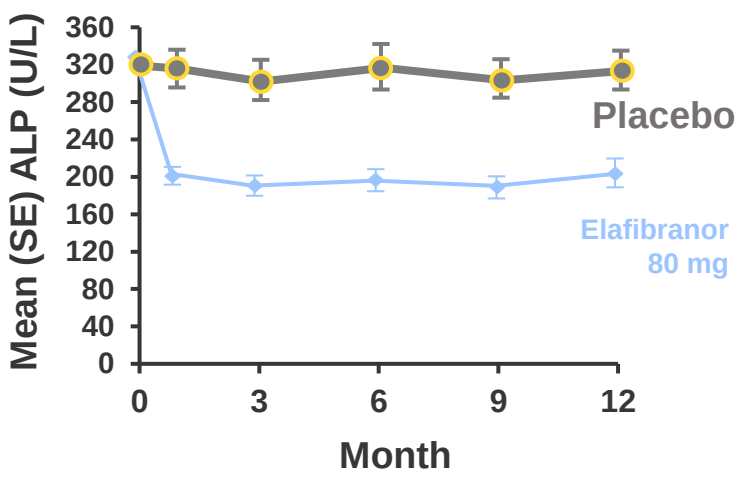
OCA (Study 301)[a]



Seladelpar[b]



Elafibranor[c]



a. Study 747-301 CSR NDA 207999 (Serial 0001); b. Adapted from Hirschfield et al., *N Engl J Med* 2024;390(9); c. Adapted from Kowdley et al., *N Engl J Med* 2024;390(9) (Supplemental Material)

Current PBC Treatment Options are Limited

- **First-line:**
  - UDCA
- **Second-line:**
  - FXR agonist (OCA)
  - PPAR agonists
    - Elafibranor, seladelpar
    - Off-label: fenofibrate, bezafibrate (not available in US)

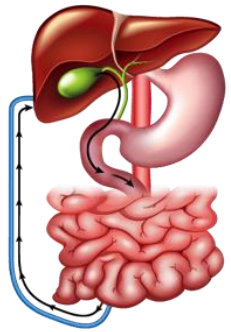
FXR=farnesoid X receptor, PPAR=peroxisome proliferator-activated receptor

Different Mechanisms of Action Needed to Lower ALP

PRIMARY DISEASE PROCESS TARGET

Complementary Mechanisms of Action

CHOLESTASIS

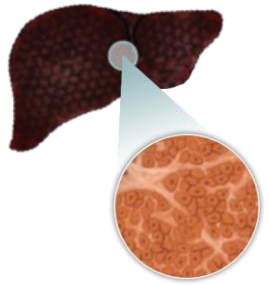


Bile Acid

INFLAMMATION

Inflammation of liver and intestine

FIBROSIS



Hepatic stellate cell activity

UDCA (bile acid modifier)

PPAR agonism

FXR agonism

Colapietro et al., *J Transl Autoimmun* 2023;6:100188; Crosignani et al., *World J Gastroenterol* 2008;14(21); Claudel et al., *Biochim Biophys Acta* 2011;1812(8); Verbeke et al., *Sci Rep* 2016;6:33453

How Do We Use OCA Today?

Before Starting OCA

Indication

- PBC
- Inadequate UDCA response or UDCA intolerance

Contraindications

- Cirrhosis with portal hypertension
  - Ascites, gastroesophageal varices, persistent thrombocytopenia
- Decompensated cirrhosis (e.g., CP Class B or C) or a prior decompensation event
- Complete biliary obstruction

How Do We Manage Patients on OCA Today?

When Starting OCA

Starting dose:

- Start with OCA 5 mg once daily
- Consider dose titration only after >3 months

Monitoring and Management

Routinely monitor patients with laboratory assessments, imaging, and clinical assessments

Discontinue OCA if:

- Laboratory or clinical evidence of hepatic decompensation
- Develop new portal hypertension
- Clinically significant hepatic adverse reactions

Methods Used to Assess Clinical Benefit

Andrew Damokosh, PhD

Senior Vice President, Biostatistics

Intercept Pharmaceuticals, Inc
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Outline of Topics

Primary Objective of Study 302 and Use of ITT Analysis

Functional Unblinding

- What is the Concern?
- Informative Treatment Crossover
- Informative Censoring

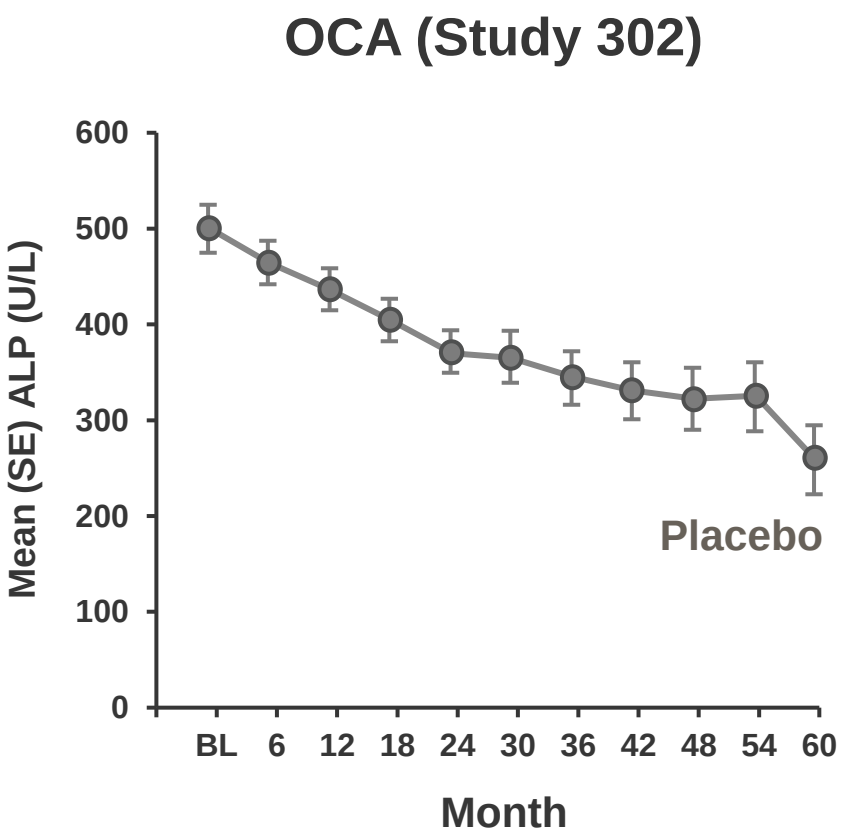
Impact of Functional Unblinding

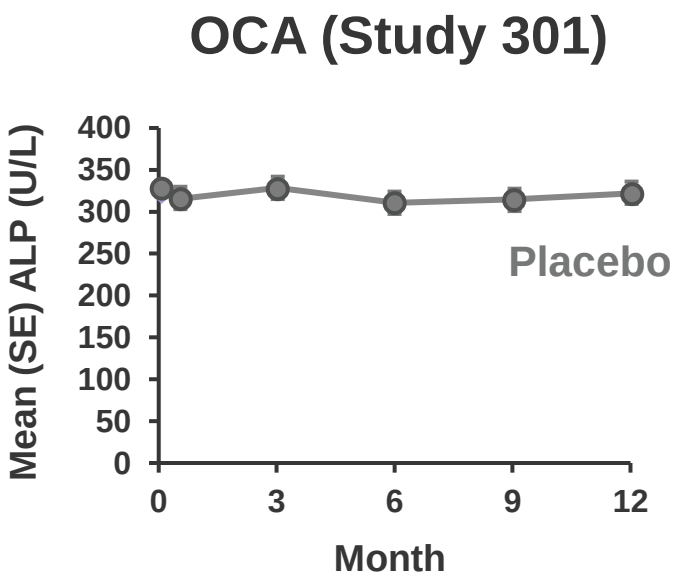
Interpretability of Study Conclusions

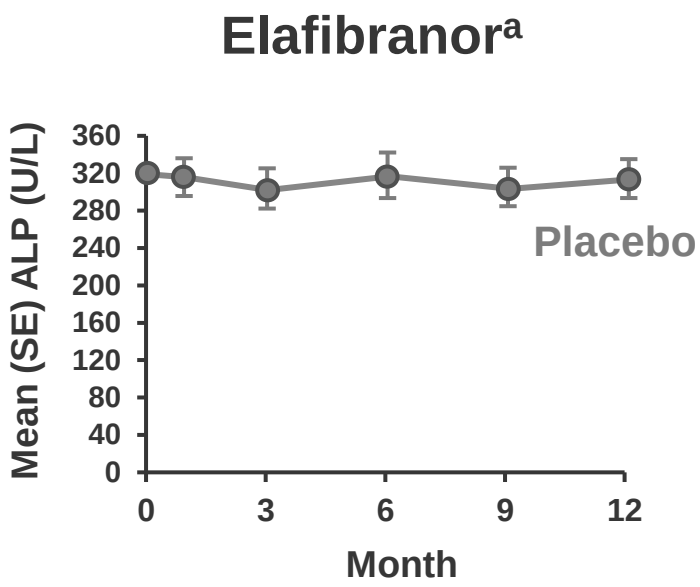
Study 302 Objective and Use of ITT Analysis

- Primary objective:
  - Assess the clinical benefit of OCA by comparing outcomes in a group of patients treated with OCA vs. a group of patients not treated with OCA (i.e., placebo)
- The analysis utilized a conventional ITT approach
  - "Analyzed as randomized"
  - Includes all follow-up, regardless of intercurrent events such as treatment crossover
- 302 ITT analysis cannot answer the primary objective of confirming OCA's clinical benefit

Functional Unblinding: What is the Concern?







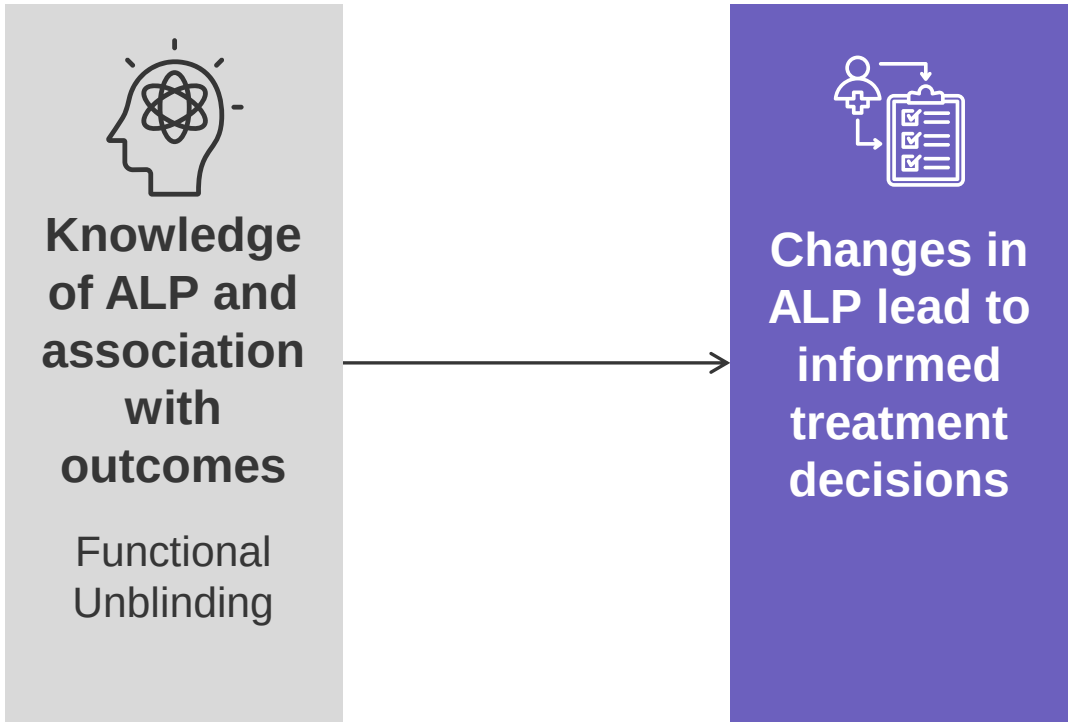
a. Adapted from Kowdley et al., *N Engl J Med* 2024;390(9) (Supplemental Material)

Functional Unblinding

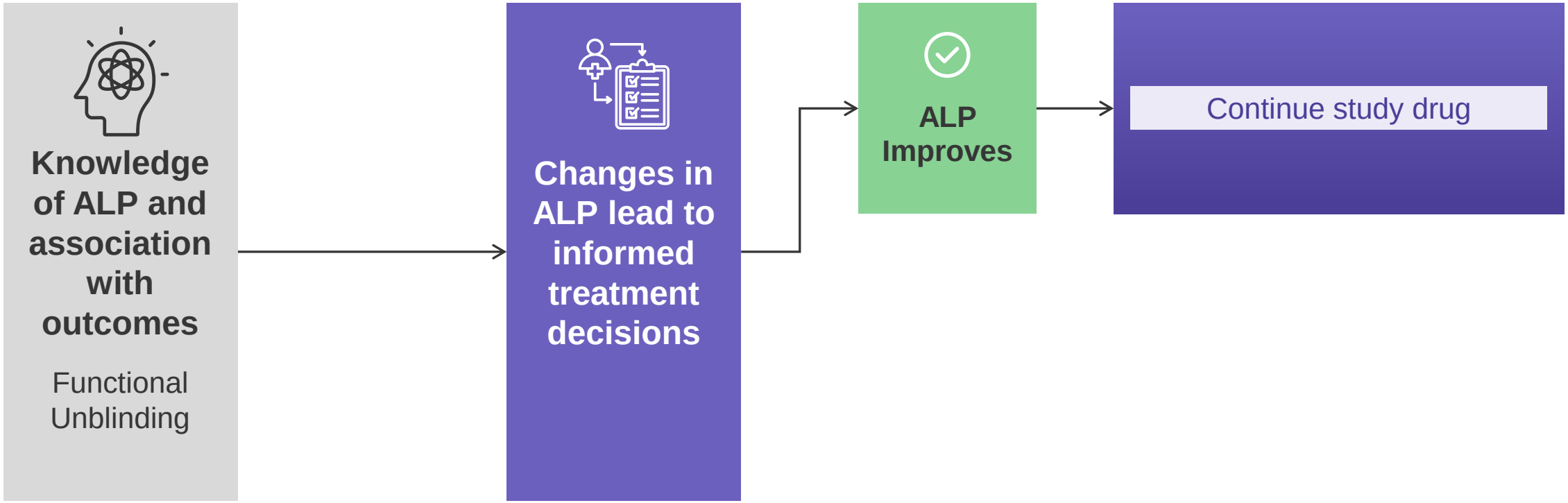
Knowledge of ALP and association with outcomes

Functional Unblinding

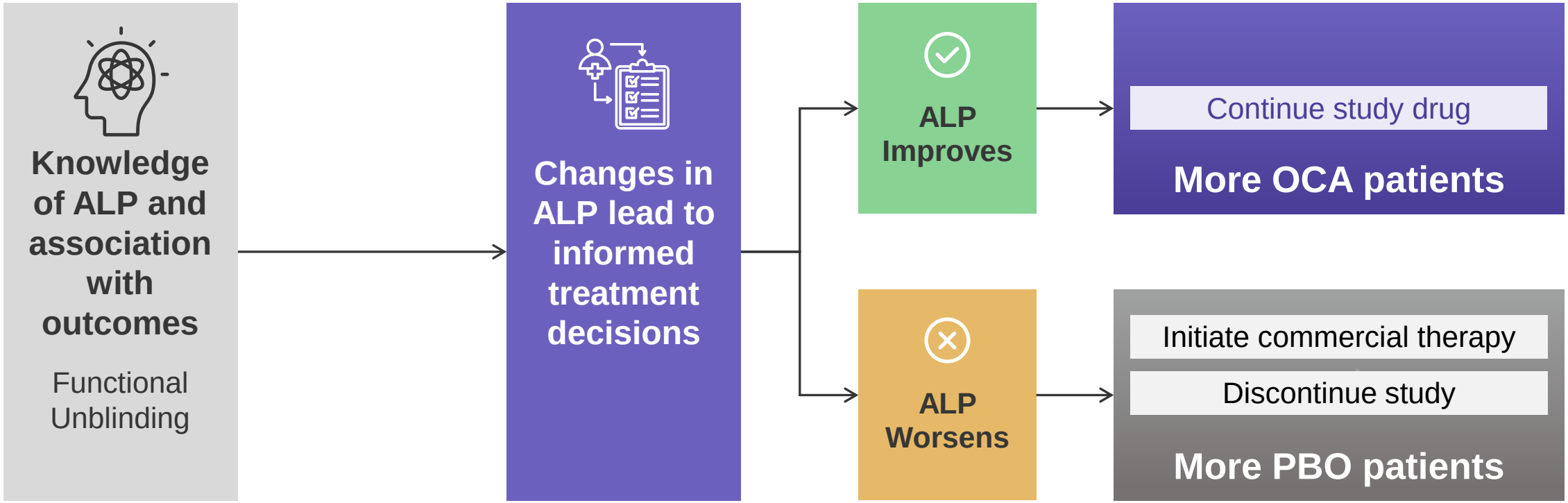
Functional Unblinding



Functional Unblinding

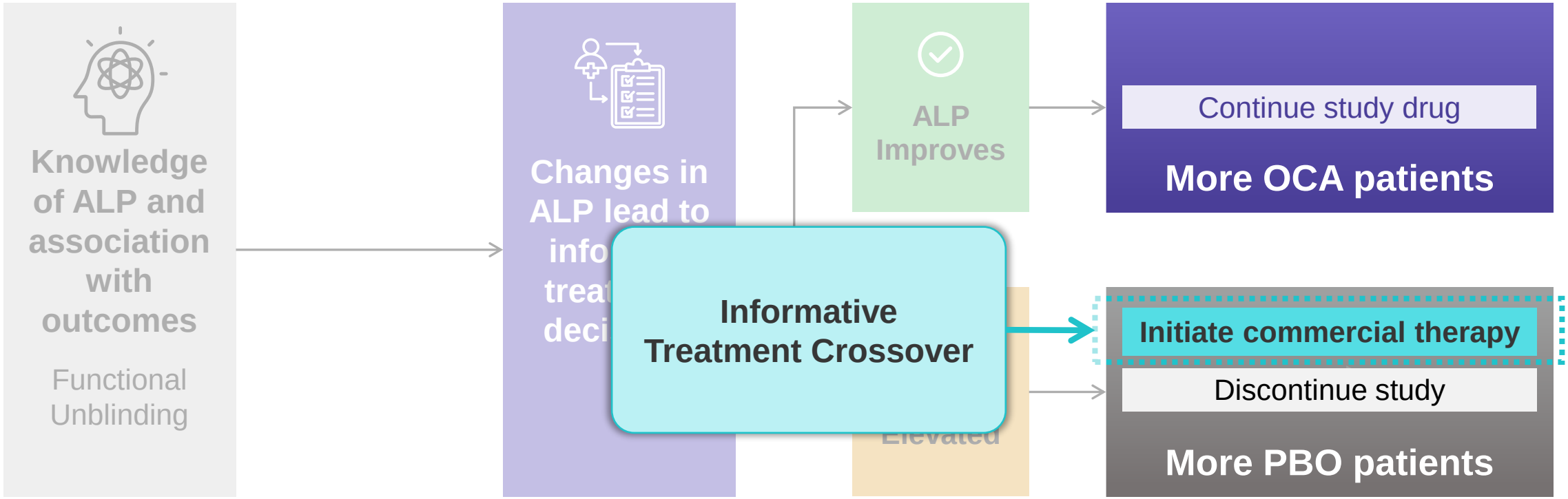


Functional Unblinding



PBO=Placebo

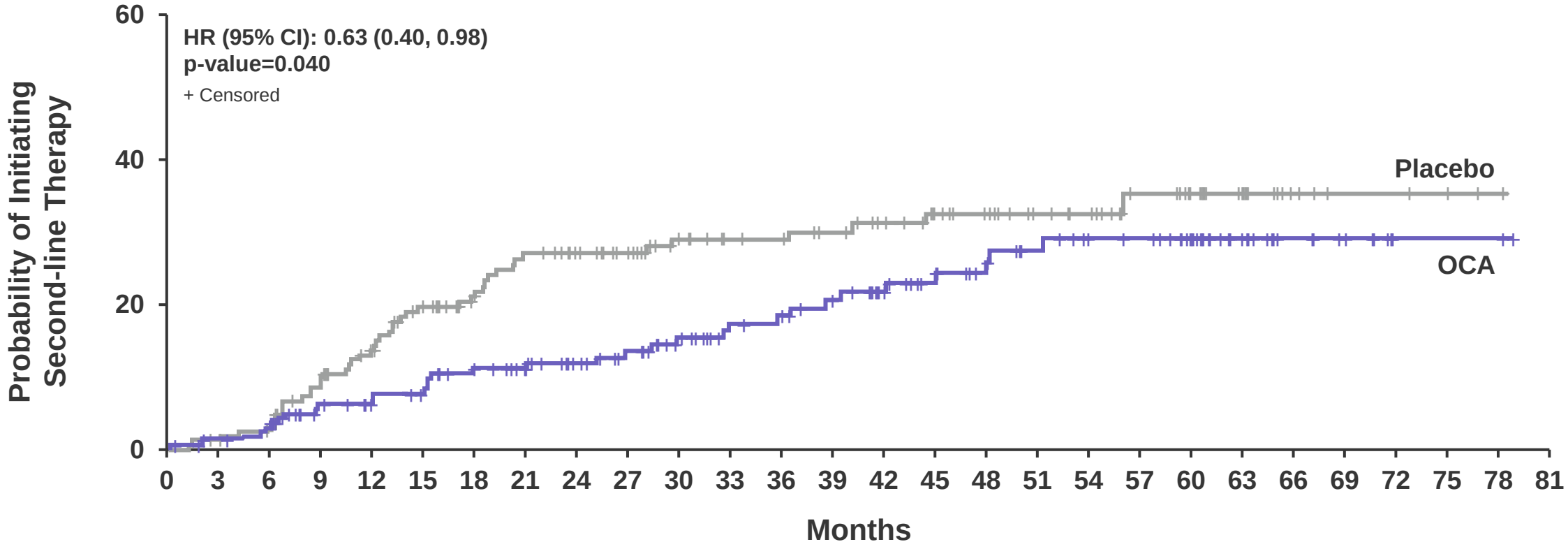
Functional Unblinding



More patients on placebo arm initiating commercial therapy creates bias

PBO=Placebo

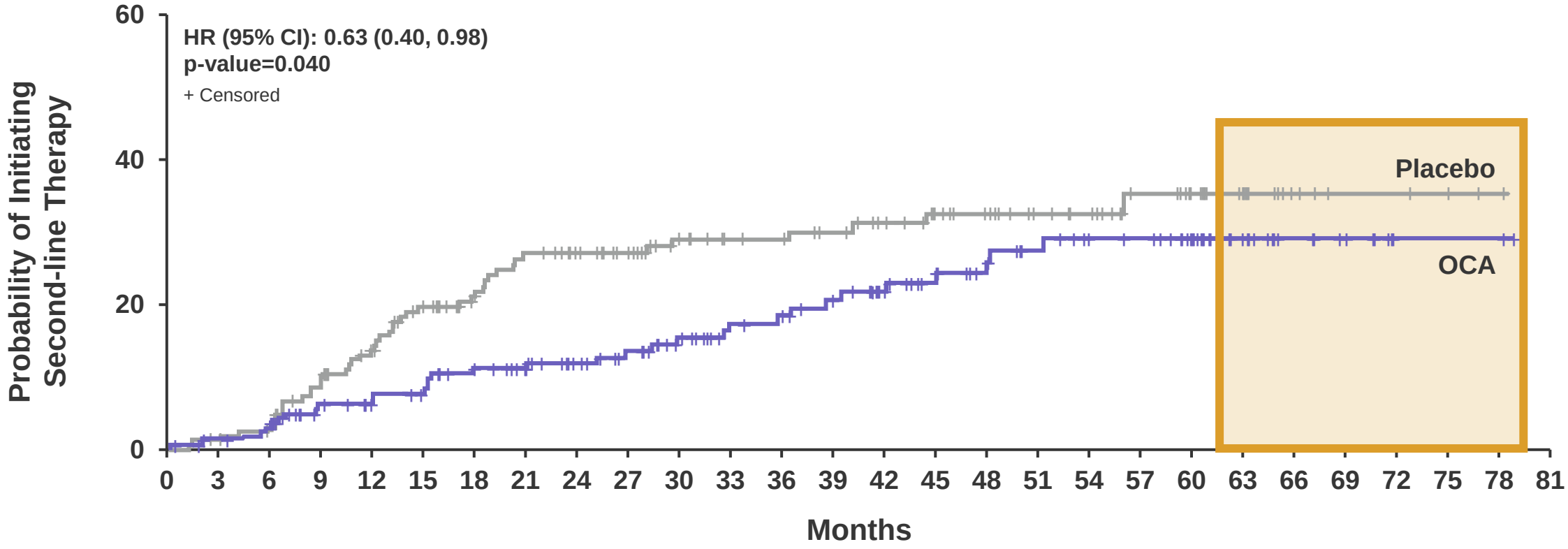
Functional Unblinding: Informative Treatment Crossover



Number of Patients at Risk

Placebo	166	162	158	143	133	119	104	97	91	83	73	68	65	61	52	45	41	35	32	24	19	13	6	4	4	2	1	0
OCA	168	163	157	144	136	133	125	119	109	102	93	82	79	73	63	55	48	44	38	37	28	18	11	7	2	2	2	0

Functional Unblinding: Informative Treatment Crossover



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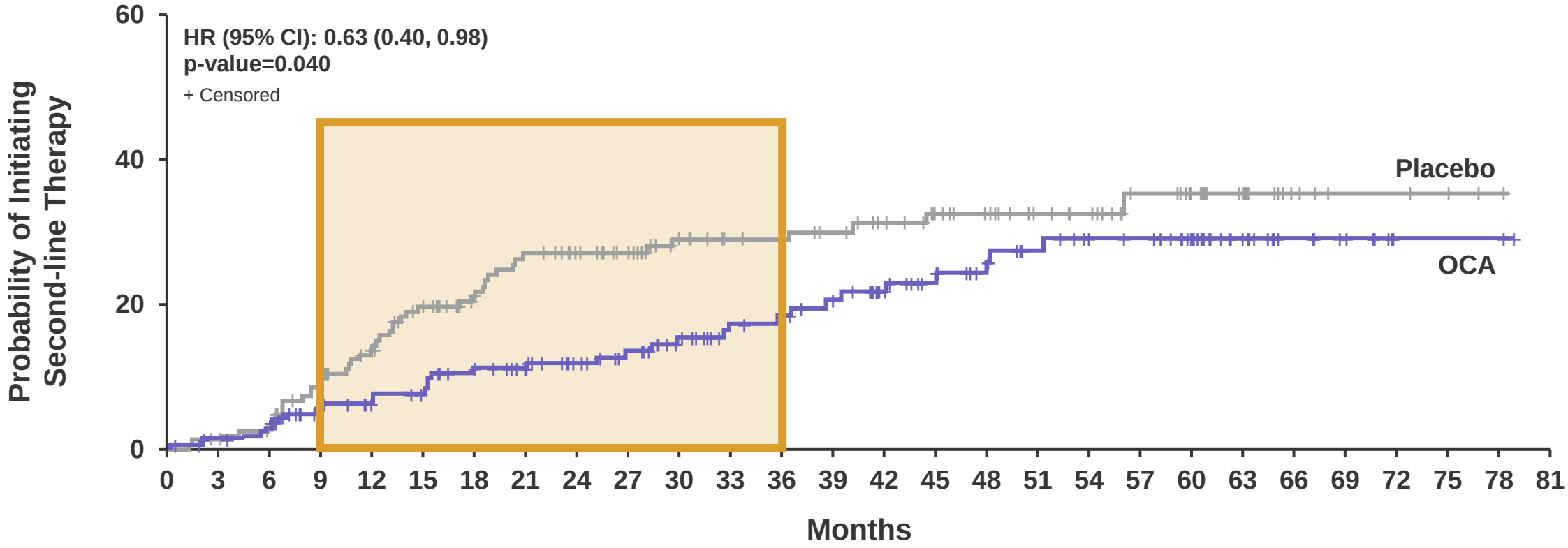
Functional Unblinding: Informative Treatment Crossover



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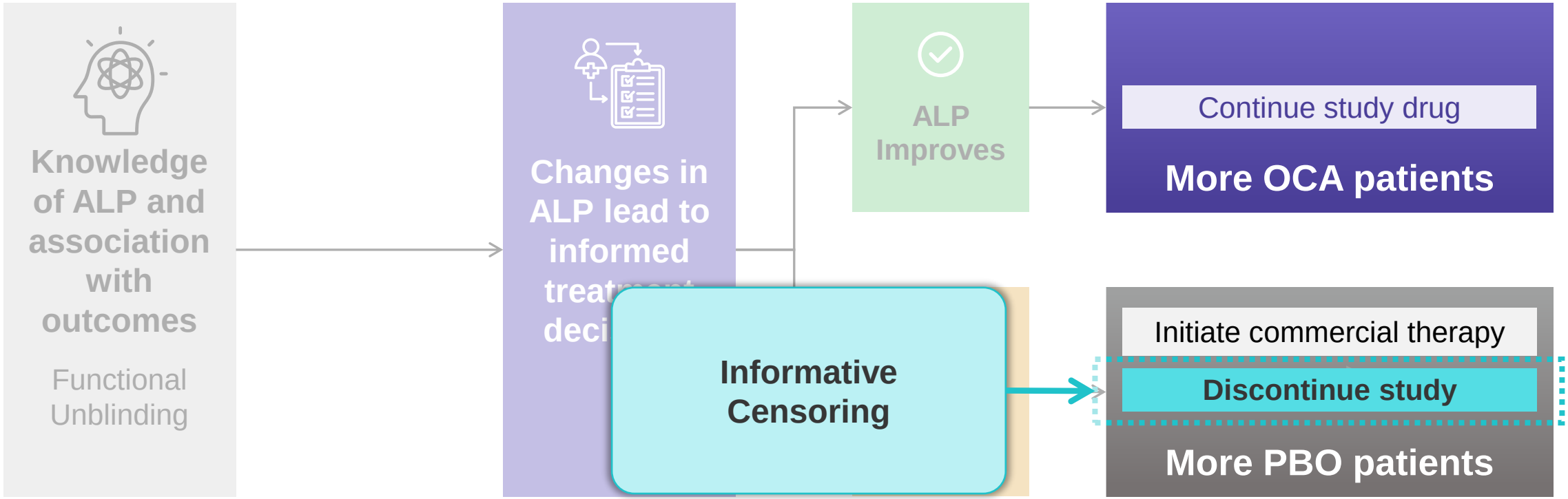
Functional Unblinding



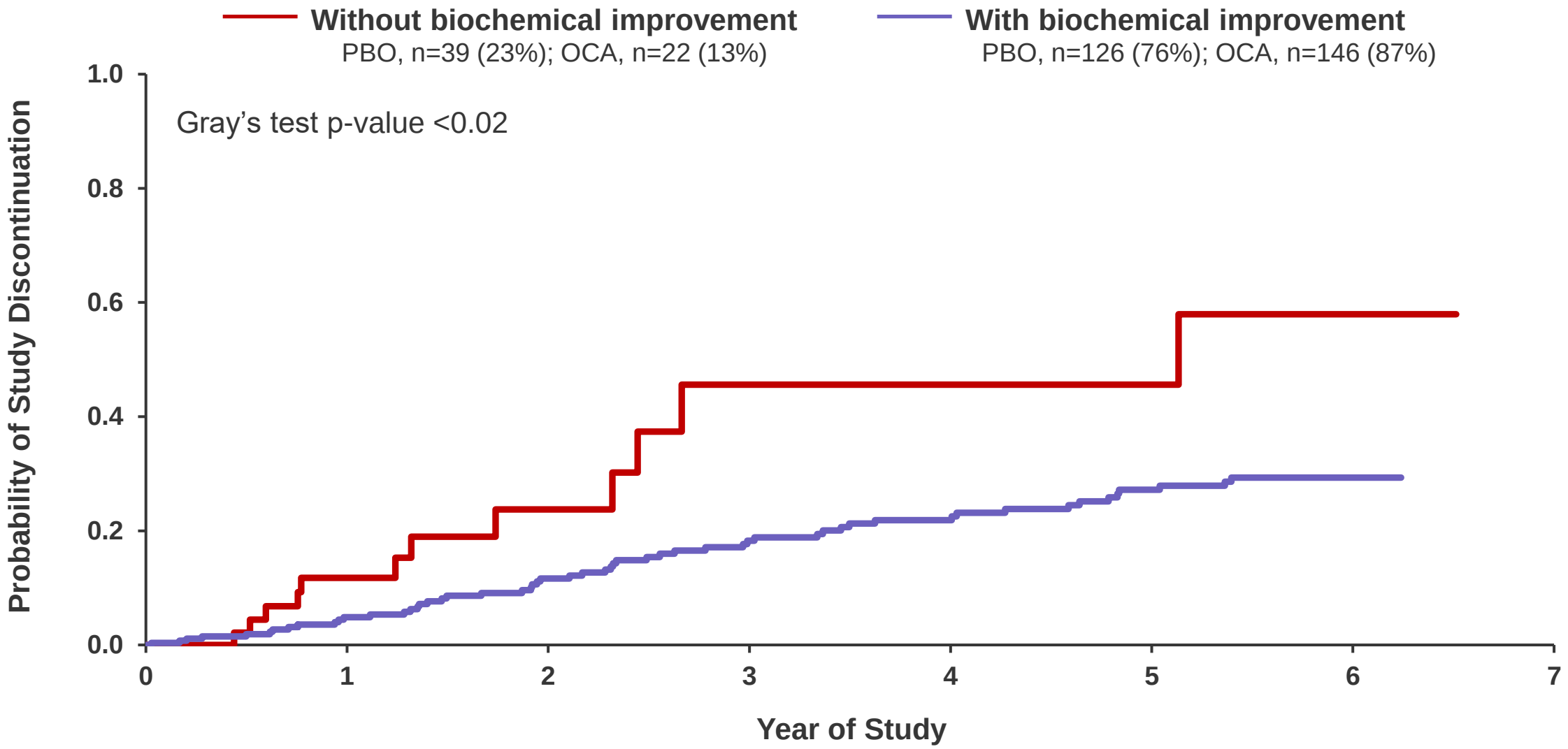
More patients on placebo arm discontinuing study creates bias

Functional Unblinding: Informative Censoring

- Occurs when the reason for study discontinuation is related to risk of event
- In Study 302:
  - Patients with worsening ALP were more likely to drop out prior to having an event
  - Missing these events leads to an underestimation of the event rate
- Imbalance in treatment arms leads to a biased estimation of clinical benefit in ITT analysis

Higher placebo dropout rate compared to OCA underestimates OCA's benefit

Informative Censoring: Patients Without Biochemical Improvement Discontinued Early



Biochemical improvement was defined as reduction from baseline of at least 40% in ALP or a reduction of TBili within the first 12 months

Functional Unblinding: How Do We Know This is Important?

	Pre-defined	Sensitivity Analyses	
	ITT with treatment policy	**As-treated analysis**	**IPCW**
Methodology	Treatment Policy Strategy for managing intercurrent events (ICE)	Placebo patients who receive ≥1 dose of commercial OCA reassigned to randomized OCA arm	Down-weights patients censored for early discontinuation
Adjustment for Informative Treatment Crossover	No	**Yes**	No
Adjustment for Informative Censoring	No	No	**Yes**

Sensitivity analyses showed a greater magnitude of clinical benefit compared to ITT

IPCW=Inverse Probability of Censoring Weight

Conclusions

- ITT analysis in Study 302 is flawed due to biases:
  - Informative treatment crossover
  - Informative censoring
- Corrections for these biases support clinical benefit of OCA
- ITT analysis cannot be used to reach conclusions regarding study success

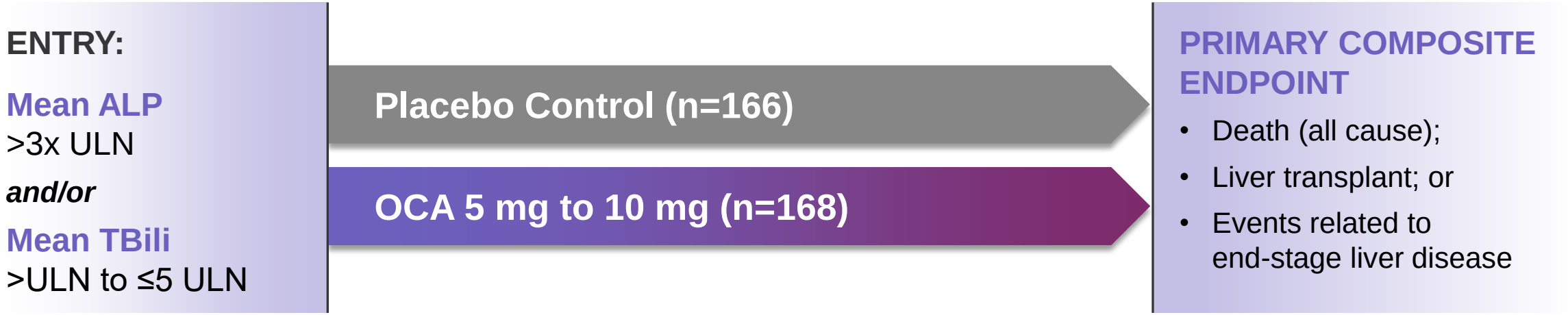
Study 302 Efficacy and Safety

Tom Capozza, MD FACP

Vice President, Clinical Research

Intercept Pharmaceuticals, Inc
AlfaSigmaGroup

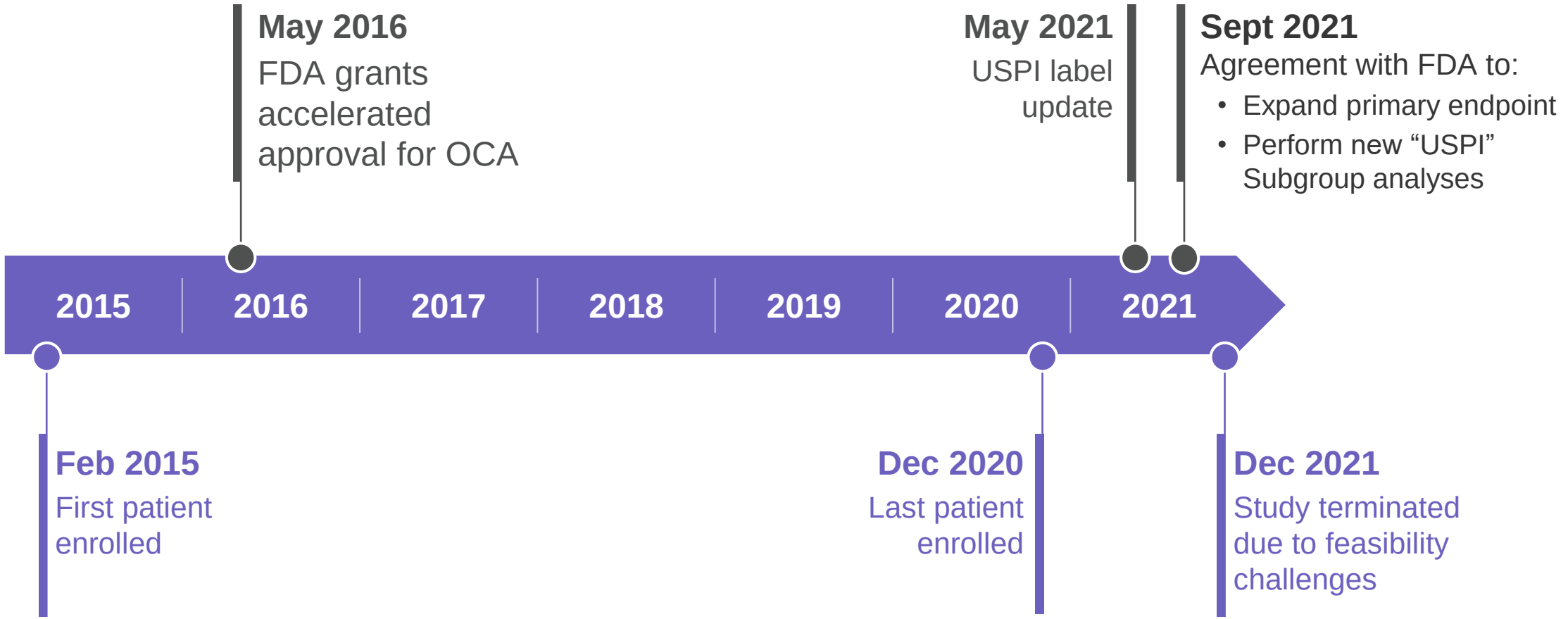
Study 302: Study Design



6 Years of Follow-up

COMMERCIAL OCA OR FIBRATES WERE NOT PROHIBITED

Study 302: Key Milestones



Study 302: Expanded Primary Endpoint

Defined and agreed with FDA prior to unblinding

Original Primary Endpoint

Time to first occurrence of:

- **Death**
- **Liver transplant**
- **MELD ≥15**
- **Uncontrolled ascites**
- **Hospitalization for new onset or recurrence of:**
  - Variceal bleed
  - Hepatic encephalopathy
  - Spontaneous bacterial peritonitis

+

Progression to clinical evidence of portal hypertension without decompensation

Progression to hepatic decompensation or portal hypertension syndromes

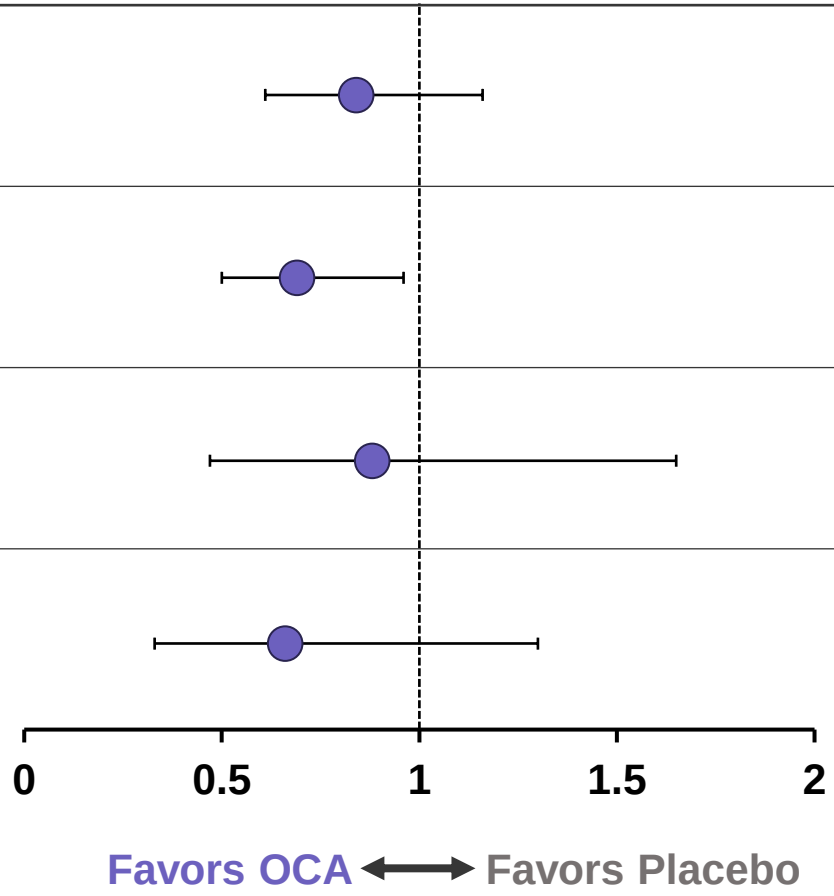
MELD=Model for end-stage liver disease

Study 302: Primary Efficacy Analysis

Analysis	Description
302 Primary Analysis: ITT Included all follow-up time based on randomized treatment	No censoring for: • Discontinuation of investigational product • Initiation of fibrates or commercial OCA
Corrected for Bias	Corrected for both treatment crossover and informative censoring (as-treated, IPCW approach)

Study 302: Primary Expanded Endpoint Results

	Events, n/N (%)		Hazard Ratio (95% CI)
	Placebo	OCA	
Primary Expanded (ITT), N=334	**80/166 (48.2)**	**71/168 (42.3)**	**0.84 (0.61, 1.16)**
Corrected for Both Treatment Crossover and Informative Censoring	**69/140 (49.3)**	**82/194 (42.3)**	**0.69 (0.50, 0.96)**
Primary Expanded (ITT "USPI" Subgroup), n=149	**19/68 (27.9)**	**21/81 (25.9)**	**0.88 (0.47, 1.65)**
Corrected for Both Treatment Crossover and Informative Censoring	**18/60 (30.0)**	**22/89 (24.7)**	**0.66 (0.33, 1.30)**



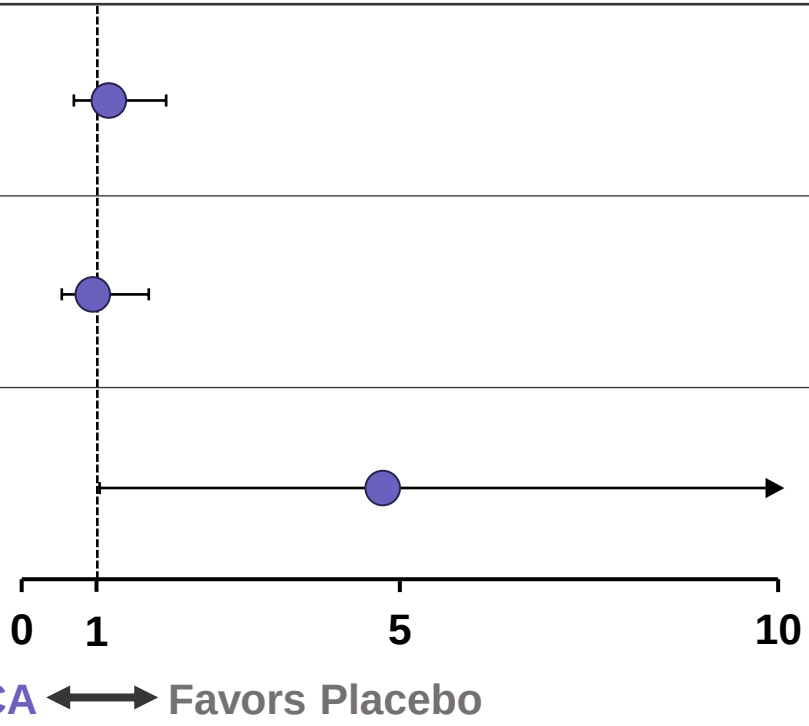
Study 302: “USPI” Subgroup Analysis Limitations

- Not prospectively defined
  - Evidence of misclassification (e.g., portal hypertension)
- Not a randomized population
  - Potential imbalance between arms
- Not managed to 2021 USPI during study
  - Study largely conducted prior to 2021 label update

A Hazard Ratio of 4.77 is Clinically Not Plausible

Death and Liver Transplants

	Events, n/N (%)		Hazard Ratio (95% CI)
	Placebo	OCA	
Study 302 (ITT Overall), N=334	28/166 (16.9)	32/168 (19.0)	1.15 (0.69, 1.91)
Study 302 (Contraindicated Subgroup), n=185	26/98 (26.5)	21/87 (24.1)	0.94 (0.53, 1.68)
Study 302 ("USPI" Subgroup), n=149	2/68 (2.9)	11/81 (13.6)	4.77 (1.03, 22.09)



Hepatic Safety Topics

- **Liver Transplants and Deaths**
- Drug-Induced Liver Injury Adjudication
- Postmarketing Data

Liver Transplants in “USPI” Subgroup Are Not DILI Events

- High risk patients with PBC
- Disease progression in this population is expected
- Latency not consistent with DILI
- All events occurred prior to 2021 USPI update

Study 302 “USPI” Subgroup: Liver Transplants

FDA Patient No.	IP	Baseline TBili (mg/dL)	Outcome Event (Study Day)	Time off IP to Event	Time from Contraindication to Event	Clinical Details
1	Placebo	1.5	Liver Transplant (1078)	93 days*	2.5 years	Portal HTN at Month 6, switched to commercial OCA on Day 269
2	OCA	2.1	Liver Transplant (1580)	1.8 years	3.3 years	Cirrhosis w/ longstanding UC; Portal HTN at Month 12
3	OCA	1.8	Liver Transplant (1412)	2.2 years	2.9 years	Portal HTN at Month 12
4	OCA	2.6	Liver Transplant (812)	145 days	1.8 years	F3-4 on baseline biopsy, rifampicin, cholestyramine and fenofibrate for pruritus at baseline
5	OCA	1.9	Liver Transplant (1356)	2.1 years	2.7 years	Portal HTN at Month 12
6	OCA	0.6	Liver Transplant (234)	13 days	-	Prior to study entry refractory pruritus, trial of MARS; MELD 6 at transplant
7	OCA	1.0	Liver Transplant (639)	1.2 years	1.8 years	Portal HTN at baseline, alcohol-use disorder, chronic pancreatitis, insulin-dependent DM, rifampicin
8	OCA	2.4	Liver transplant (823)	1.1 years	1.6 years	Increased TBili at Month 12

Total bilirubin upper limit of normal=1.2 mg/dL; portal HTN=portal hypertension; UC=ulcerative colitis; DM=diabetes mellitus; MARS=molecular adsorbent recirculation system
*Switched from commercial OCA on Day 269

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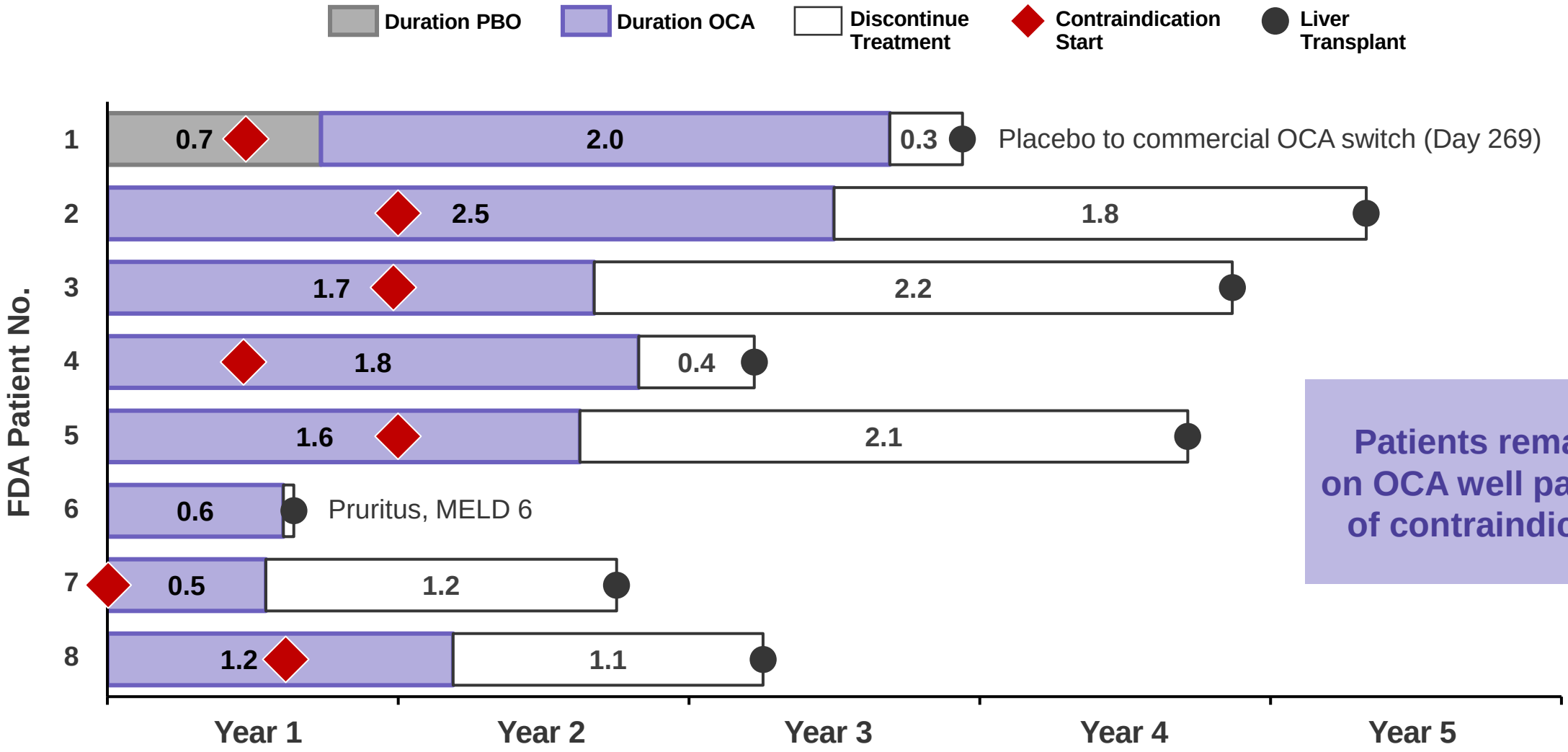

Patients remained on OCA well past time of contraindication

FDA Briefing Document, Figure 8

Study 302 “USPI” Subgroup: Deaths

FDA Patient No.	IP	Baseline TBili (mg/dL)	Outcome Event (Study Day)	Time off IP to Event	Time from Contraindication to Event	Cause of Death
9	**Placebo**	0.3	Non-liver Related Death (512)	133 days	N/A	Complications from paraplegia post-hip surgery
10	**OCA**	2.3	Non-liver Related Death (618)	397 days	N/A	Subdural hematoma
11	**OCA**	1.2	Non-liver Related Death (317)	21 days	N/A	Stage IV B-cell Lymphoma
12	**OCA**	2.0	Liver-Related Death (937)	48 days	1.4 years	Variceal hemorrhage leading to ischemic cerebral injury (baseline contraindicated)
13	**OCA**	0.9	Non-liver Related Death (887)	664 days	N/A	*C. difficile* colitis

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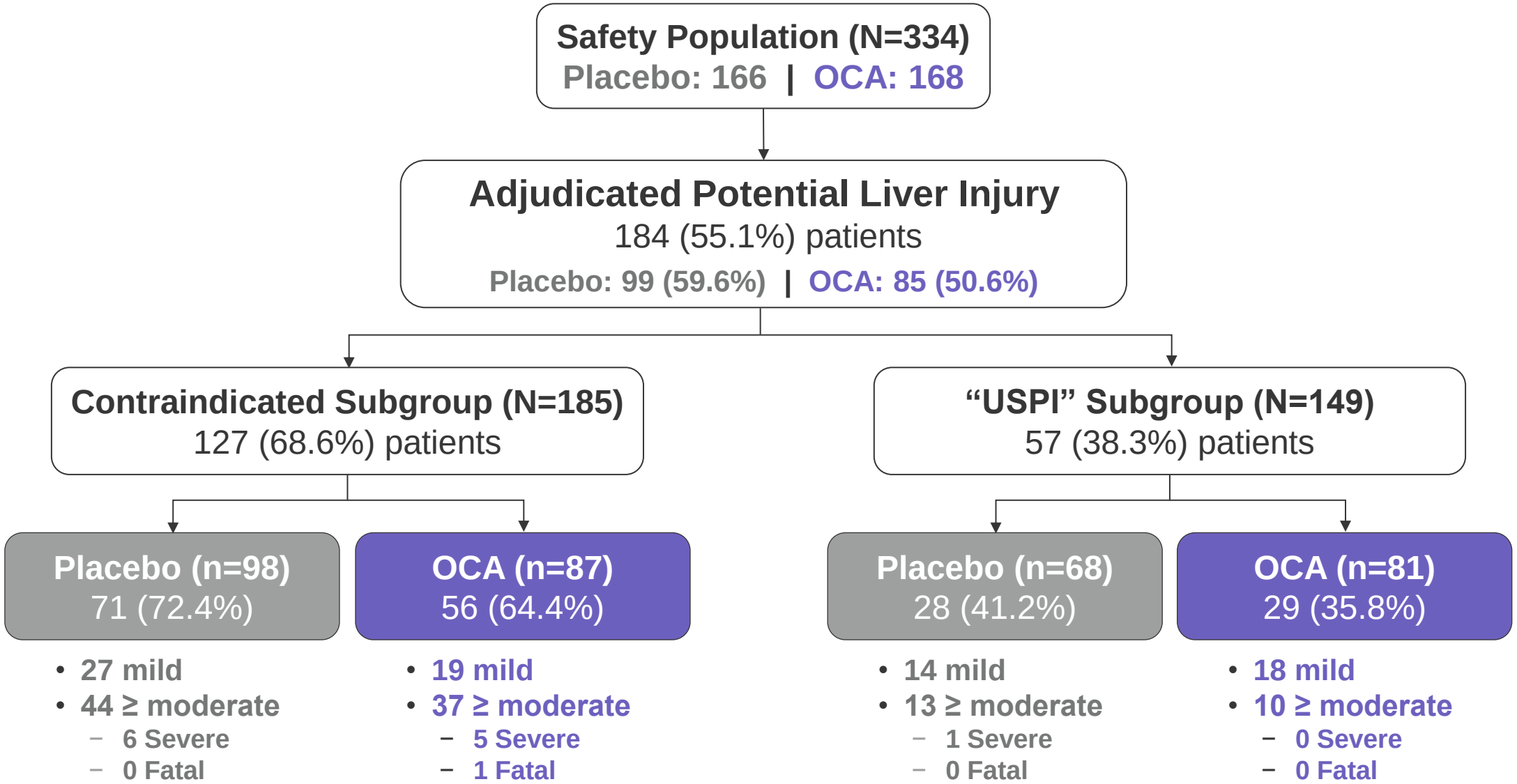
Hepatic Safety Topics

- Liver Transplants and Deaths
- **Drug-Induced Liver Injury Adjudication**
- Postmarketing Data

OCA's Hepatic Safety is Manageable

- OCA is a bile acid derivative
- All hydrophobic bile acids have potential for a *direct, exposure-dependent* toxicity
  - OCA exposure increases with hepatic impairment
- USPI revised in 2021 for OCA:
  - Contraindicates use in patients with portal hypertension or hepatic decompensation
  - Provides guidance for monitoring and management

Study 302: DILI Adjudication by Severity



Study 302 “USPI” Subgroup: Possible DILI Cases

FDA Patient No./ Treatment	HSAC Causality/ Severity	Confounders	Onset Study Day	Lab Observations	Base/ Peak ALT (U/L)	Base/ Peak AST (U/L)	Base/ Peak ALP (U/L)	Base/ Peak TBili (mg/dL)	Intervention	Outcome
14 / OCA	Possible/ **Moderate**	Gallstones (Day 49)	Day 80	AST/ALT/TBili elevation	185 / 764	85 / 378	574 / 688	1.0 / 6.6	DC OCA (Day 87) Cholecystectomy (Day 121)	Resolved (Day 139)
15 / OCA	Possible/ **Moderate-severe**	Rifampicin (Started Day 16)	Day 85	AST/ALT elevation	87 / 680	90 / 791	585 / 567	1.4 / 1.7	DC Rifampicin (Day 90) DC OCA (Day 93)	Resolved (Day 126)
16 / OCA	Possible/ **Mild**	PBC disease	Day 91	Fluctuating high ALP	17 / 51	22 / 84	543 / 2610*	0.3 / 0.7	DC OCA (Day 241)	Resolved (Day 285)
17 / Placebo	Possible/ **Moderate**	Rifampicin (Started Day 87)	Day 104	AST/ALT/ALP/ GGT/TBili elevation	109 / 136	108 / 126	426 / 537	1.4 / 2.5	DC PBO (Day 107) DC Rifampicin (Day 118)	Undetermined

HSAC=Hepatic Safety Adjudication Committee
*ALP ULN of 300 U/L for peak lab

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- Drug-Induced Liver Injury Adjudication
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Global Postmarketing Experience: Impact of 2021 USPI Update

	Pre-2021 Update ~20,000 PY* Events per 100 PYs	**Post-2021 Update ~25,000 PY*** Events per 100 PYs
Hepatic AEs		
All hepatic AEs	**11.57**	**6.99**
Serious hepatic AEs	**3.80**	**1.61**
Liver injury	**0.08**	**0.03**
Liver transplant	**0.30**	**0.10**
Fatal (all-cause) AEs	**1.63**	**0.69**
Fatal hepatic AEs	**0.26**	**0.03**

~80% of postmarketing safety reports for Ocaliva are solicited
Postmarketing data is reconciled against the FAERS database on a quarterly basis

*Postmarketing exposure estimated based on sales. Each unit (bottle) of OCA is assumed to be prescribed at one tablet per day for one patient. Data are converted to an estimate of patient-years (PY=total units*30 days per unit/365.25 days per year)

Multiple Layers of Risk Mitigation and Management

Specialty Practices

- Second-line therapy managed by hepatologists and gastroenterologists

Specialty Pharmacy

- Labs required
- Prior authorization for initial prescription and refills

Patient Hub Program (InterConnect®)

- Requires providers attest to eligibility

Summary

EFFICACY

- Study 302 ITT analysis is flawed
- Corrections for bias show a trend for benefit
- "USPI" Subgroup HR for death and liver transplant is inconsistent with totality of evidence which shows benefit for event-free survival

SAFETY

- OCA hepatoxicity risk is low, monitorable, manageable, and reversible in the 2021 USPI population
- Safety profile is well-characterized with more than 8 years (>42,000 PY) of postmarketing experience

Drug-Induced Liver Injury

Lily Dara, MD

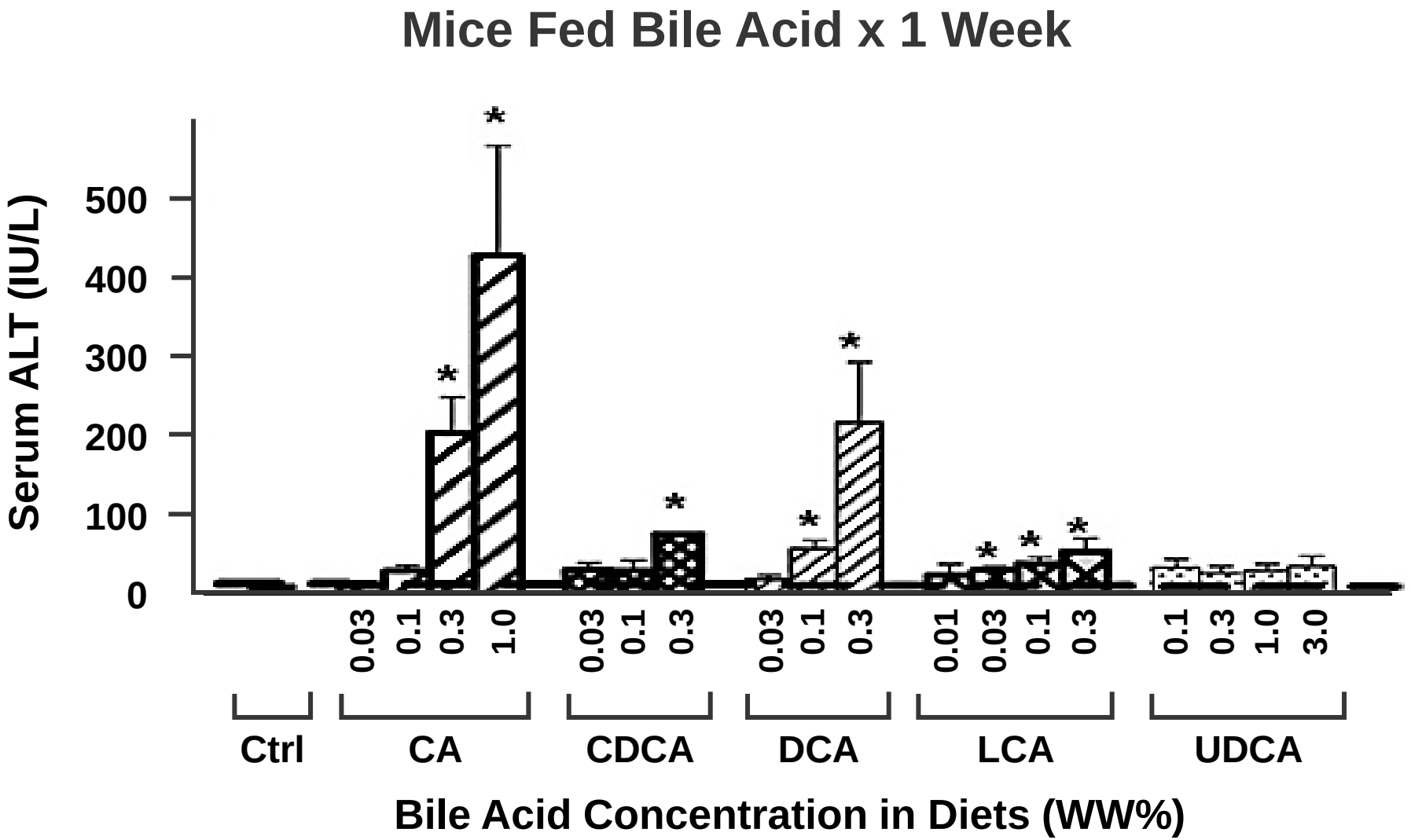
Assistant Professor of Medicine, Department of Medicine, Division of GI/Liver,
USC Research Center for Liver Disease, Keck School of Medicine, University of Southern California

Mechanisms of Drug-Induced Liver Injury (DILI)

Mechanistic Classification	Direct Hepatotoxicity	Idiosyncratic Hepatotoxicity	Indirect Hepatotoxicity
Incidence	Common	Rare	Intermediate
Dose relatedness	Yes	No	No
Predictability	Yes	No	Partially
Latency	Short (days)	Variable	Weeks/Months
Examples	Acetaminophen, niacin, Hydrophobic Bile Acids	Amoxicillin-clavulanate, cephalosporins, isoniazid, nitrofurantoin	Immune checkpoint inhibitors

AASLD Guidelines: Fontana et al., *Hepatology* 2023;77(3)

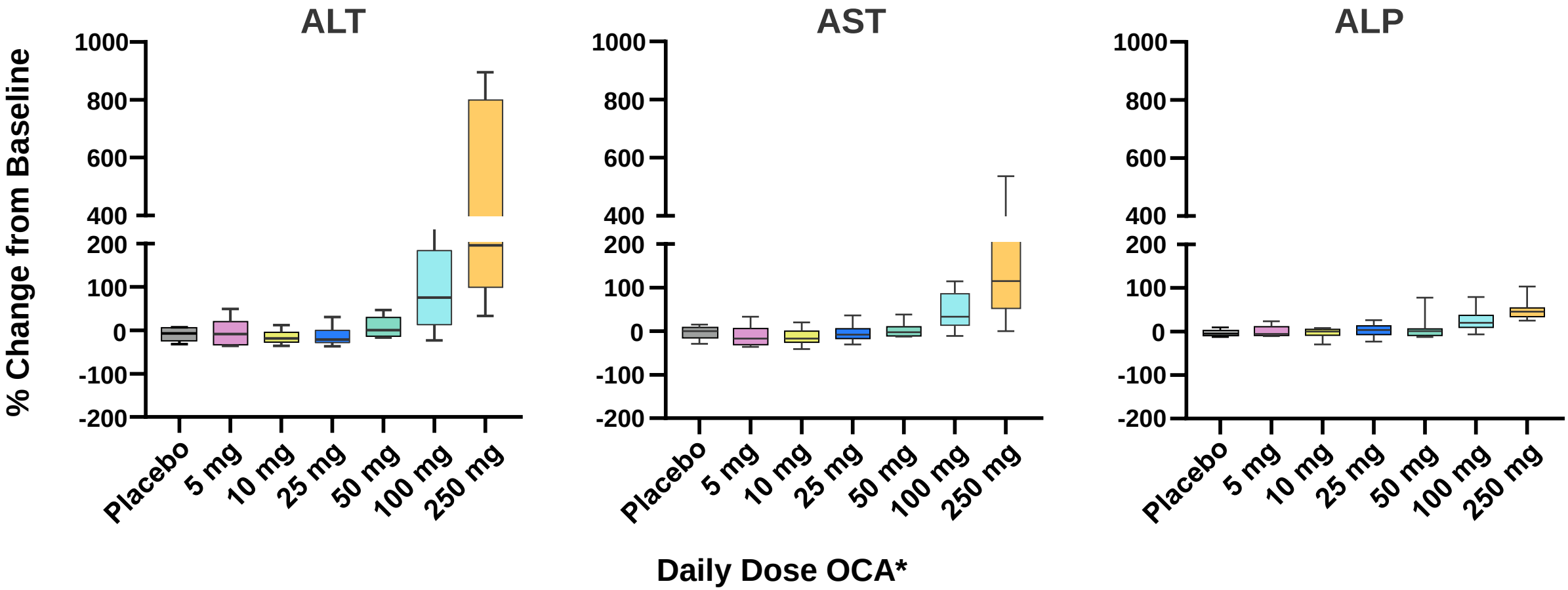
Bile Acids and Direct Hepatoxicity



Ctrl=Control, CA=cholic acid, CDCA=chenodeoxycholic acid, DCA=deoxycholic acid, LCA=lithocholic acid, UDCA=ursodeoxycholic acid
Song et al, *Toxicology Sciences* 2011;123(2)

Dose Dependent, Hepatocellular Pattern

ALT, AST, and ALP % Change in Healthy Volunteers



*Healthy Volunteer PK Population, Studies 102 (12-days), 105 (14-days), 118 (28-days)

Causality Assessment

- Rule out confounders
  - Other liver disease
  - Comorbid diseases
  - Concomitant medications and herbal supplements
- Latency
- Known phenotype of DILI (hepatocellular, cholestatic, mixed)
- De-challenge

OCA DILI is Monitorable and Manageable in PBC

- Monitoring is routine in PBC
- Managed by gastroenterologists and hepatologists
- Select right patient population
- Stop when liver tests are abnormal or when patient is not responding
- Reversible in this patient population

Study 405 and Other RWE

Leona Bessonova, PhD

Executive Director, Medical Affairs Research

Intercept Pharmaceuticals, Inc
AlfaSigmaGroup

Outline of Topics

Study 405

Other Real-World Evidence

- Study 301 LTSE EC
- Study 302 EC
- RECAPITULATE + Global PBC

Summary

Study 405: Observational, Retrospective Study

Patients who failed first-line UDCA

- **Second-line OCA**
- **Controls** (eligible patients not treated with OCA)

INCLUSION/EXCLUSION FOLLOWED STUDY 301, SIMILAR TO USPI:

- Excluded advanced disease
- Fibrate use excluded
- Criteria were equally applied to both study arms

PRIMARY ENDPOINT:

- Time to first of:
  - Hospitalization for hepatic decompensation
  - Liver transplant
  - All-cause death

Study 405 Used Rigorous Study Design and Analysis

- Follows current best practices in pharmacoepidemiology
- Pre-specified protocol-defined:
  - Patient, Intervention, Comparison, Outcome and Time (PICOT)
  - Robust analytical approach to minimize bias
    - Multiple index dates
    - Weighted Cox regression
    - As-treated analyses in line with RCT-DUPLICATE[a]
- Consistent with evolving FDA guidances
  - 8 real-world evidence guidances released by FDA (2018 – 2024)
- Database selection for reliability and relevance

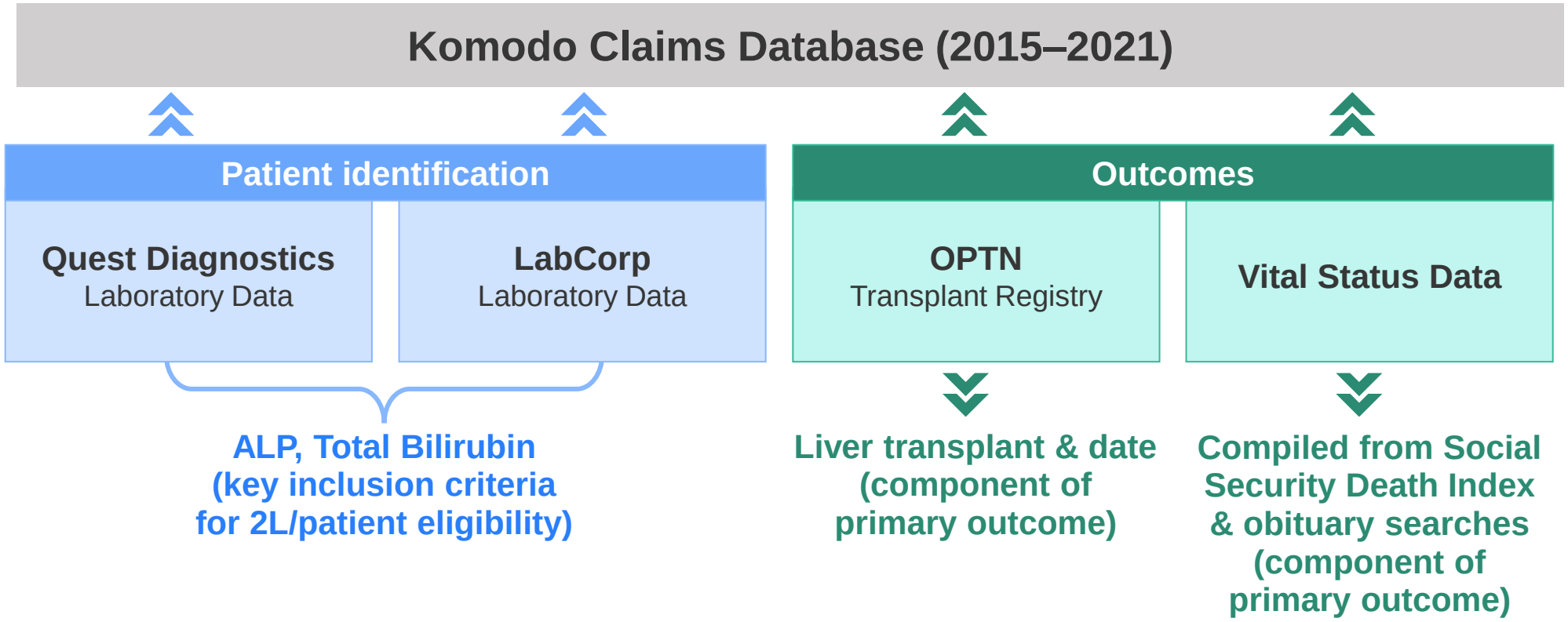
a. RCT-DUPLICATE, Wang et al., *JAMA* 2023;329(16)

Study 405 Utilized Komodo as Primary Data Source

- Komodo captures patients taking OCA with longitudinal follow-up
- Closed claims reviewed and adjudicated by payers
- Data to evaluate enrollment criteria and outcomes of hospitalization for hepatic decompensation, liver transplants, and deaths
- Komodo database represents the US PBC population
  - Similar prevalence and demographics to published literature[a]

a. Lu et al., *Clin Gastroenterol Hepatol* 2018;16(8):P1333-1341; Lu et al., *Clin Gastroenterol Hepatol* 2018;16(8):1342-1350

Study 405 Utilized Additional Supplemental Data



Study 405 used Datavant token with over 98% precision[a]

2L=Second-line, OPTN=Organ Procurement Transplantation Network
a. Bernstam et al., *Applied Clinical Informatics* 2022;13(4)

Study 405: Identification of PBC Population

FDA COMMENTS

- *Algorithm identified PBC with unknown accuracy*

- *Study 405 used methods with unknown or uncertain reliability when defining PBC with poor response to UDCA*

INTERCEPT POSITION

- PBC population identified using **published algorithm** (Myers 2010)[a]
  - Sensitivity: 94%
  - PPV: 73%-89%

- For both arms, patients were required to have record of:
  - UDCA exposure, and
  - ALP/TBili > ULN, and
  - No record of other exclusionary diagnoses such as PSC or other serious liver disease

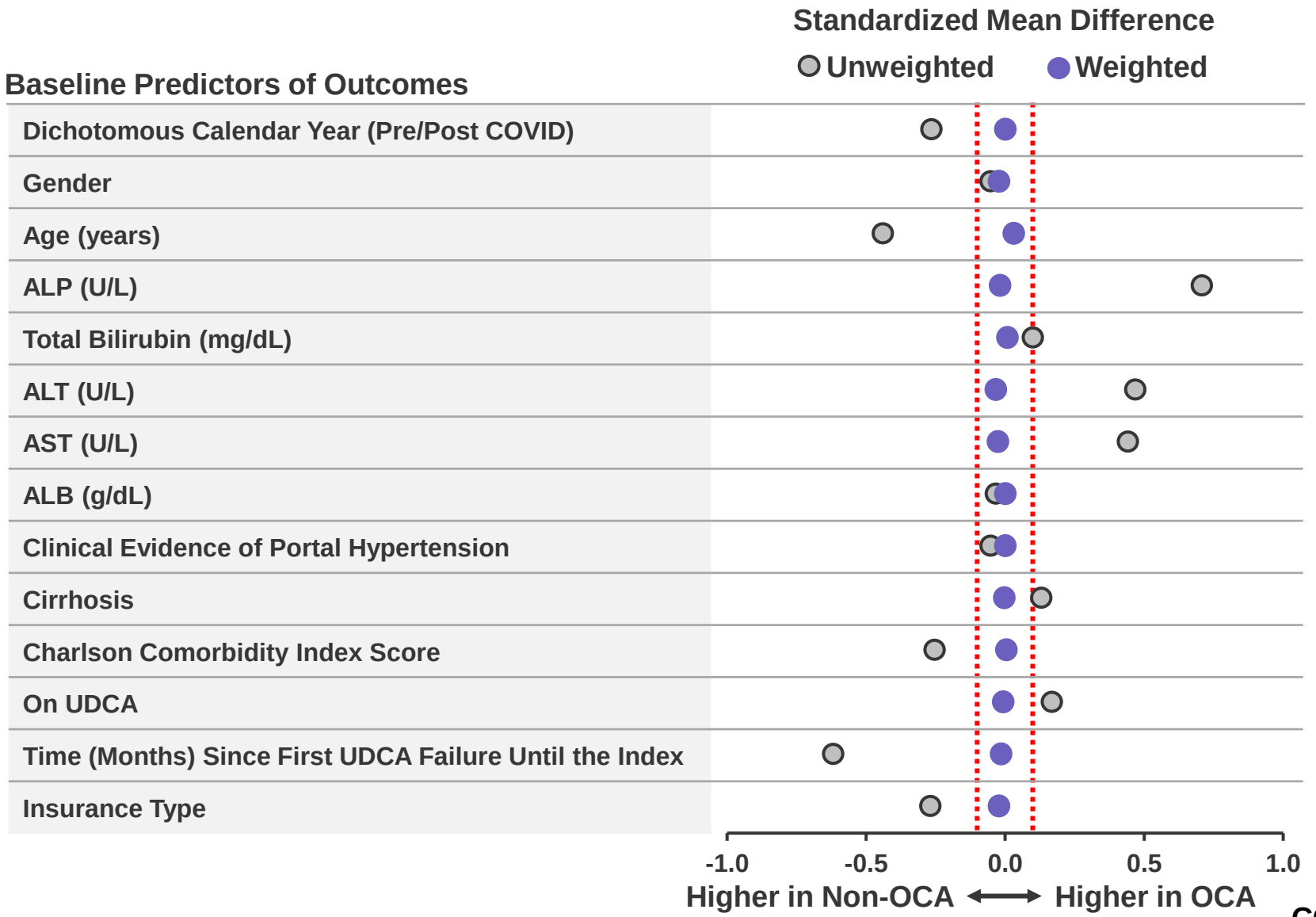
PPV=Positive predictive value
a. Myers et al., *Can J Gastroenterol* 2010 Mar;24(3)

Study 405: Prespecified Prognostic Factors are Balanced After Weighting

Baseline predictors prespecified by independent Medical Team

Propensity score-based weighting addressed differences in covariate distribution

SMR weights achieved balance between OCA and non-OCA arms



Study 405: Primary Efficacy Analysis

	OCA-treated Indexes	Non-OCA-treated Indexes
405 Primary Analysis: As-treated Conventionally used with RWD; actual treatment received	Censored: • **90 days after OCA discontinuation** • Initiation of fibrates	Censored at initiation of: • Commercial OCA • Fibrates • UDCA (if previously discontinued UDCA)

RWD=Real-world data

Study 405: Censoring Rules for Treatment Crossover

Censoring Rule Set, by Analysis

Criterion	Applicant's As-Treated (3-Point Composite)	
	OCA	CNTL
OCA end	✓	
OCA start		✓
Fibrate start	✓	✓
UDCA restart		✓*
Closed claims end	✓	✓
Study end	✓	✓

- Censored for change in active treatment
- Additionally, IPCW adjusts for informative censoring

*Applicable to control periods identified by laboratory test abnormality that fulfilled UDCA discontinuation criteria; Table 12, FDA Briefing Document

Study 405: Censoring Rules for Treatment Crossover

	Censoring Rule Set, by Analysis					
	Applicant's As-Treated (3-Point Composite)		Applicant's ITT 1 (3-Point Composite)		Applicant's ITT 2 (3-Point Composite)	
Criterion	OCA	CNTL	OCA	CNTL	OCA	CNTL
OCA end	✓					
OCA start		✓		✓		
Fibrate start	✓	✓	✓	✓	✓	✓
UDCA restart		✓*		✓*		
Closed claims end	✓	✓	✓	✓	✓	✓
Study end	✓	✓	✓	✓	✓	✓

- ITT 1 and ITT 2 allowed follow-up after OCA discontinuation
- ITT 2 allowed follow-up for controls after starting OCA

*Applicable to control periods identified by laboratory test abnormality that fulfilled UDCA discontinuation criteria; Table 12, FDA Briefing Document

Study 405: Censoring Rules for Treatment Crossover

	Censoring Rule Set, by Analysis							
	Applicant's As-Treated (3-Point Composite)		Applicant's ITT 1 (3-Point Composite)		Applicant's ITT 2 (3-Point Composite)		FDA ITT[1] (2-Point Composite)	
Criterion	OCA	CNTL	OCA	CNTL	OCA	CNTL	OCA	CNTL
OCA end	✓							
OCA start		✓		✓				
Fibrate start	✓	✓	✓	✓	✓	✓		
UDCA restart		✓*		✓*				
Closed claims end	✓	✓	✓	✓	✓	✓		
Study end	✓	✓	✓	✓	✓	✓	✓	✓

ITT analyses introduce treatment misclassification

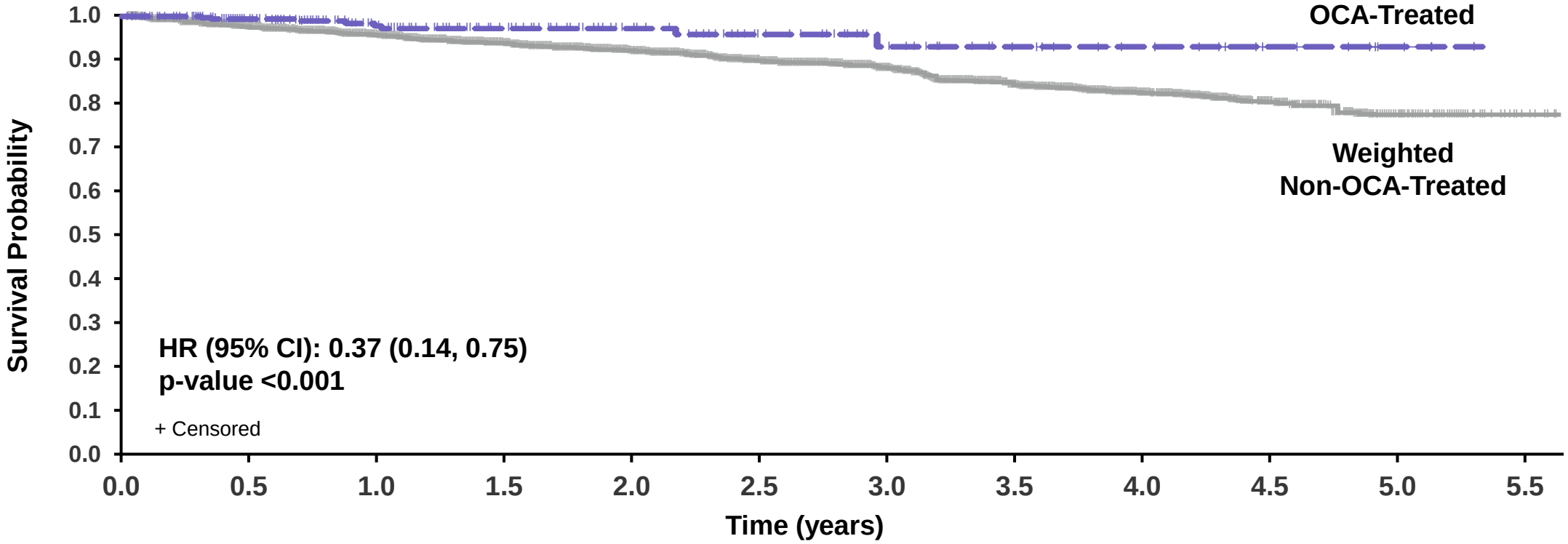
*Applicable to control periods identified by laboratory test abnormality that fulfilled UDCA discontinuation criteria; Table 12, FDA Briefing Document
1. FDA's ITT analyses of death and liver-transplant (2-point composite versus Applicant's 3-point composite of death, liver transplantation, and hepatic decompensation events)

Inclusion of Hospitalization for Hepatic Decompensation

FDA COMMENTS	INTERCEPT POSITION
• *Misclassification of the hepatic decompensation outcome presents a major threat to the validity of the results*	• **Hospitalization for hepatic decompensation well-captured in payer-reviewed claims**, with high positive predictive value >80-90% in most published literature[a]
• *FDA's quantitative bias analysis (QBA) identified plausible scenarios whereby differential outcome misclassification might explain a substantial portion of the treatment benefit observed*	• FDA QBA presents unlikely hypothetical scenario • **No clinical rationale that hospitalization events are differentially captured** between OCA and Controls

a. Bengtsson et al., *Scand J Gastroenterol* 2020;55(10); Goldberg et al., *Pharmacoepidemiol Drug Saf* 2012;21(7); Hayward et al. *BMJ Open Gastroenterol* 2020;7(1); Kanwal et al. *Gastroenterology* 143(1); Lapointe-Shaw et al. *Plos One* 2018; 13(8); Mapakshi et al., *Clin Gastroenterol Hepatol* 2018, 16(10)

Study 405: Primary Analysis Demonstrated Event-free Survival Benefit

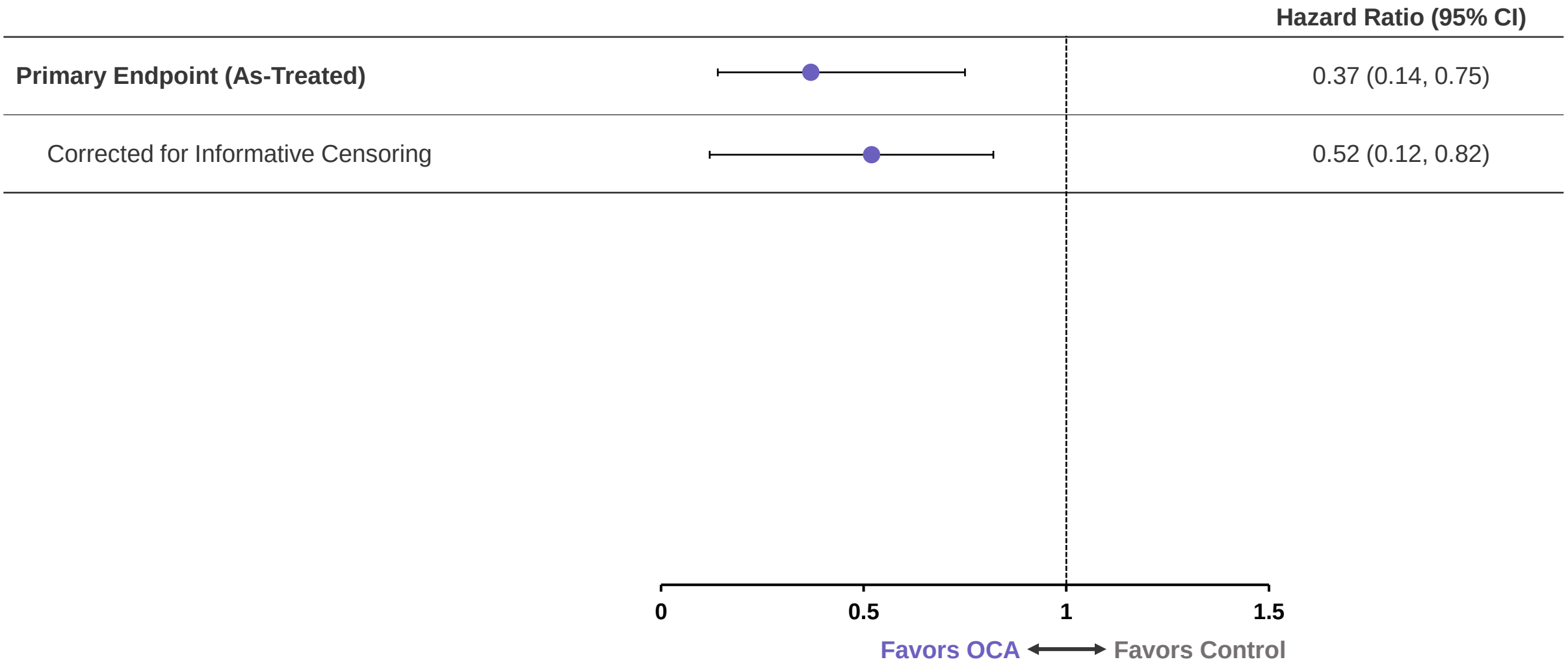


Non-OCA-treated	405	300	226	187	149	113	86	62	39	23	10	1
OCA	403	269	165	108	78	52	31	20	15	9	4	0

OCA treatment was associated with 63% decreased risk of hepatic decompensation, liver transplant, or death

Sensitivity Analyses Show Robustness of Study 405 Results

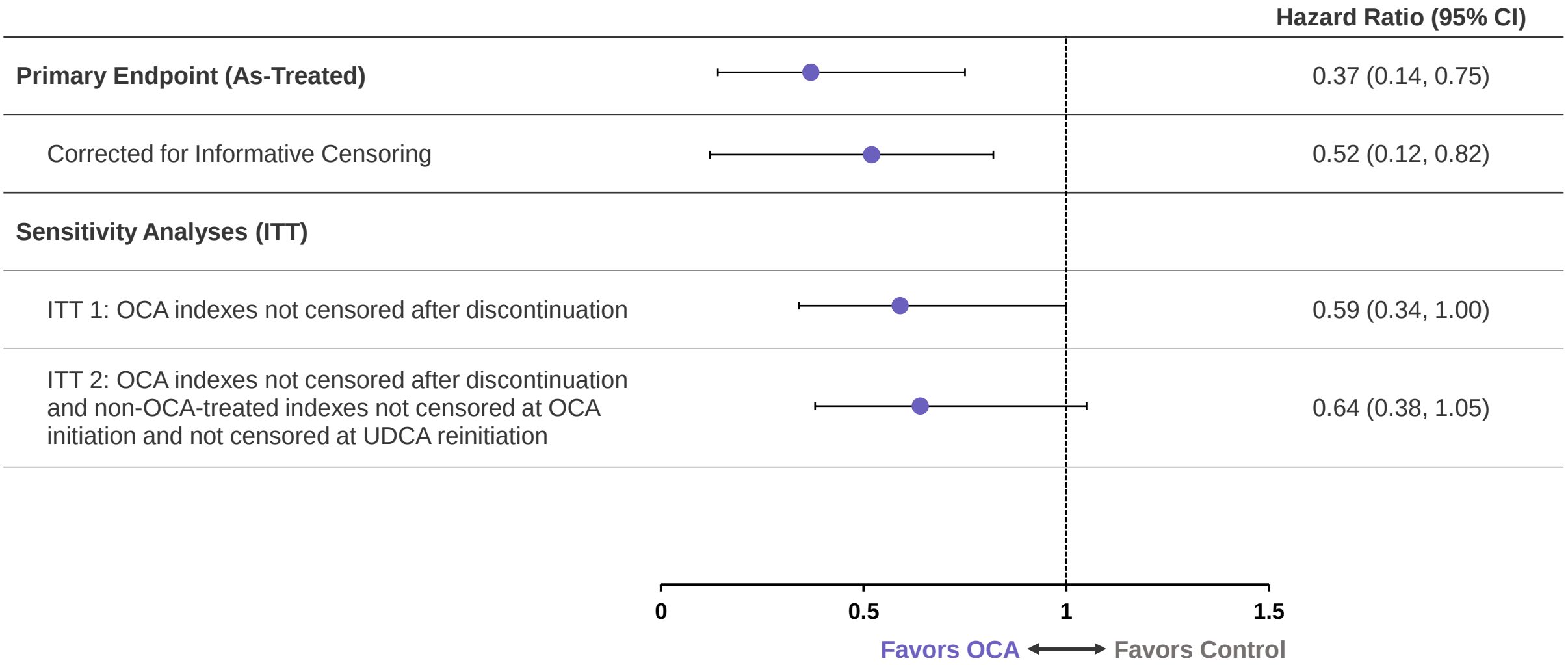
Time to Hospitalization for Hepatic Decompensation, Liver Transplant, or Death



OCA N=403; Control N=405.4 (Weighted)

Sensitivity Analyses Show Robustness of Study 405 Results

Time to Hospitalization for Hepatic Decompensation, Liver Transplant, or Death

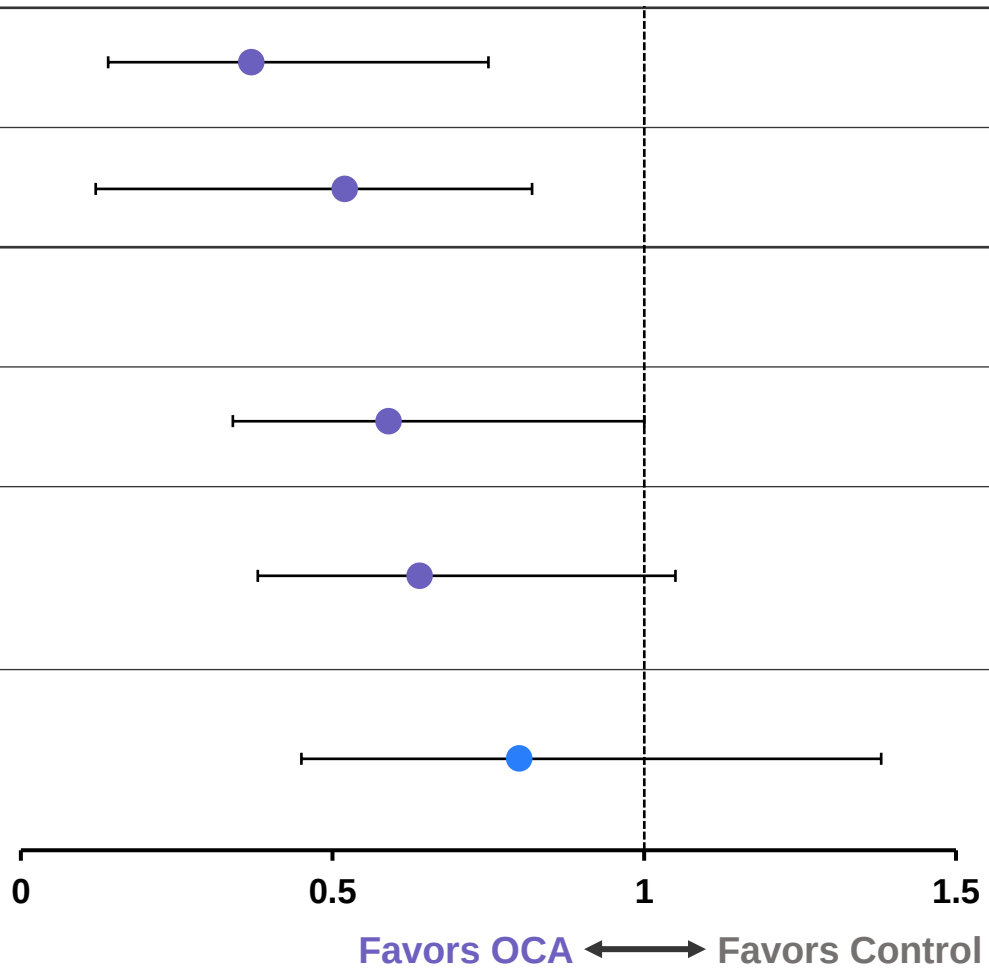


OCA N=403; Control N=405.4 (Weighted)

Sensitivity Analyses Show Robustness of Study 405 Results

Time to Hospitalization for Hepatic Decompensation, Liver Transplant, or Death

	Hazard Ratio (95% CI)
Primary Endpoint (As-Treated)	0.37 (0.14, 0.75)
Corrected for Informative Censoring	0.52 (0.12, 0.82)
Sensitivity Analyses (ITT)	
ITT 1: OCA indexes not censored after discontinuation	0.59 (0.34, 1.00)
ITT 2: OCA indexes not censored after discontinuation and non-OCA-treated indexes not censored at OCA initiation and not censored at UDCA reinitiation	0.64 (0.38, 1.05)
FDA ITT: No censoring for treatment switch, start of fibrates, or end to closed claims: **liver transplant and death only, excludes hepatic decompensation**	0.80 (0.45, 1.38)



OCA N=403; Control N=405.4 (Weighted)

CC-100

Outline of Topics

Study 405

Other Real-World Evidence

- Study 301 LTSE EC
- Study 302 EC
- RECAPITULATE + Global PBC

Summary

Other RWE of OCA Efficacy Uses Registry Data

	Study 301 EC
Lead Investigator	Global-PBC Study Team
Time Period Captured	Global-PBC: 2012–2016 UK-PBC: 2008–2020
Patients Captured	
OCA	OCA patients in Study 301 LTSE: 209
Non-OCA	Global-PBC: 1381 UK-PBC: 2135
Analytical Approach to Censoring	Censored at the end of observation period: no censoring for treatment changes
Endpoints	Global-PBC: Event-free survival, transplant-free survival UK-PBC: Transplant-free survival

Study 301 OCA arm similar to 2021 USPI followed up to 6 years

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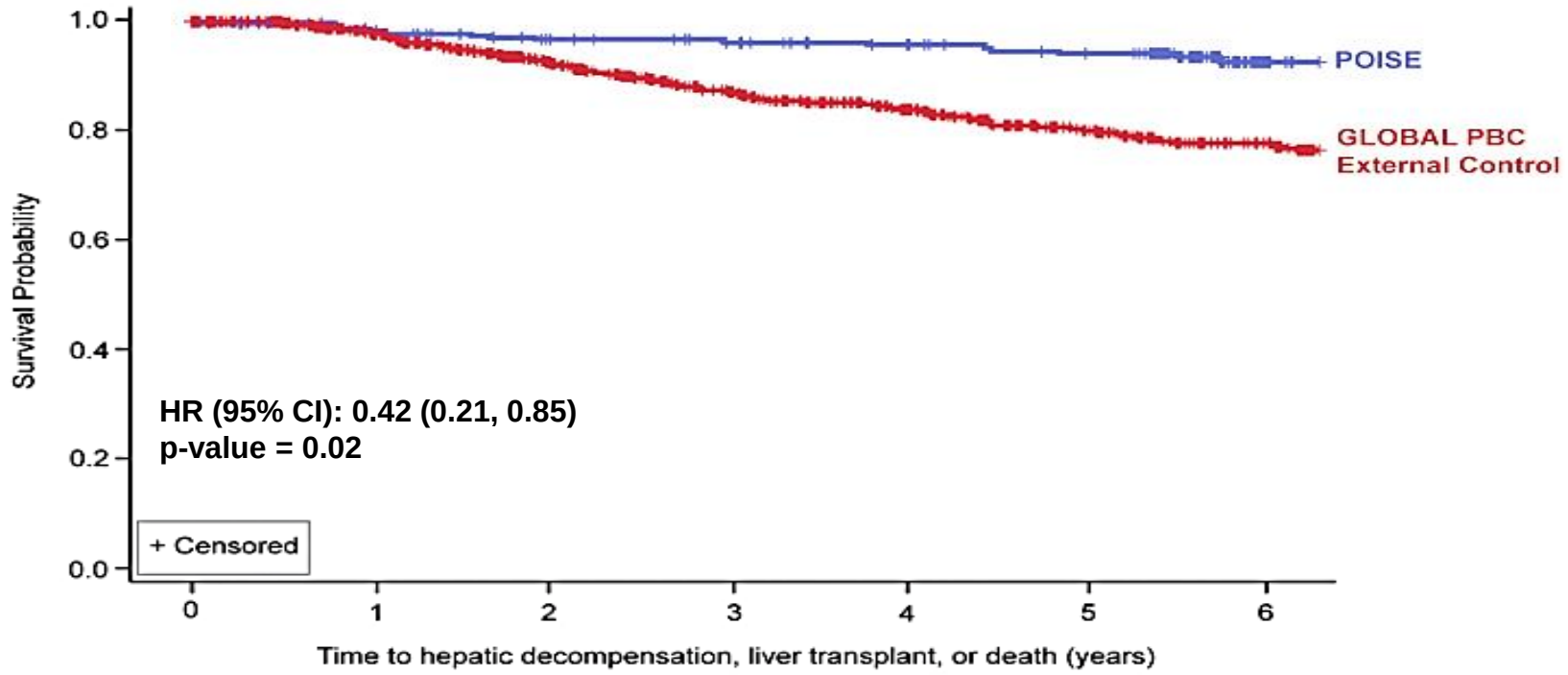
Conducted largely prior to commercial OCA availability

Peer-reviewed evidence

Murillo-Perez et al., *Gastroenterology* 2022;163(6)

Study 301 EC: Demonstrated OCA Benefit on Event-free Survival



	Study 301 N=209 n (%)	GLOBAL PBC N=1381 n (%)
Total number of events	16 (7.7)	212 (15.4)
Hepatic decompensation	12 (5.7)	126 (9.1)
Liver transplantation	1 (0.5)	23 (1.7)
Death	3 (1.4)	63 (4.6)

OCA associated with 58% decreased risk of hepatic decompensation, liver transplant or death

Murillo-Perez et al., *Gastroenterology* 2022;163(6)

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Other RWE of OCA Efficacy Uses Registry Data

	Study 301 EC	Study 302 EC
Lead Investigator	Global-PBC Study Team	Intercept Pharmaceuticals
Time Period Captured	Global-PBC: 2012–2016 UK-PBC: 2008–2020	2014–2021
Patients Captured		
OCA	OCA patients in Study 301 LTSE: 209	OCA patients in Study 302: 168
Non-OCA	Global-PBC: 1381 UK-PBC: 2135	Komodo: 1051
Analytical Approach to Censoring	Censored at the end of observation period: no censoring for treatment changes	OCA: 90 days after d/c of OCA Non-OCA: initiation of OCA, or database disenrollment
Endpoints	Global-PBC: Event-free survival, transplant-free survival UK-PBC: Transplant-free survival	Event-free survival

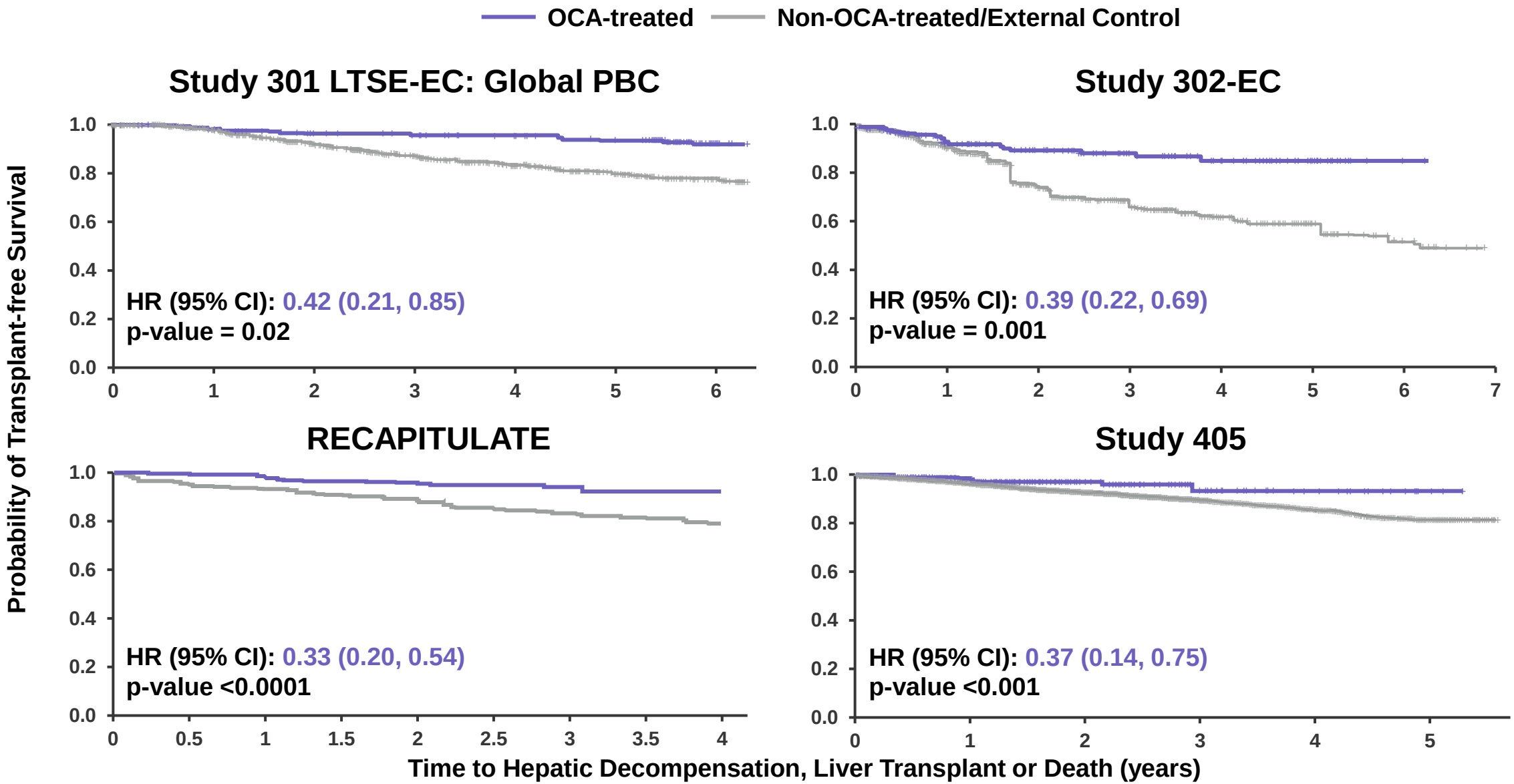
Murillo-Perez et al., *Gastroenterology* 2022;163(6)

Other RWE of OCA Efficacy Uses Registry Data

	Study 301 EC	Study 302 EC	RECAPITULATE + Global PBC
Lead Investigator	Global-PBC Study Team	Intercept Pharmaceuticals	RECAPITULATE and Global-PBC Study Teams
Time Period Captured	Global-PBC: 2012–2016 UK-PBC: 2008–2020	2014–2021	RECAPITULATE: starting in 2016 Global-PBC: 2000–2016
Patients Captured			
OCA	OCA patients in Study 301 LTSE: 209	OCA patients in Study 302: 168	RECAPITULATE: 437
Non-OCA	Global-PBC: 1381 UK-PBC: 2135	Komodo: 1051	Global-PBC: 831
Analytical Approach to Censoring	Censored at the end of observation period: no censoring for treatment changes	OCA: 90 days after d/c of OCA Non-OCA: initiation of OCA, or database disenrollment	Both ITT and As-treated conducted
Endpoints	Global-PBC: Event-free survival, transplant-free survival UK-PBC: Transplant-free survival	Event-free survival	Event-free survival Transplant-free survival

Murillo-Perez et al., *Gastroenterology* 2022;163(6); Vespasiani-Gentilucci PBC Day 2023; Milan Italy

Consistent Benefit in Event-free Survival Across Study 405 and Other RWE Studies



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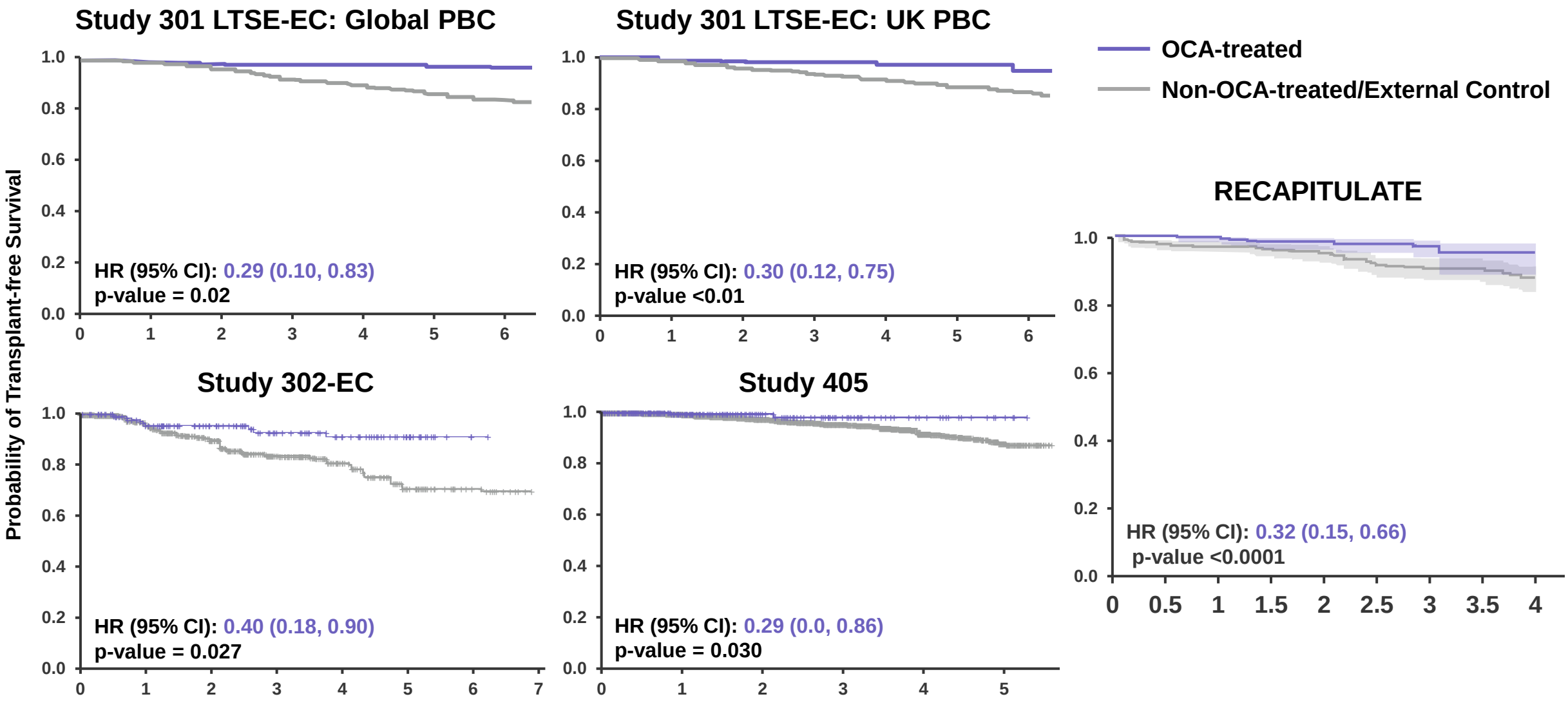
Consistent Benefit in Transplant-free Survival Across Study 405 and Other RWE Studies



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Outline of Topics

Study 405

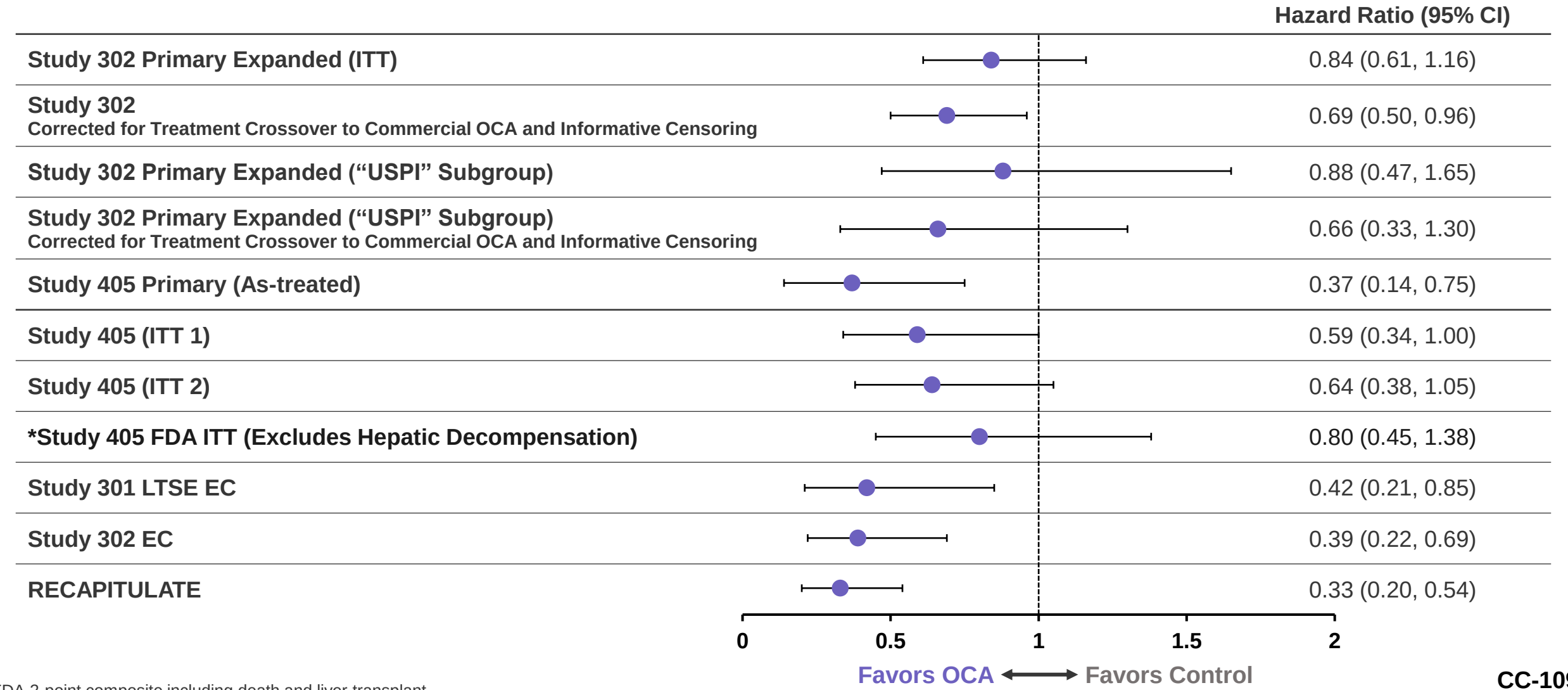
Other Real-World Evidence

- Study 301 LTSE EC
- Study 302 EC
- RECAPITULATE + Global PBC

Summary

Totality of Evidence Shows Consistent Benefit

Hepatic Decompensation, Liver Transplant or Death



*FDA 2-point composite including death and liver transplant

Clinical Perspective

David Jones, OBE

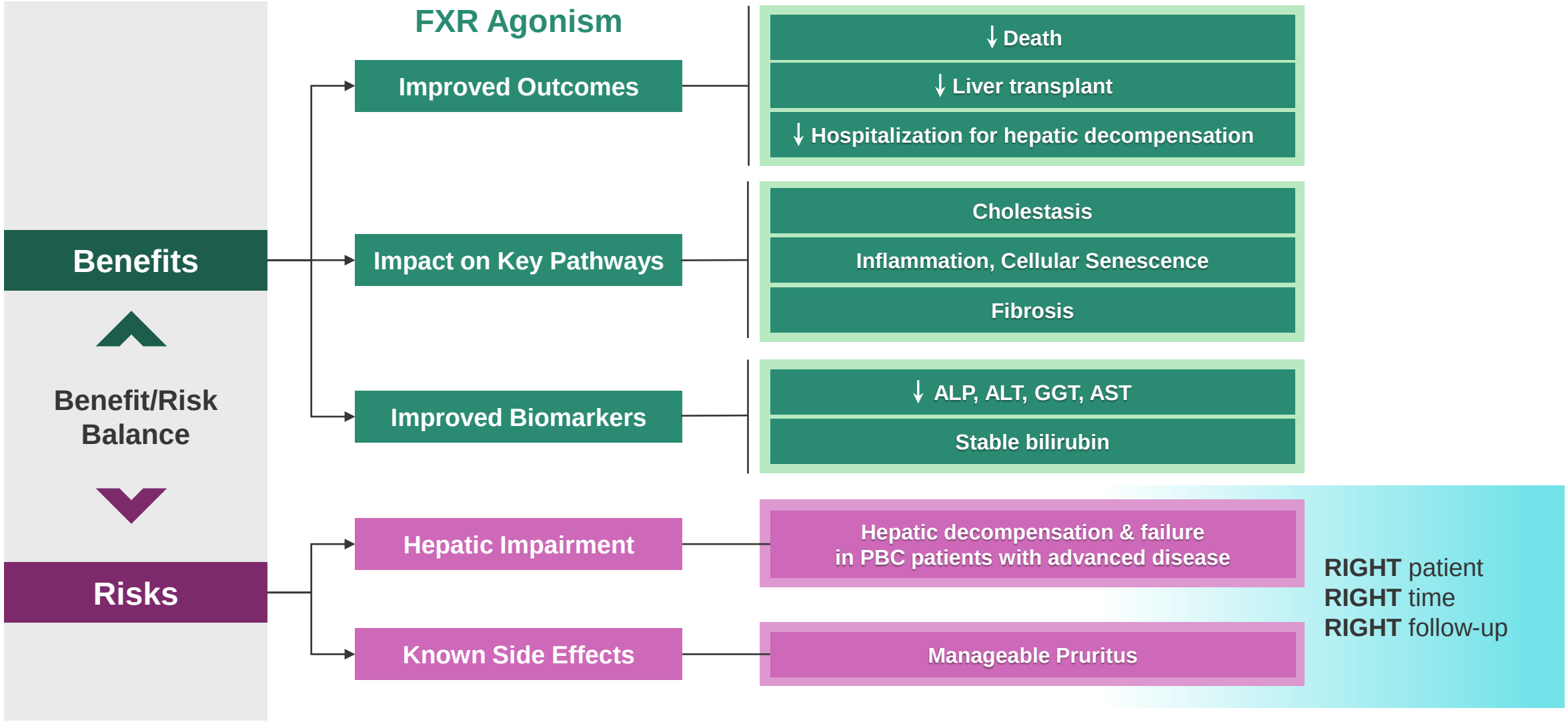
Chair of the PBC Foundation Medical Advisory Board

Professor of Liver Immunology
Faculty of Medical Science at Newcastle University

PBC is Now a Different Disease But Unmet Need Remains

- Progressive evolution in PBC natural history over time with UDCA and OCA
- High-risk patients who are early in disease benefit the most

Benefit/Risk Profile for OCA is Positive in 2021 USPI Population



CC-112

Why Do We Need OCA for Patients with PBC?

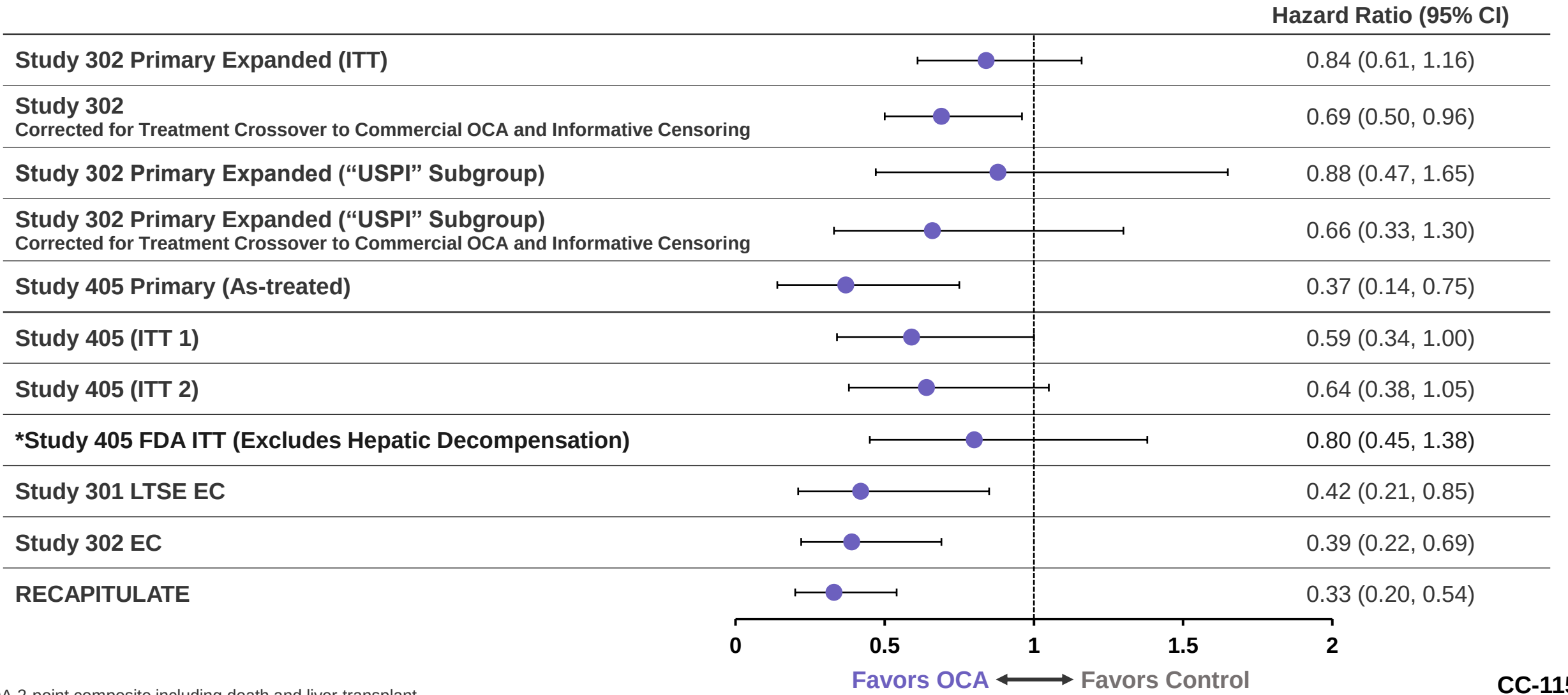
- Mechanisms of action through FXR modify the critical disease process
  - Only approved FXR agonist
  - Distinct yet complementary mechanism of action to UDCA and PPAR agonists
- Safe and effective part of treatment armamentarium
- More than 8 years of world-wide clinical practice experience with OCA
- Right patient, right time, right follow-up

Conclusions

Sangeeta Sawhney, MD

Question 3: Totality of Evidence Verifies Benefit

Hepatic Decompensation, Liver Transplant or Death



*FDA 2-point composite including death and liver transplant

Intercept Will Further Confirm Benefit

- Proposed Study 407 complements existing RWE and builds on Study 405
  - In depth capture of clinical information
- Utilizes third source of real-world data
  - ✓ Claims
  - ✓ Registry
  - ➢ Electronic Health Records (EHR)
- Evaluating data sources as “fit for use”

Question 4: Benefit Outweighs Risk in the USPI-labeled Population for Patients Living with PBC

BENEFIT

Study 302: Adjusting for Bias Shows Benefit

Consistent Benefit Across RWE

- Study 405
- Study 301 EC: Global PBC
- Study 301 EC: UK PBC
- Study 302 EC
- RECAPITULATE

RISK

Clinicians Know How to Use OCA in PBC

- "USPI" Subgroup analysis of death and liver transplants, is inconsistent and clinically implausible
- Labeling reflects appropriate patient and appropriate follow-up
- Specialty prescribing and pre-authorization procedures

Obeticholic Acid (OCA) for the Treatment of Patients with Primary Biliary Cholangitis (PBC) in Combination with Ursodeoxycholic Acid (UDCA)

NDA 207999

Gastrointestinal Drugs Advisory Committee
September 13, 2024

CC-118

Sponsor Backup Slides Shown

Study 405: Definition of Hospitalization for Hepatic Decompensation

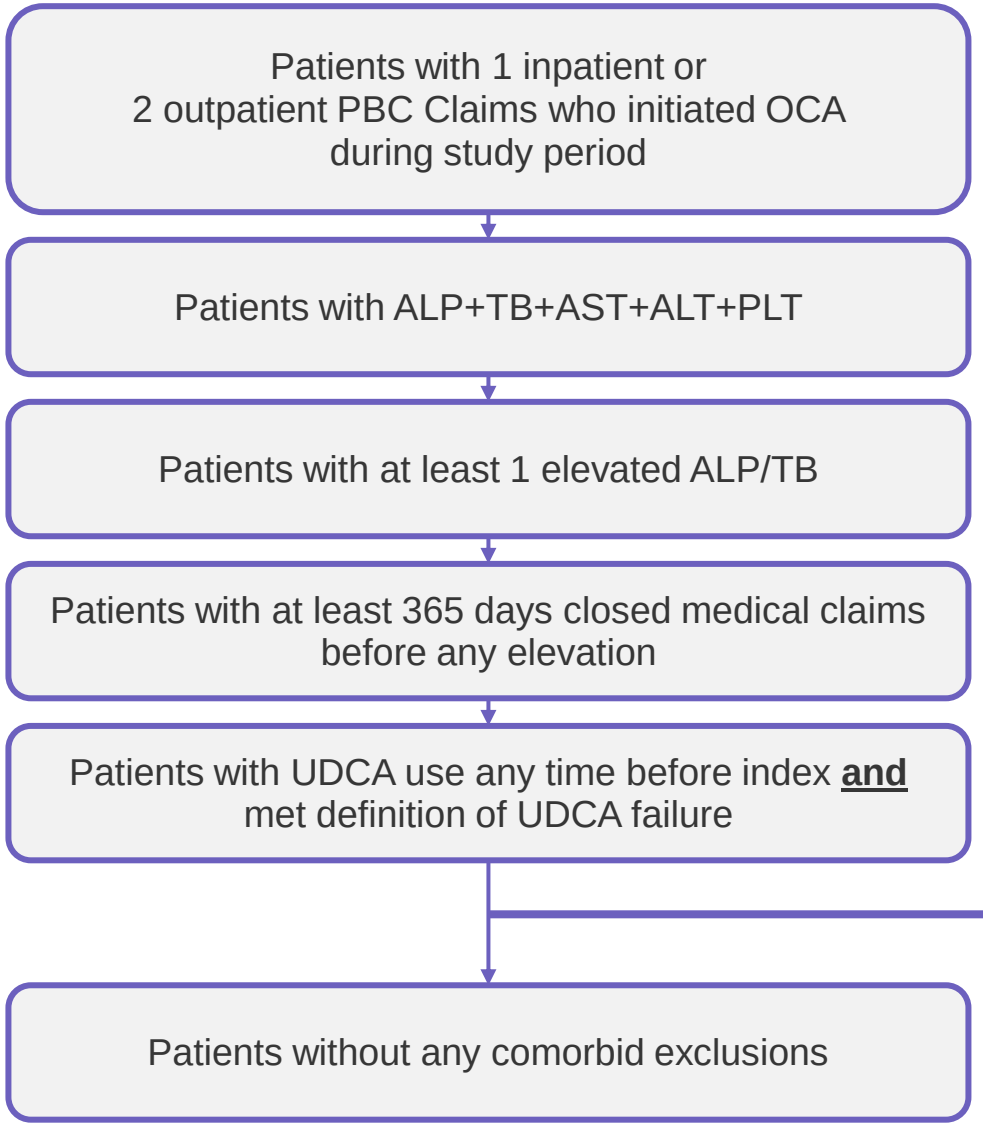
The definition for hospitalization for hepatic decompensation included inpatient admission codes that appeared in any position, and included:

- Variceal bleed: ICD-10: I85.01, I85.11, I86.4 and ICD-9: 456.1, 456.21, 456.8
- Ascites: ICD-10: K70.11, K70.31, K71.51, R18.0, R18.8, J94.8, K65.2 and ICD-9: 567.23, 571.2, 789.51, 789.59, 511.8, 567.23
- Hepatic encephalopathy: ICD-10: B15.0, B16.0, B16.2, B17.11, B19.0, B19.11, B19.21, G93.40, K70.41, K72.11, K72.90, K72.91 and ICD-9: 348.30, 572.2, 070.0, 070.20, 070.41, 070.6, 070.71

Study 405: Region and Insurance

	Unweighted		Weighted	
	Non OCA-treated N=11246 n (%)	OCA-treated N=403 n (%)	Non OCA-treated N=405.37 n (%)	OCA-treated N=403 n (%)
Region				
Northeast	2490 (22.1)	82 (20.3)	84.3 (20.8)	82 (20.3)
Midwest	1075 (9.6)	38 (9.4)	38.3 (9.4)	38 (9.4)
West	2735 (24.3)	97 (24.1)	105.90 (26.1)	97 (24.1)
South	4893 (43.5)	186 (46.2)	175.35 (43.3)	186 (46.2)
Territory	13 (0.1)	0	0.40 (0.1)	0
Insurance Type				
Commercial	5015 (44.6)	194 (48.1)	195.5 (48.2)	194 (48.1)
Self-insured/Exchanges	1803 (16.0)	68.0 (16.9)	67.4 (16.6)	68.0 (16.9)
Medicare	2763 (24.6)	60.0 (14.9)	58.2 (14.4)	60.0 (14.9)
Medicaid	1524 (13.6)	73 (18.1)	75.9 (18.7)	73 (18.1)
Dual eligible	94 (0.8)	6 (1.5)	6.1 (1.5)	6 (1.5)
Other	47 (0.4)	2 (0.5)	2.2 (0.6)	2 (0.5)

Study 405: Patient Eligibility and Exclusions



Comorbidity Exclusion Similar to Study 301

- **Age <18 years at the index**
- **Hepatic decompensating events (e.g., Ascites, Hepatic encephalopathy, SBP, etc.)**
- **Other concomitant liver diseases (e.g., PSC, HCC, Hepatitis C, etc.)**
- **History of liver transplant**
- **Laboratory values indicative of hepatic decompensation or significant hepatobiliary injury (i.e., TB >3 mg/dL, ALP >10x ULN, ALT and/or AST >10x ULN)**
- **Other non-hepatic conditions (i.e., non-skin malignancy/melanoma, HIV, Fractures)**
- **Fibrate Use**

Quantitative Bias Analysis Shows Results are Robust

Assuming 5% Unmeasured Confounder Prevalence

Point Estimate = 0.37

Association btwn Confounder & Treatment →

Association btwn Confounder & Outcome ↓

OR(P_{Z1}/P_{Z0})	1	2	3	4	5	6	7	8	9	10
P_{Z1}	0.05	0.10	0.14	0.17	0.21	0.24	0.27	0.30	0.32	0.34
0.9	0.37	0.37	0.37	0.38	0.38	0.38	0.38	0.38	0.38	0.38
0.8	0.37	0.37	0.38	0.38	0.38	0.39	0.39	0.39	0.39	0.39
0.7	0.37	0.38	0.38	0.39	0.39	0.39	0.40	0.40	0.40	0.41
0.6	0.37	0.38	0.38	0.39	0.40	0.40	0.41	0.41	0.42	0.42
0.5	0.37	0.38	0.39	0.40	0.40	0.41	0.42	0.42	0.43	0.44
0.4	0.37	0.38	0.39	0.40	0.41	0.42	0.43	0.44	0.45	0.45
0.3	0.37	0.38	0.40	0.41	0.42	0.43	0.44	0.45	0.46	0.47
0.2	0.37	0.38	0.40	0.41	0.43	0.44	0.45	0.47	0.48	0.49
0.1	0.37	0.39	0.40	0.42	0.44	0.45	0.47	0.48	0.50	0.51

Assuming 50% Unmeasured Confounder Prevalence

Point Estimate = 0.37

Association btwn Confounder & Treatment →

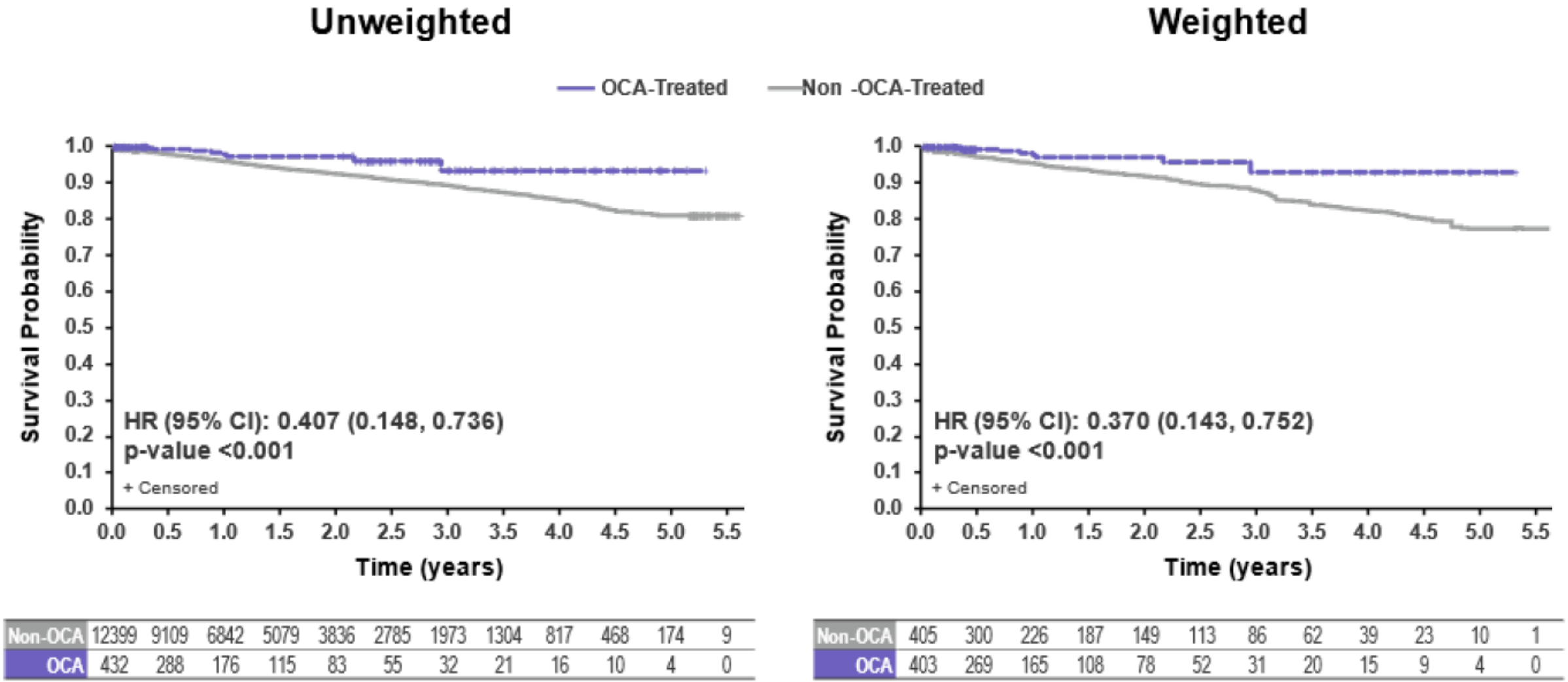
OR(P_{Z1}/P_{Z0})	1	2	3	4	5	6	7	8	9	10
P_{Z1}	0.50	0.67	0.75	0.80	0.83	0.86	0.88	0.89	0.90	0.91
0.9	0.37	0.38	0.38	0.38	0.38	0.38	0.39	0.39	0.39	0.39
0.8	0.37	0.38	0.39	0.40	0.40	0.40	0.40	0.41	0.41	0.41
0.7	0.37	0.39	0.41	0.41	0.42	0.42	0.43	0.43	0.43	0.43
0.6	0.37	0.40	0.42	0.44	0.44	0.45	0.46	0.46	0.46	0.47
0.5	0.37	0.42	0.44	0.46	0.48	0.49	0.49	0.50	0.51	0.51
0.4	0.37	0.43	0.47	0.50	0.52	0.53	0.55	0.56	0.56	0.57
0.3	0.37	0.45	0.51	0.55	0.58	0.60	0.62	0.64	0.65	0.66
0.2	0.37	0.48	0.56	0.62	0.67	0.71	0.74	0.77	0.79	0.81
0.1	0.37	0.51	0.63	0.73	0.81	0.89	0.96	1.02	1.07	1.12

Resulting HR: <0.4 | 0.4 - <0.8 | 0.8 - <1.0 | ≥1.0

Only when an unmeasured confounder is >50% prevalence and is highly associated with treatment choice and outcome

P_{Z0}=prevalence of the confounder among the OCA-treated;
P_{Z1}=calculated prevalence of the confounder among the non-OCA-treated; SMR=standardized mortality/morbidity ratio

Figure 22: Study 405 – Time to First Occurrence of Hospitalization for Hepatic Decompensation, Liver Transplant, or Death (Unweighted and Weighted)



Non-OCA	12399	9109	6842	5079	3836	2785	1973	1304	817	468	174	9
OCA	432	288	176	115	83	55	32	21	16	10	4	0

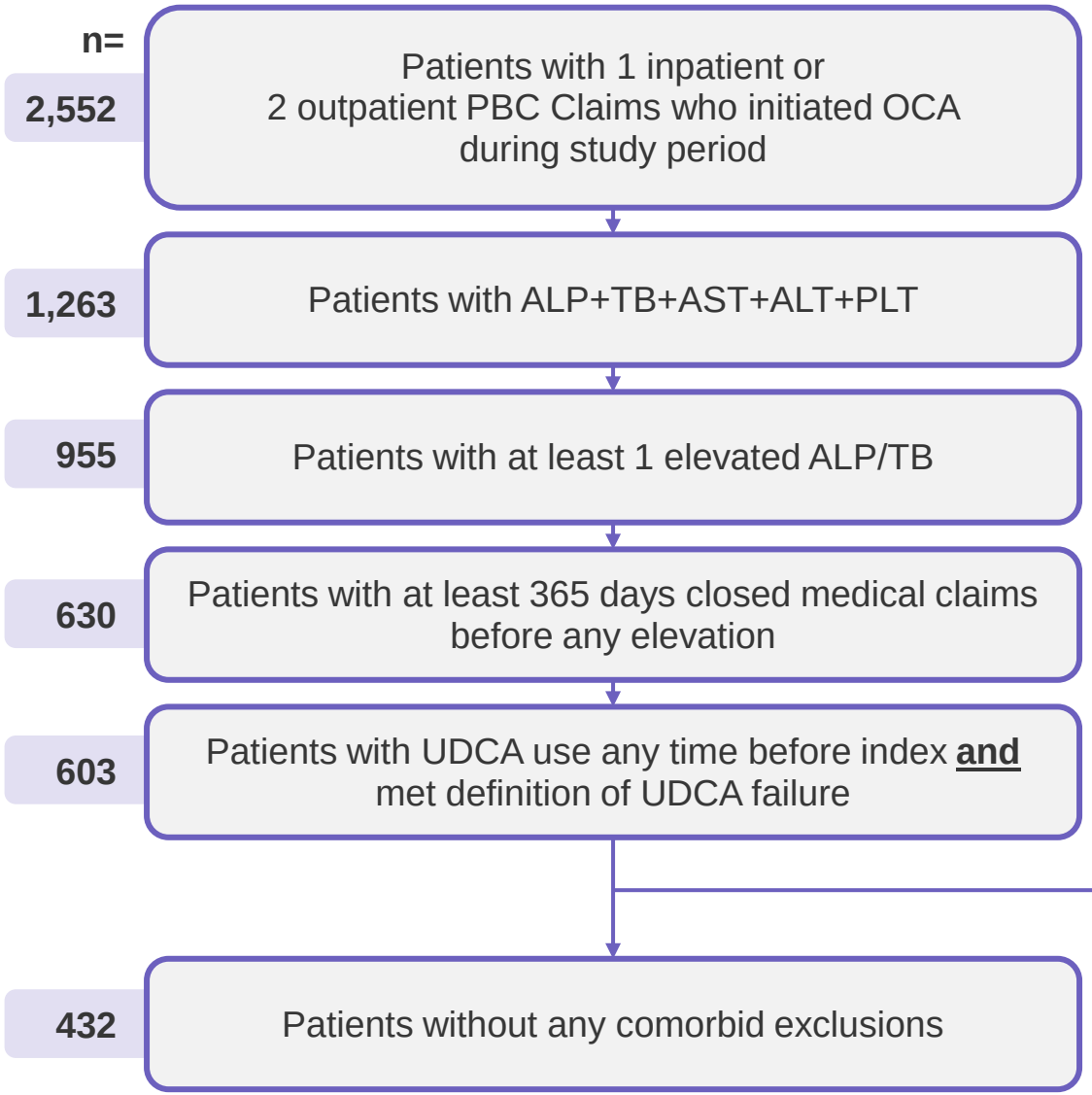
Non-OCA	405	300	226	187	149	113	86	62	39	23	10	1
OCA	403	269	165	108	78	52	31	20	15	9	4	0

Study 405: Exploratory Analysis (Hepatic Decompensation): Cumulative Incidence by Competing Risk Event (Liver Transplant or Death)

Treatment Group	Time (years)	Cumulative Incidence (%)	95% CI (%)
Non-OCA-treated	1	3.53	1.57–5.48
	2	5.76	3.02–8.50
	3	8.41	4.93–11.88
	4	11.96	5.96–17.95
	5	14.80	5.98–23.62
	6	14.80	5.98–23.62
OCA-treated	1	1.61	0–3.41
	2	2.20	0.14–4.26
	3	5.02	0–10.52
	4	5.02	0–10.52
	5	5.02	0–10.52
	6	5.02	0–10.52

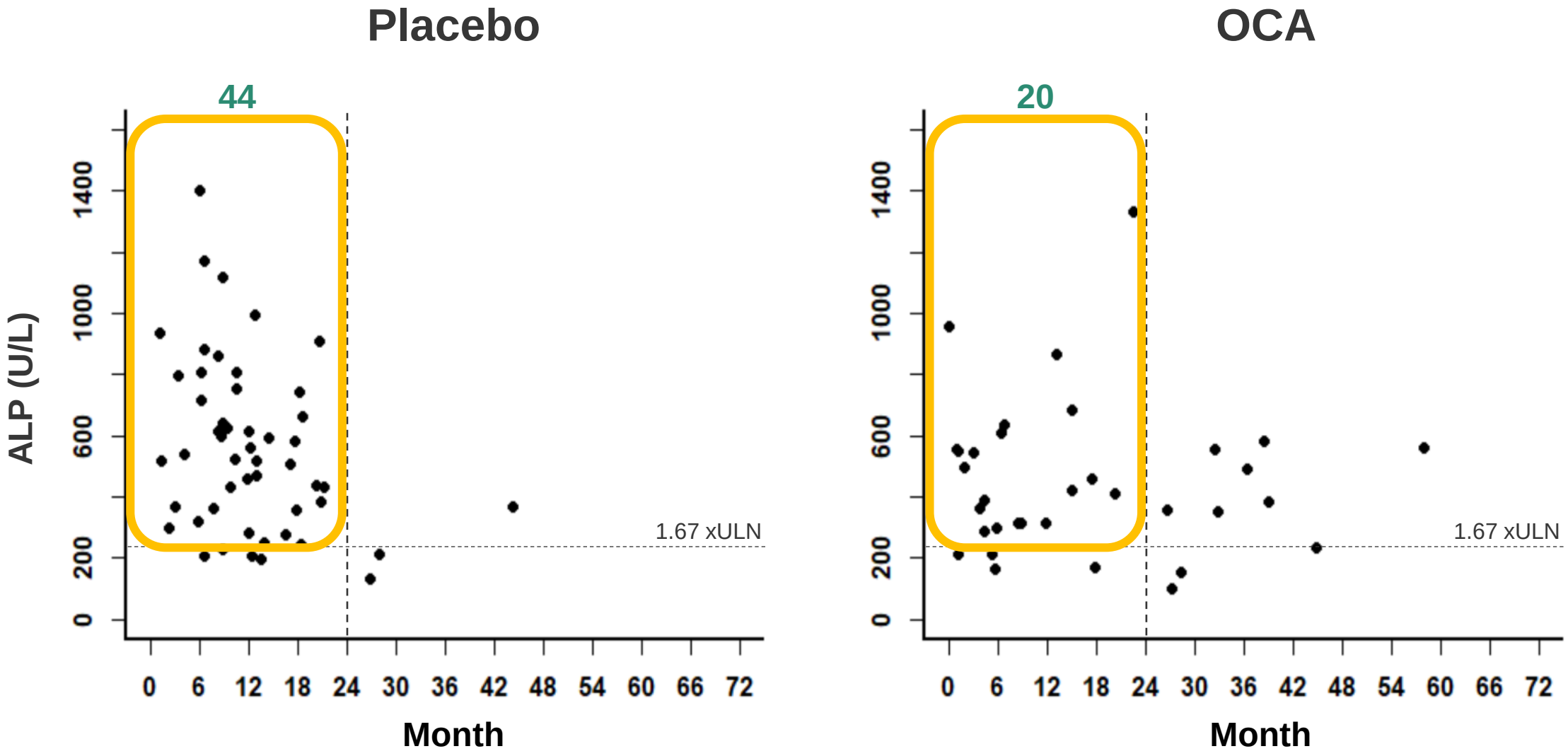
In this analysis, liver transplantation and death were treated as competing events using a Fine-Gray proportional subdistribution hazards model (Fine JP, Gray RJ. *J Am Stat Assoc*. 1999;94:496-509). There were 179 hepatic-decompensation patients among 4174 distinct patients in the non-OCA-treated group and 6 hepatic-decompensated patients among 403 distinct patients in the OCA-treated group. The hazard ratio (95% CI) was 0.37 (0.09–0.85) (*P*=0.012)

Study 405: OCA-treated Patient Eligibility and Exclusions



- Age <18 years at the index
- Hepatic decompensating events (e.g., Ascites, Hepatic encephalopathy, SBP, etc.)
- Other concomitant liver diseases (e.g., PSC, HCC, Hepatitis C, etc.)
- History of liver transplant
- Laboratory values indicative of hepatic decompensation or significant hepatobiliary injury (i.e., TB >3 mg/dL, ALP >10x ULN, ALT and/or AST >10x ULN)
- Other non-hepatic conditions (i.e., non-skin malignancy/melanoma, HIV, Fractures)
- Fibrate Use

Study 302: Patients Discontinuing Study Visits or Starting Commercial Therapy in Placebo Arm Did so Early and Had High ALP



ALP ULN=135 U/L (Female) and 131 U/L (Male)

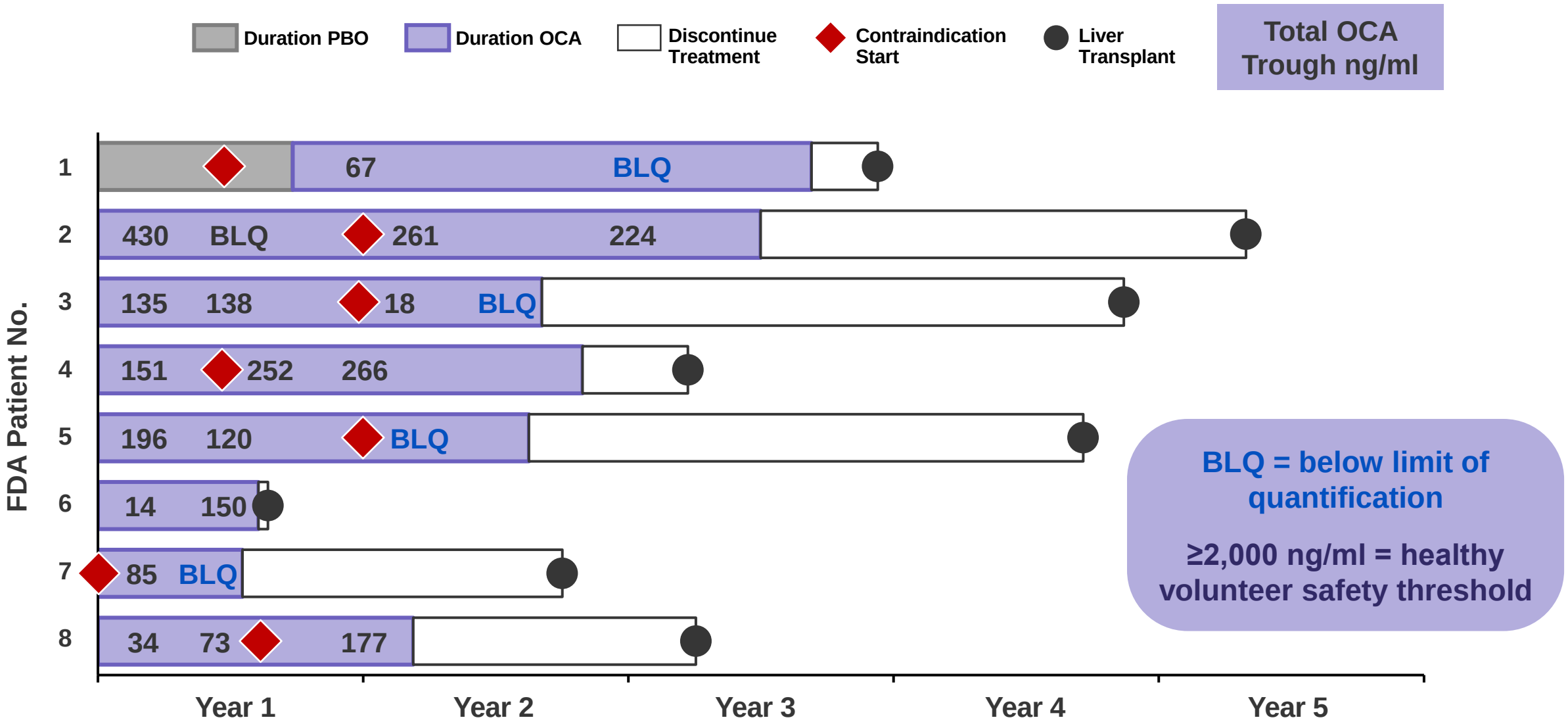
BU-858

Study 302: Incomplete Availability of Clinical Data at Baseline to Assess for Portal Hypertension

	Clinical Practice	Study 302
Transient elastography (FibroScan)	✓	Not available for all patients
Ultrasound for Dx of portal hypertension	✓	Splenomegaly not systematically recorded in CRF
Platelet Count (ie, thrombocytopenia)	✓	✓
Endoscopy (eg, varices)	✓	Not available for all patients

CRF=case report form

Study 302 “USPI” Liver Transplants: Plasma Total OCA Levels



BU-1033