Intercept

Application for Accelerated Approval: Obeticholic Acid (OCA) for the Treatment of Adult Patients with Pre-cirrhotic Liver Fibrosis due to Nonalcoholic Steatohepatitis (NASH)

Gastrointestinal Drugs Advisory Committee

19 MAY 2023

CC-1

Intercept

Introduction

M. Michelle Berrey, MD, MPH
President of Research & Development,
Chief Medical Officer
Intercept Pharmaceuticals

CC-2

Agenda

Introduction	**M. Michelle Berrey, MD, MPH** President, Research & Development; Chief Medical Officer, Intercept Pharmaceuticals
Medical Need	**Kris Kowdley, MD, AGAF, FAASLD, FACG, FACP, FASG** Director, Liver Institute Northwest Professor of Medicine, Elson S. Floyd College of Medicine Washington State University, Seattle, WA
Non-Invasive Tests (NITs)	**Rohit Loomba, MD, MHSc** Director, NAFLD Research Center; Professor of Medicine, Vice Chief, Gastroenterology; Director, Hepatology, University of California at San Diego, San Diego, CA
Efficacy Results	**Thomas Capozza, MD, FACP** Executive Director, Clinical Research, Intercept Pharmaceuticals
OCA Safety	**Sangeeta Sawhney, MD** Vice President, Clinical Development, Intercept Pharmaceuticals
Clinical Perspective	**Arun Sanyal, MD** Chair of NIDDK NASH Clinical Research Network Steering Committee Professor of Medicine, VCU School of Medicine, Richmond, VA

CC-3

Additional Experts

Pierre Bedossa, MD, PhD	Professor of Pathology University of Paris Director of Liverpat
Jamie Dwyer, MD	Associate Dean for Clinical Research and Professor of Medicine University of Utah Health, Salt Lake City, UT
Darren McGuire, MD, MHSc	Jere H. Mitchell, M.D. Distinguished Chair in Cardiovascular Science Professor of Medicine University of Texas, Southwestern Medical Center, Dallas, TX
Paul Watkins, MD	Director of UNC Institute for Drug Safety Sciences Professor of Medicine University of North Carolina, Chapel Hill, Durham, NC

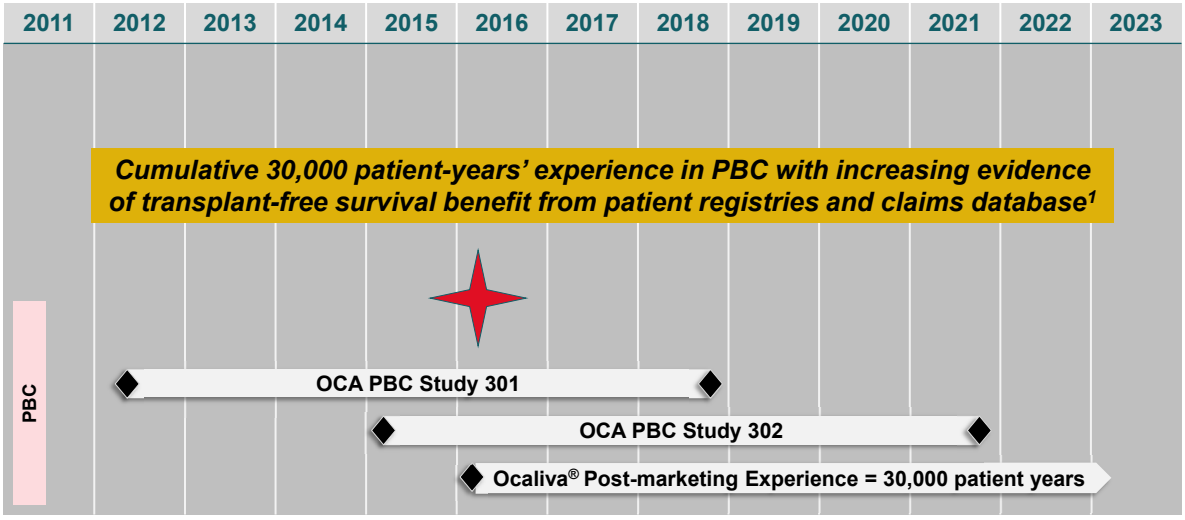
CC-4

Obeticholic Acid Approved in 2016 under Accelerated Approval for Primary Biliary Cholangitis

- Primary Biliary Cholangitis (PBC): rare cholestatic liver disease
- OCA is a synthetic bile acid, a potent FXR agonist, and an antifibrotic
- 2016: Accelerated Approval in US, Ocaliva® approved in 40+ countries
  - OCA 5 mg and 10 mg QD in non-cirrhotic and compensated cirrhosis
  - Initial indication included decompensated patients
- 2021: label updated to contraindicate patients with clinically significant portal hypertension or decompensation events; added monitoring and stopping rules
- Physician and patient education, enhanced pharmacovigilance program resulted in a decrease in number of hepatic safety events
- Prescribers limited to hepatologists/gastroenterologists through payers

CC-5

Robust Safety Database through PBC and NASH Programs



1. Fiorella et al, *Gastro* 2022

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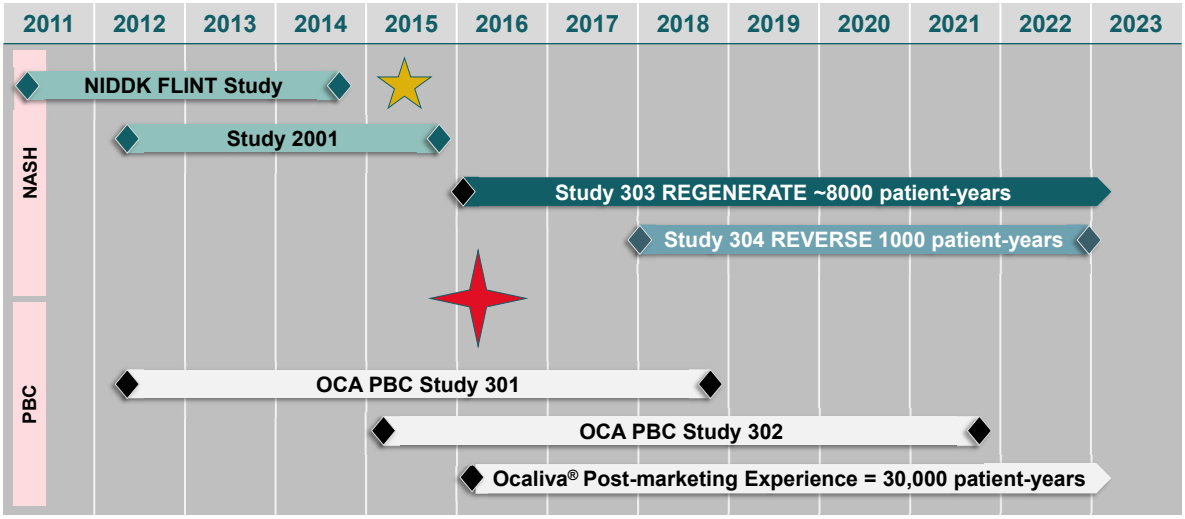
Robust Safety Database through PBC and NASH Programs



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OCA: Proposed NASH Indication, Dosing, and Management

Indication and Dosing

- Adult patients with **pre-cirrhotic liver fibrosis** due to NASH
- OCA 25 mg oral tablet, once daily
- Contraindicates patients with cirrhosis, portal hypertension, or signs of hepatic decompensation

Clinical Management

- Supervised and managed by a hepatologist or gastroenterologist
- Non-invasive tests (NITs) to identify and monitor patients, per AASLD guidance
- Stopping rules for safety or progression of disease

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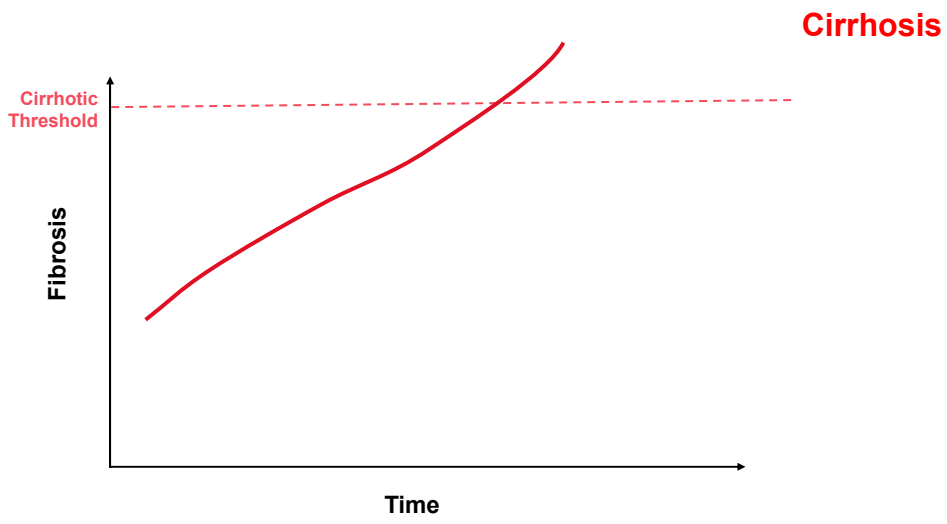
Goal of Therapy is To Prevent Progression to Cirrhosis



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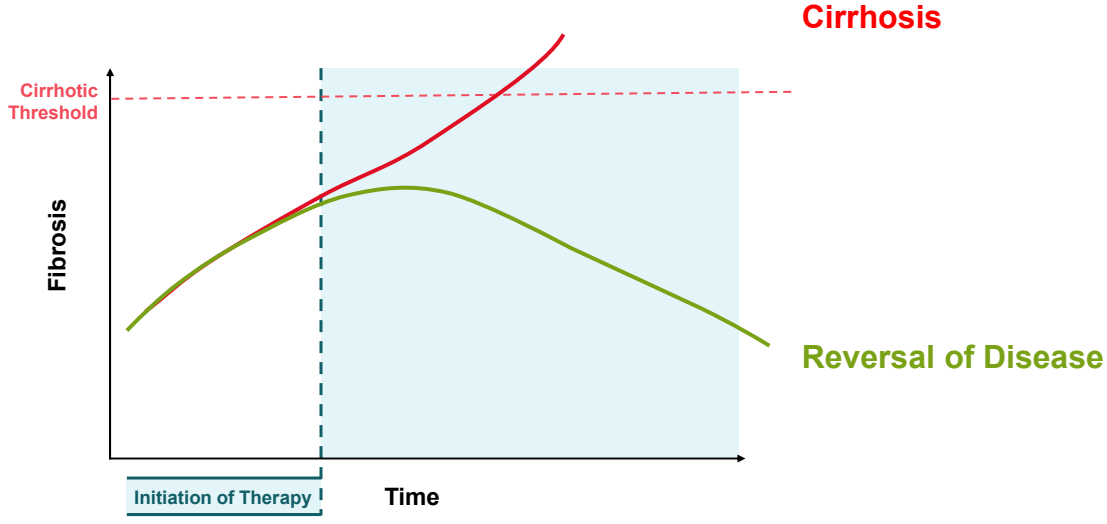
Goal of Therapy is To Prevent Progression to Cirrhosis



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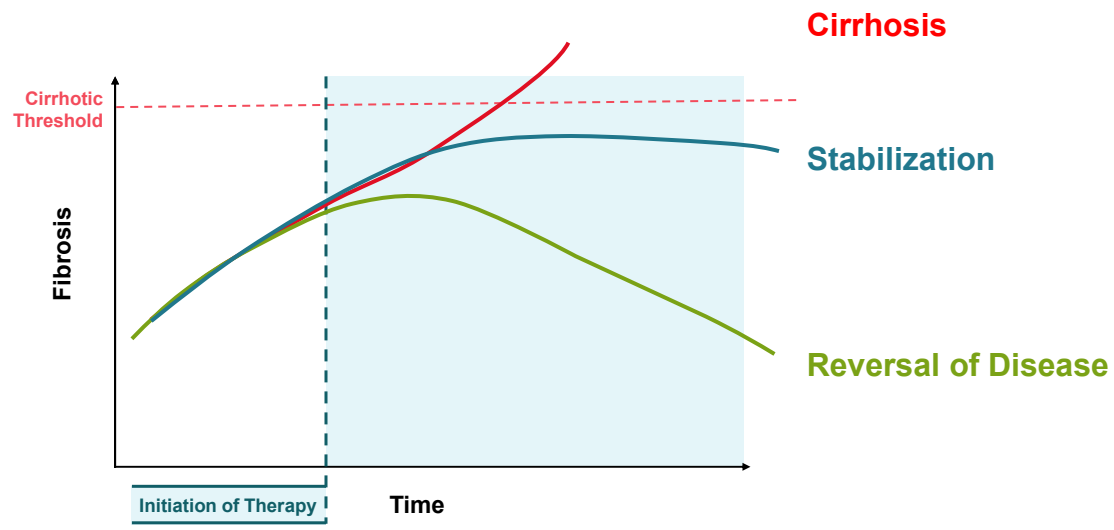
Goal of Therapy is To Prevent Progression to Cirrhosis



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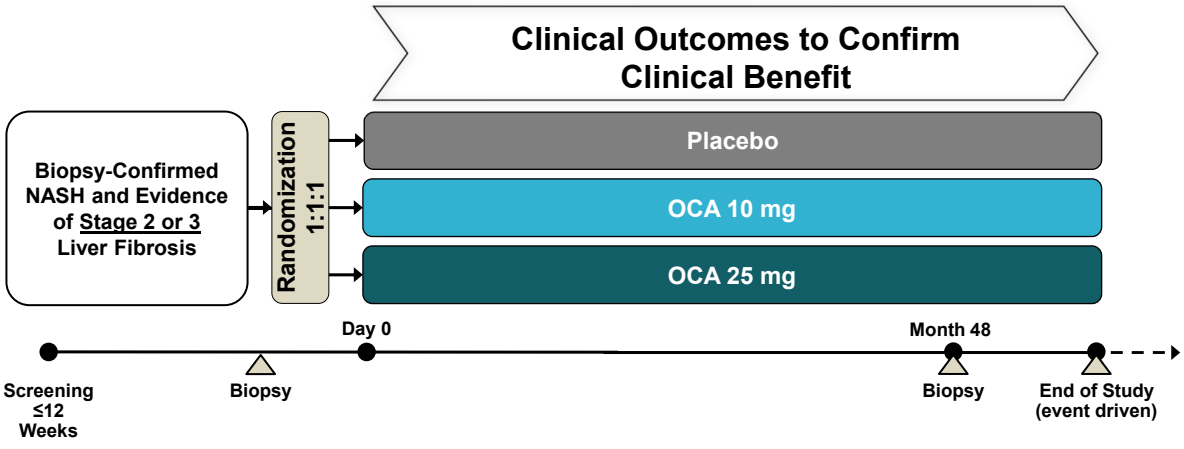
Study 303: Ongoing, Randomized, Double-Blind, Long-Term Placebo-Controlled Study (N=2477)



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Study 303: Composite Endpoint (End of Study)

- Time to first occurrence of adjudicated events:
  - Death (all-cause)
  - MELD score ≥15
  - Liver transplant
  - Hospitalization for:
    - Variceal bleed
    - Hepatic encephalopathy
    - Spontaneous bacterial peritonitis
- Ascites requiring medical intervention
- **Progression to cirrhosis**
  - **Histological or NIT evidence of progression to cirrhosis**

MELD=Model of end stage liver disease

CC-13

Noncirrhotic NASH With Liver Fibrosis
Draft FDA Guidance December 2018

- ***"Fibrosis is considered the strongest predictor*** *of adverse clinical outcomes, including liver-related death."*
- *"The ultimate goal of NASH treatment is to* ***slow the progress of, halt, or reverse disease progression*** *and improve clinical outcomes."*
- *"Because of the slow progression of NASH and the time required to conduct a trial that would evaluate clinical endpoints such as progression to cirrhosis or survival, the FDA recommends sponsors consider* ***liver histological improvements as endpoints reasonably likely to predict clinical benefit*** *to support accelerated approval."*

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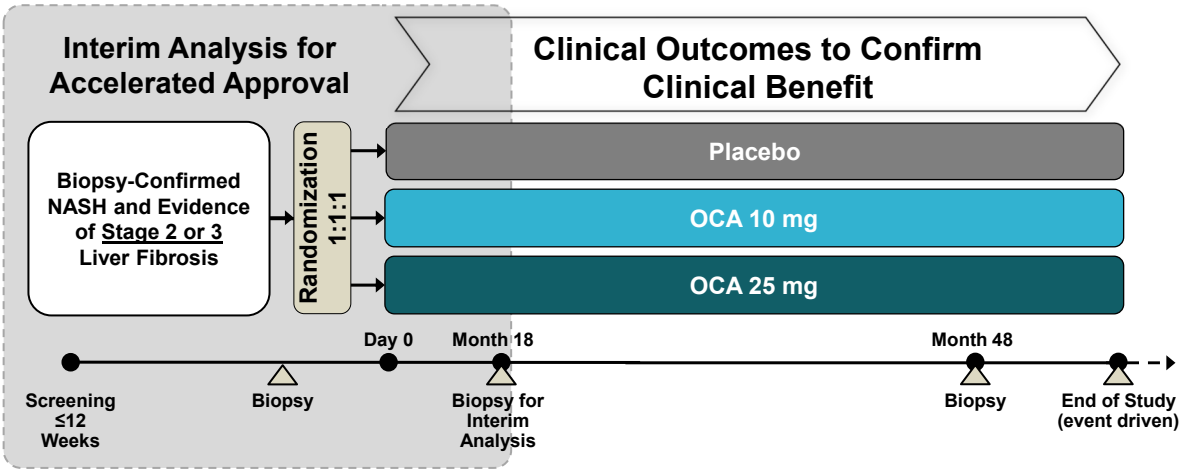
Study 303: Ongoing, Randomized, Double-Blind, Long-Term Placebo-Controlled Study



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FDA Agreement: One of Two Primary Endpoints Required to Achieve Study Success

Fibrosis Primary

- Improvement ≥1 stage fibrosis and no worsening of NASH
  - No worsening of NASH: required no worsening of ANY of the NAS parameters
    1. Steatosis
    2. Lobular inflammation
    3. Hepatocellular Ballooning

OR

Steatohepatitis Primary

- Resolution of NASH and no worsening of fibrosis
  - NASH resolution based on scoring of:
    1. Hepatocellular Ballooning=0
    2. Lobular inflammation=0-1

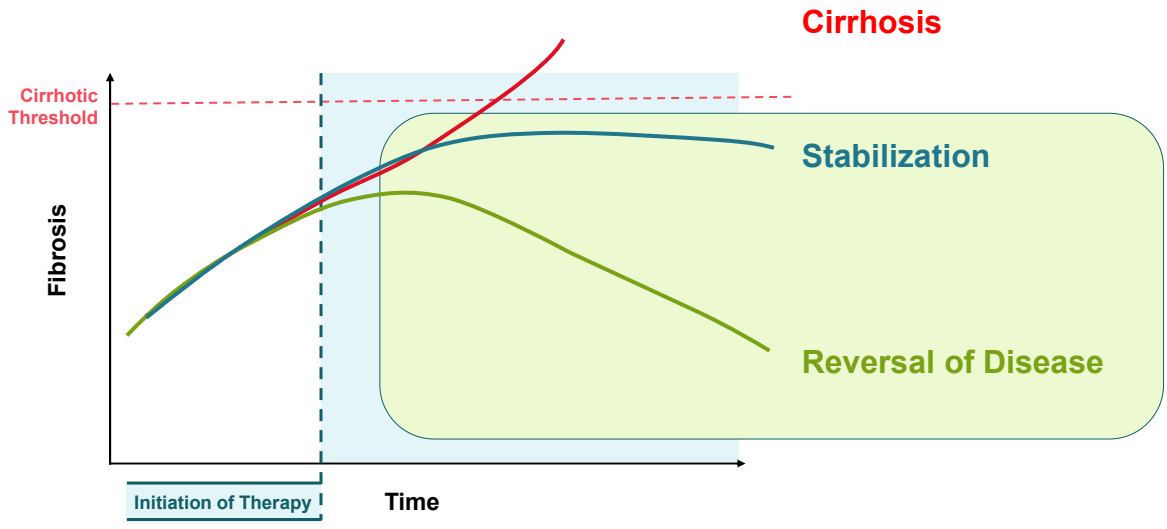
CC-16

OCA 25 mg Effect Size is Clinically Meaningful

- Statistical significance can be discussed only for pre-specified ITT_old analysis population (n=931); confirmed with re-read by consensus methodology
  - *FDA references an 8.6% treatment effect from the ITT_histology population (N=1607)*
- 12.8% treatment effect on regulatory fibrosis endpoint underestimates benefit
  - Requires a full stage reversal of fibrosis without worsening of NASH within 18 months
  - Excludes patients able to halt or stabilize disease progression on histology
    - Non-invasive tests (NITs) show improvements in hepatocellular injury in OCA patients without a full stage change in fibrosis

CC-17

Goal of Therapy is To Prevent Progression to Cirrhosis



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Hepatic Safety Can Be Managed by Specialists

- Cases of liver injury have been observed in the first 12 months of therapy, in patients with cirrhosis, and are reversible with prompt discontinuation
  - Two cases of irreversible liver injury will be reviewed; these two are the basis of the FDA's "18-fold higher" than is acceptable for hepatocellular injury. Both likely would have been avoided with implementation of proposed mitigation plans
- Intercept has successfully implemented contraindications and increased monitoring paradigms in Study 303 and in post-marketing for PBC
- Gastroenterologists and Hepatologists have the expertise to monitor and manage disease progression and potential drug-induced liver injury (DILI)

CC-19

Appropriate Patients Can Be Identified & Managed Safely

- Patients can be identified for treatment using NITs according to multiple physician society guidelines
- Liver biopsies are not required to monitor for disease progression or DILI
- The proposed schedule of visits following initiation of OCA would include Month 1, every 3 months for the first 12 months of therapy, and every 6 months thereafter
- Stopping rules mandated for any acute illness, hospitalization, excursion of liver lab values, or progression of disease by NITs or clinical signs/symptoms, as has been successfully implemented in PBC

CC-20

OCA: Favorable Benefit-Risk for Accelerated Approval

1. Pre-cirrhotic fibrosis due to NASH has High Unmet Need	▪ Serious, progressive and life-threatening disease ▪ No FDA-approved therapy ▪ Can be diagnosed and monitored with NITs
2. OCA is Anti-Fibrotic	▪ Clinically meaningful dose-dependent anti-fibrotic benefit ▪ Confirmed by two independent reading methodologies ▪ Regulatory endpoint underestimates benefit
3. Fibrosis Predicts Outcomes	▪ Single strongest predictor of liver-specific & all-cause mortality ▪ Halting/reversing fibrosis is reasonably likely to reduce events ▪ Study 303 fully enrolled, progressing toward clinical outcomes
4. Safety Profile is Monitorable and Manageable	▪ Well-characterized, supports chronic dosing ▪ US PI guides on monitoring with routine tests ▪ Managed by hepatologists and gastroenterologists

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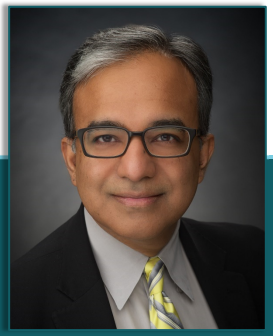
Medical Need



Kris Kowdley, MD, AGAF, FAASLD, FACG, FACP

Director, Liver Institute Northwest
Professor of Medicine, Elson S. Floyd College of Medicine
Washington State University
Seattle, WA

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NASH is a Serious Liver Disease with High Unmet Need

- High morbidity and mortality
- 2nd leading cause of liver transplant
- Comorbidities related to NASH are on the rise
  - Obesity
  - Type 2 Diabetes
  - Insulin resistance
  - High triglycerides/dyslipidemia
  - Hypertension

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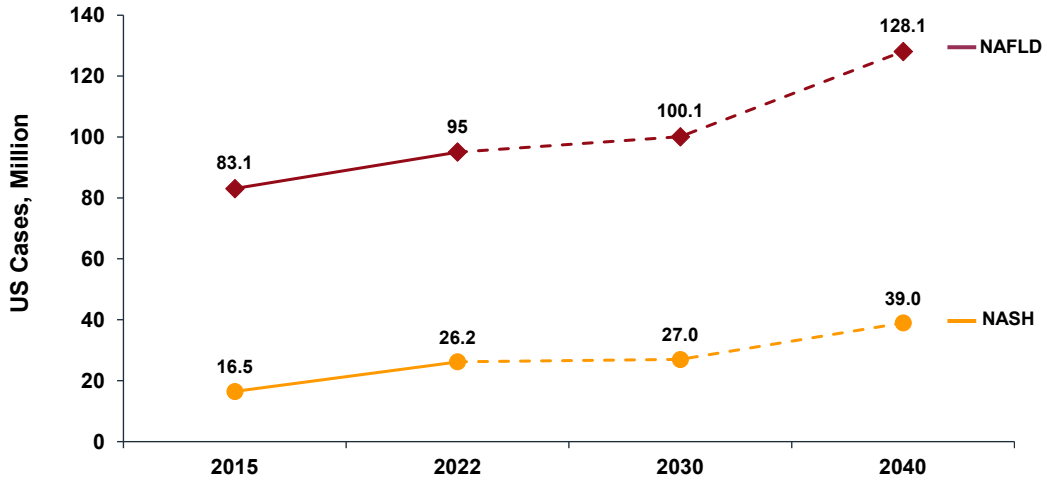
Prevalence of NAFLD/NASH is Increasing



Adapted from Razavi H, Estes C. Presented at: NASH 2022; September 8-9, 2022; Paris, France.

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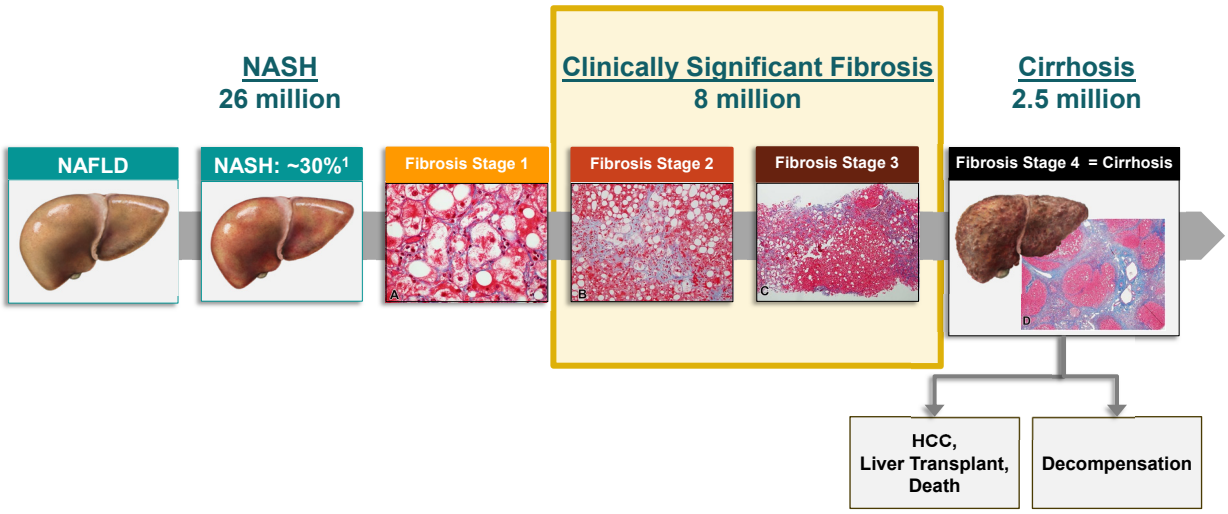
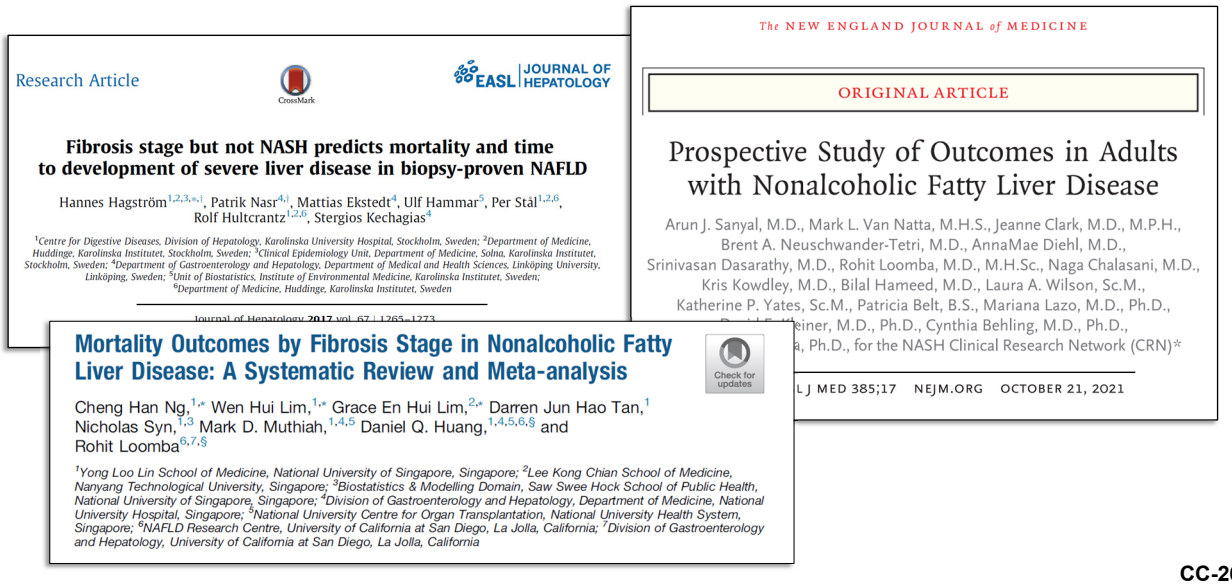
Clinically Significant Fibrosis is Key Point for Intervention



Adapted from Razavi H, Estes C. Presented at: NASH 2022; September 8-9, 2022; Paris, France.

CC-25

Fibrosis Stage, Not NASH, Predicts Mortality



Research Article

JOURNAL OF HEPATOLOGY

Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD

Hannes Hagström[1,2,3,*,†], Patrik Nasr[4,†], Mattias Ekstedt[4], Ulf Hammar[5], Per Stål[1,2,6], Rolf Hultcrantz[1,2,6], Stergios Kechagias[4]

[1]Centre for Digestive Diseases, Division of Hepatology, Karolinska University Hospital, Stockholm, Sweden; [2]Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden; [3]Clinical Epidemiology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden; [4]Department of Gastroenterology and Hepatology, Department of Medical and Health Sciences, Linköping University, Linköping, Sweden; [5]Unit of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Sweden; [6]Department of Medicine, Huddinge, Karolinska Institutet, Sweden

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prospective Study of Outcomes in Adults with Nonalcoholic Fatty Liver Disease

Arun J. Sanyal, M.D., Mark L. Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., Brent A. Neuschwander-Tetri, M.D., AnnaMae Diehl, M.D., Srinivasan Dasarathy, M.D., Rohit Loomba, M.D., M.H.Sc., Naga Chalasani, M.D., Kris Kowdley, M.D., Bilal Hameed, M.D., Laura A. Wilson, Sc.M., Katherine P. Yates, Sc.M., Patricia Belt, B.S., Mariana Lazo, M.D., Ph.D., ...einer, M.D., Ph.D., Cynthia Behling, M.D., Ph.D., ...a, Ph.D., for the NASH Clinical Research Network (CRN)*

...L J MED 385;17 NEJM.ORG OCTOBER 21, 2021

Mortality Outcomes by Fibrosis Stage in Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis

Check for updates

Cheng Han Ng,[1,*] Wen Hui Lim,[1,*] Grace En Hui Lim,[2,*] Darren Jun Hao Tan,[1] Nicholas Syn,[1,3] Mark D. Muthiah,[1,4,5] Daniel Q. Huang,[1,4,5,6,§] and Rohit Loomba[6,7,§]

[1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [2]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; [3]Biostatistics & Modelling Domain, Saw Swee Hock School of Public Health, National University of Singapore, Singapore; [4]Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospital, Singapore; [5]National University Centre for Organ Transplantation, National University Health System, Singapore; [6]NAFLD Research Centre, University of California at San Diego, La Jolla, California; [7]Division of Gastroenterology and Hepatology, University of California at San Diego, La Jolla, California

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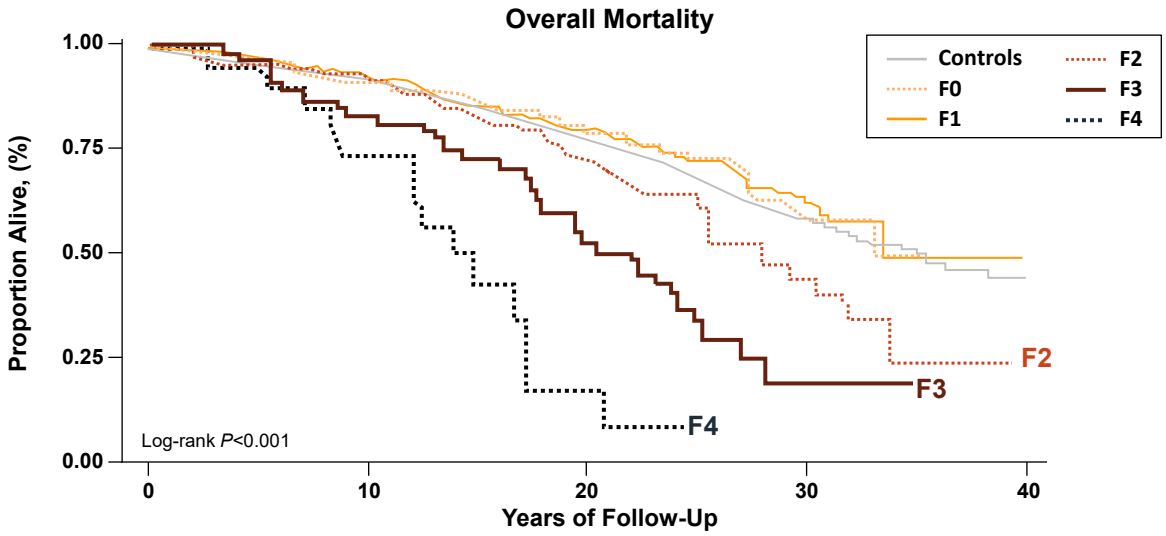
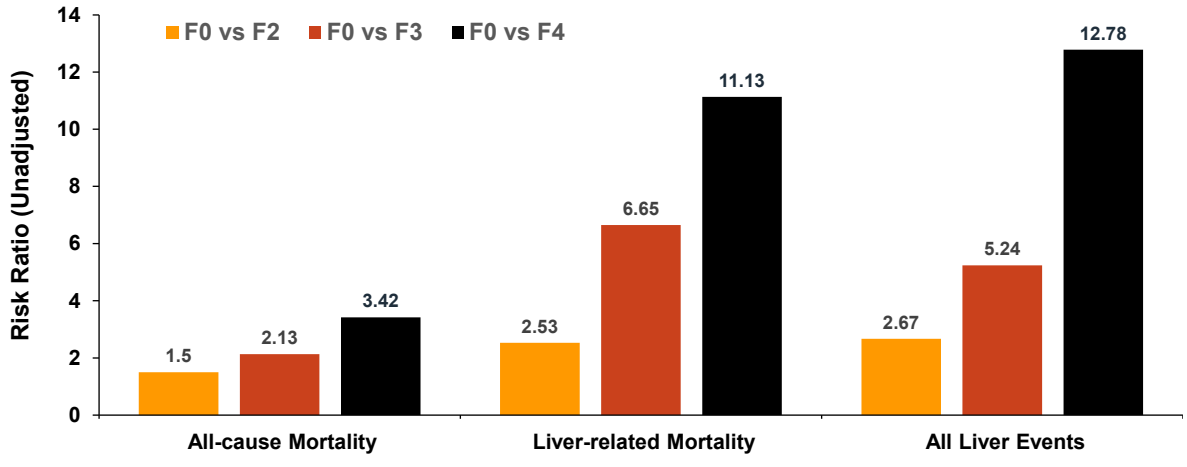
Fibrosis is The Strongest Predictor of Overall Mortality
(Retrospective Study)



Adapted from Hagström H, et al. *J Hepatol.* 2017;67:1265–1273.

CC-27

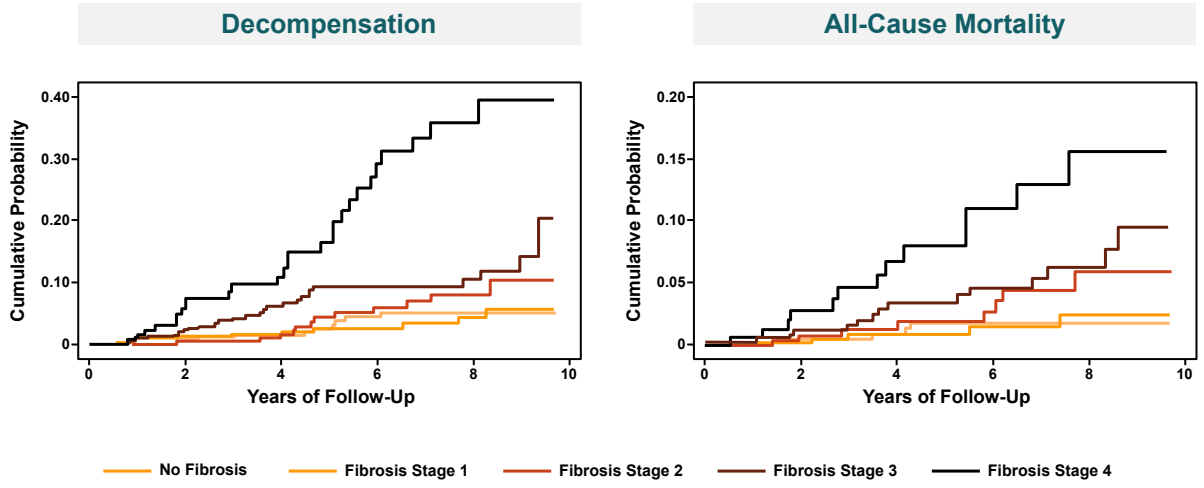
Fibrosis Predicts Both Mortality and Morbidity
(Meta-Analysis)



Adapted from Taylor RS, et al. Gastroenterology. 2020;158(6):1611-1625.e12.

CC-28

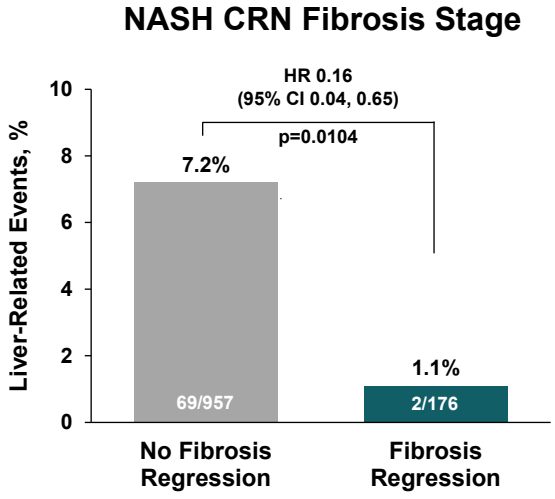
Fibrosis Predicts Negative Outcomes (Prospective Study)



Adapted from Sanyal AJ, Kowdley K, et al. *N Engl J Med*. 2021;385(17):1559–1569.

CC-29

Reversal of Fibrosis Decreased Liver-Related Events by >6X



- Fibrosis regression decreased the rate of:
  - New ascites
  - GI hemorrhage due to portal hypertension
  - Hepatic encephalopathy
  - Liver transplant or MELD ≥15
  - Death

Adapted from Sanyal et al Hepatology 2021.

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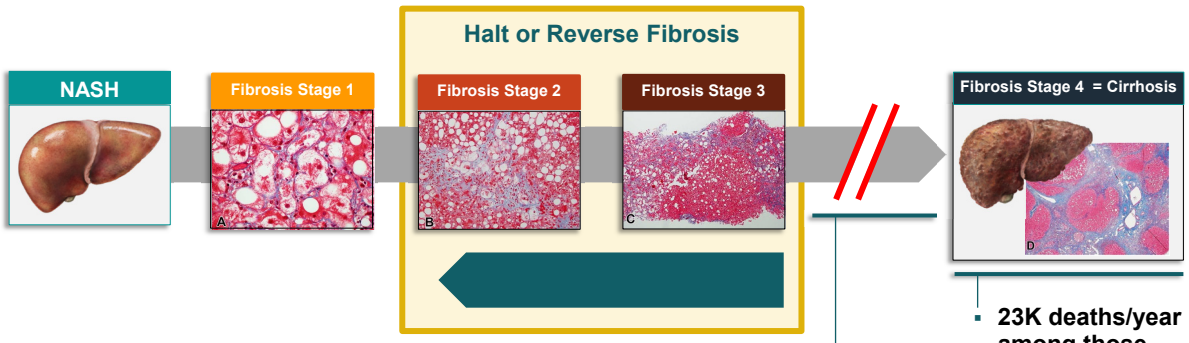
Goal is to Prevent Cirrhosis by Halting or Reversing Fibrosis



- **23K deaths/year among those with cirrhosis[3]**
- **20-25% with F3 progress rapidly to cirrhosis within 2.5-4 years[1,2]**

1. Sanyal AJ et al. *Hepatology*. 2019;70(6):1913–1927.
2. Kleiner et al. *JAMA*. 2019;2(10):e1912565.
3. Sanyal AJ, et al. *N Engl J Med*. 2021;385(17):1559–1569.

CC-31

Management Options are Limited

Lifestyle Modification, Aimed at Weight Loss	▪ Recommended as a first-line treatment; ≥10% weight loss necessary ▪ Few patients (≤10%) achieve and sustain effective weight loss
Bariatric Surgery	▪ Considered for patients who meet criteria for weight loss surgery ▪ Limited by risks and invasiveness
Liver Transplant	▪ Many patients ineligible or do not have access ▪ High rate of recurrence
Pharmacotherapies	▪ Currently, no approved pharmacotherapies available ▪ Despite weight loss, GLP-1 receptor agonists failed to demonstrate antifibrotic effect

Rinella ME, et al. *Hepatology*. 2023.

CC-32

Urgent Unmet Need for Treatment of NASH Fibrosis

- Clinically significant fibrosis leads to adverse liver outcomes
- NASH without fibrosis does not predict liver-related events
- Reversal of fibrosis improves outcomes
- Unmet need for effective anti-fibrotic therapy

CC-33

Non-Invasive Tests (NITs)

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Director, NAFLD Research Center
Professor of Medicine
Vice Chief, Gastroenterology
Director, Hepatology
University of California at San Diego, San Diego, CA

CC-34

NITs Identify At-Risk Patients Without the Need for Liver Biopsy

AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease
Mary E. Rinella, MD, Brent A. Neuschwander-Tetri, MD, Mohammad Shadab Siddiqui, MD, Manal F. Abdelmalek, MD, MPH, Stephen Caldwell, MD, Diana Barb, MD, David E. Kleiner, MD, PhD, Rohit Loomba, MD, MHSc

- NITs are routinely used by hepatologists and gastroenterologists to:
  - Risk stratify patients for treatment
  - Identify patients with cirrhosis
- Preferred over liver biopsy by patients and providers
  - Easily accessible and allow for serial, frequent monitoring

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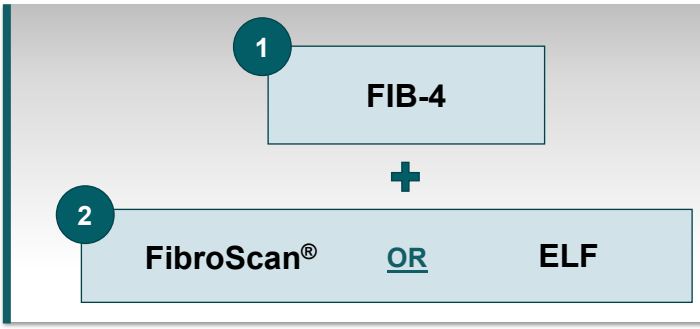
AASLD Guidance Recommends Sequential Approach for Risk Stratification



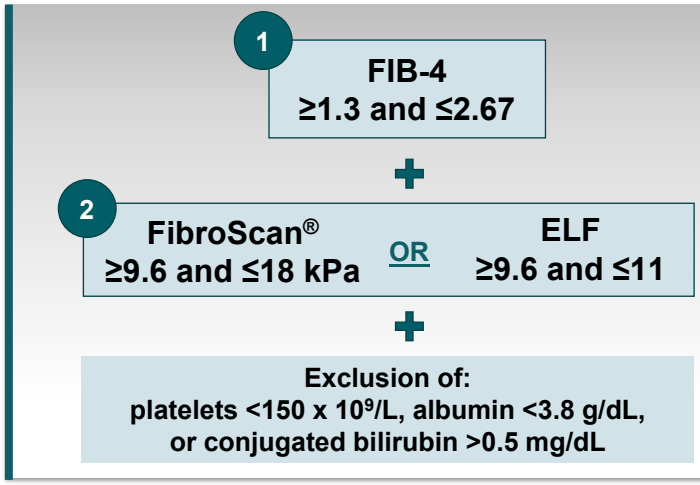
- **Identify:**
  - Low risk patients (minimal to no fibrosis)
  - High risk patients (cirrhosis)

- Additional national and international guidelines/algorithms recommend a sequential approach

ELF=Enhanced Liver Fibrosis
Adapted from Rinella M et al. *Hepatology*. 2023.

CC-36

NIT Algorithm to Identify Pre-Cirrhotic Fibrosis



- Algorithm derived from all patients screened in two Phase 3 studies (n=6060)
- Applied to identify eligible F2/F3 (by histology) in study-screened patients (F0-F4)*

ELF=Enhanced Liver Fibrosis
*n: F0=657, F1=1158, F2=1084, F3=1599, and F4=273
Loomba R et al. Submitted to EASL 2023.

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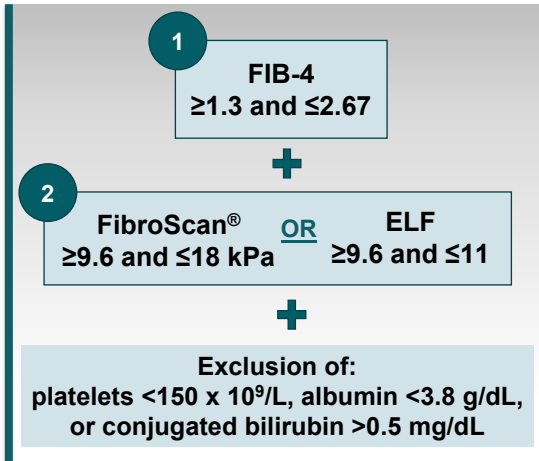
NIT Algorithm Reliably Identifies Pre-cirrhotic Fibrosis



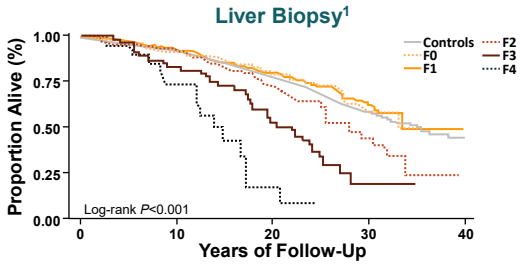
Population	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)
Pre-cirrhotic Fibrosis (F2 and F3)	31% (29, 32)	91% (89, 92)	89 (86, 91)

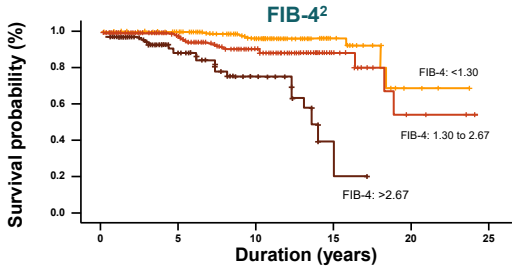
- Of the patients identified, 65% were F3

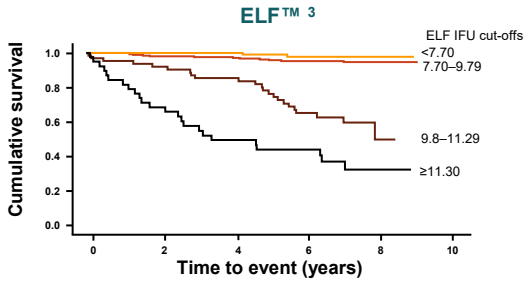
ELF=Enhanced Liver Fibrosis
Loomba R et al. Submitted to EASL 2023.

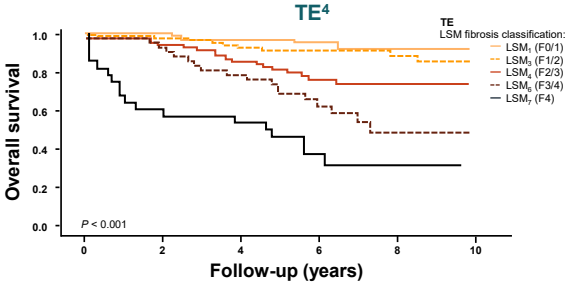
CC-38

NITs Can Risk Stratify Fibrosis Similar to Liver Biopsy









1. Hagström H et al. *J Hepatol* 2017; 2. Angulo P et al. *Gastroenterology* 2013; 3. Day J et al. *JALM* 2019; 4. Boursier J et al. *J Hepatol* 2016.

CC-39

Intercept

Efficacy Results

Tom Capozza, MD FACP
Executive Director, Clinical Research
Intercept Pharmaceuticals, Inc.

CC-40

What We Will Discuss Today

- Anti-fibrotic effect of OCA 25 mg
  - Established as proof of concept in Phase 2 FLINT
  - Confirmed in Study 303 using two independent biopsy read methodologies
- Regulatory fibrosis primary endpoint underestimates benefit
- Non-invasive tests (NITs) provide supportive evidence of benefit
  - Improvements in patients on OCA with stabilization or halting of progression, without a full stage change in fibrosis
- Findings are likely to predict clinical benefit

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NASH Clinical Research Network (CRN) Scoring System

NAFLD Activity Score (NAS)

Parameter	Grade
Steatosis	0-3
Lobular inflammation	0-3
Hepatocellular ballooning	0-2
Total score	**0-8**

Fibrosis

Fibrosis Score	
Degree	**Description**
0	None
1	Mild / Minimal
2	**Pre-cirrhotic**
3	
4	Cirrhosis

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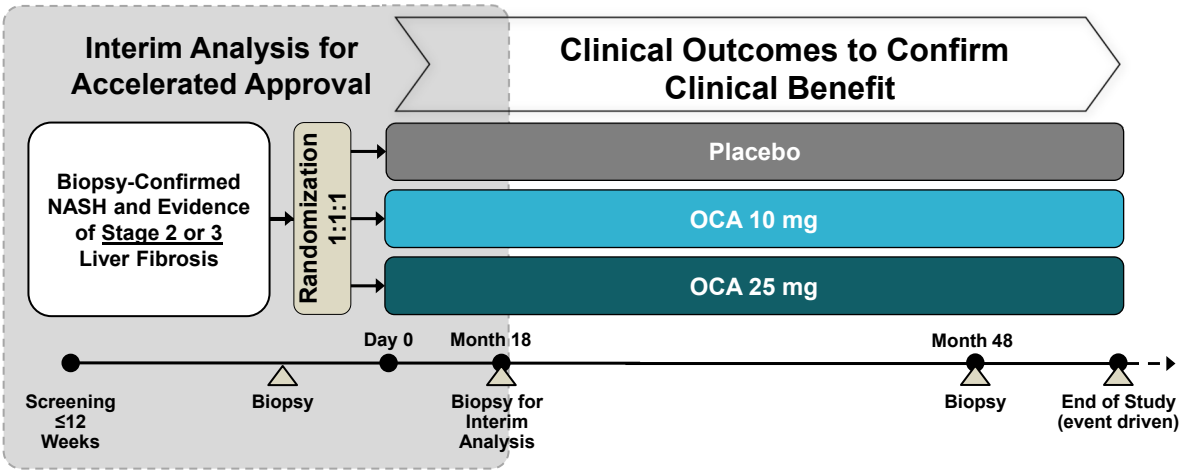
Study 303: Eligibility

- Biopsy-confirmed steatohepatitis and pre-cirrhotic fibrosis
  - NASH CRN stage 2 or 3 fibrosis by central pathologist
  - NAFLD Activity Score of at least 4 with ≥1 for each of the 3 parameters (steatosis, inflammation, ballooning)
- Excluded patients with:
  - Weight changes >10% within 3 months of Day 1
  - Current or history of significant alcohol consumption or other known chronic liver disease including cirrhosis
  - Recent history of significant ASCVD event within 1 year of Day 1

NASH CRN=NASH Clinical Research Network
NAS: steatosis (range 0-3), lobular inflammation (range 0-3), and hepatocellular ballooning (range 0-2)

CC-43

Study 303: Ongoing, Randomized, Double-Blind, Long-Term Placebo-Controlled Study



CC-44

FDA Agreement: One of Two Primary Endpoints Required to Achieve Study Success

Fibrosis Primary

- Improvement ≥1 stage fibrosis and no worsening of NASH
  - No worsening of NASH required no worsening of ANY of the NAS parameters:
    1. Steatosis
    2. Lobular inflammation
    3. Hepatocellular Ballooning

OR

Steatohepatitis Primary

- Resolution of NASH and no worsening of fibrosis
  - NASH resolution based on scoring of:
    1. Hepatocellular Ballooning=0
    2. Lobular inflammation=0-1

CC-45

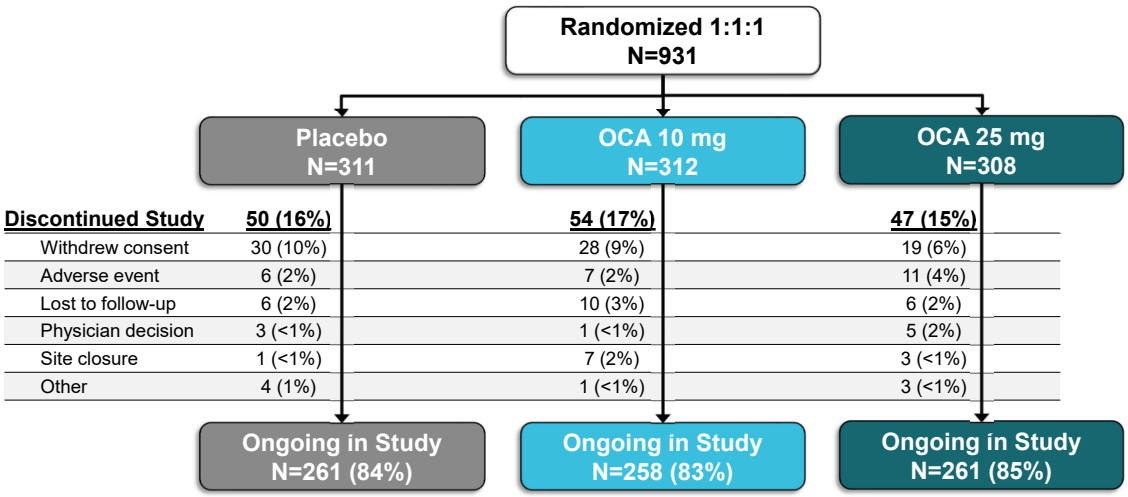
Study 303: Composite Endpoint (End of Study)

- Time to first occurrence of adjudicated events:
  - Death (all-cause)
  - MELD score ≥15
  - Liver transplant
  - Hospitalization for onset of:
    - Variceal bleed
    - Hepatic encephalopathy
    - Spontaneous bacterial peritonitis
- Ascites requiring medical intervention
- Progression to cirrhosis

MELD=Model of end stage liver disease

CC-46

Study 303: Patient Disposition – Original NDA
(ITT_old Population, N=931)



Discontinued Study	50 (16%)	54 (17%)	47 (15%)
Withdrew consent	30 (10%)	28 (9%)	19 (6%)
Adverse event	6 (2%)	7 (2%)	11 (4%)
Lost to follow-up	6 (2%)	10 (3%)	6 (2%)
Physician decision	3 (<1%)	1 (<1%)	5 (2%)
Site closure	1 (<1%)	7 (2%)	3 (<1%)
Other	4 (1%)	1 (<1%)	3 (<1%)

CC-47

Study 303: Baseline Patient Characteristics Balanced
(ITT_old Population, N=931)

	Placebo N=311	OCA 10 mg N=312	OCA 25 mg N=308
Age, Mean (Range)	55 (19-79)	55 (20-78)	55 (18-75)
≥65 Years	21%	20%	19%
Female	60%	57%	57%
White	93%	91%	87%
Hispanic or Latino	18%	15%	17%
BMI, ≥35 kg/m²	36%	37%	37%
Type 2 Diabetes	56%	55%	56%

CC-48

Clinical Characteristics Balanced and Reflective of Pre-Cirrhotic Fibrosis due to NASH (ITT_old Population, N=931)

	Placebo N=311	OCA 10 mg N=312	OCA 25 mg N=308
Fibrosis Stage 2	46%	42%	45%
Fibrosis Stage 3	54%	58%	55%
NAS Total, mean (SD)	6.0 (1.1)	5.9 (1.1)	6.0 (1.1)
ALT (U/L), mean (SD)	79.7 (56.7)	75.6 (47.0)	80.4 (56.7)
AST (U/L), mean (SD)	59.0 (40.5)	56.6 (34.0)	57.1 (34.2)
Total Bilirubin (mg/dL), mean (SD)	0.64 (0.28)	0.65 (0.30)	0.69 (0.34)
Transient Elastography (kPa), mean (SD)	12.5 (7.6)	12.0 (5.6)	12.4 (7.3)
FIB-4, mean (SD)	1.62 (0.89)	1.63 (0.88)	1.63 (0.85)
ELF, mean (SD)	9.71 (0.94)	9.73 (0.92)	9.73 (0.95)

CC-49

Two Histology Methods for Month 18 Interim Analysis

Central (N=931)

- Original NDA
- Achieved the pre-specified primary fibrosis endpoint for Month 18 interim analysis
- Two independent readers
- Inter-reader discordance led to uncertainty of the efficacy results

Consensus (N=931)

- FDA recommendation and agreement
- Rigorous new biopsy scoring method
  - 2 experts agreed on score *OR*
  - 3rd expert served as tiebreaker *OR*
  - Joint panel convened if all 3 disagreed

CC-50

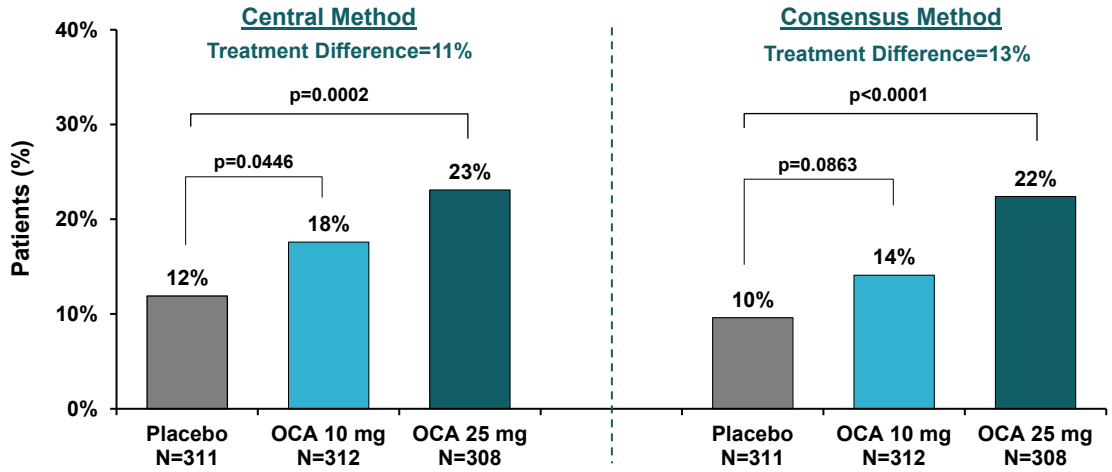
Statistical Considerations

- The pre-specified estimand for the primary objective included the ITT_old population (N=931) for the Month 18 interim analysis
- Consensus method analysis confirms efficacy results from original Central method analysis
- The ITT_histology population (N=1607) is only supportive
- Missing biopsy assessments were imputed as non-responders

CC-51

Fibrosis Improvement Confirmed by Two Independent Reading Methods (ITT_old Population, N=931)

Fibrosis Primary: Improvement ≥1 stage of fibrosis, no worsening of NASH at Month 18

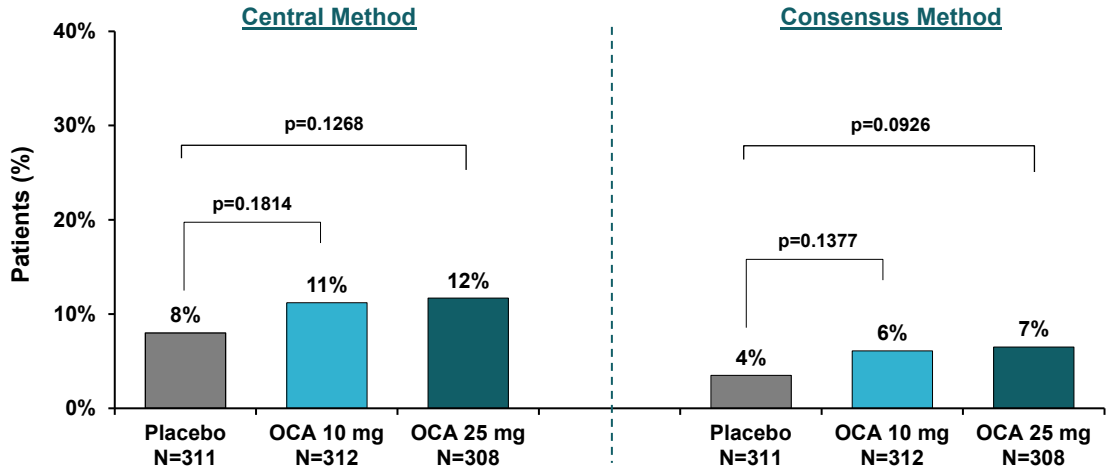


Missing M18 biopsy imputed as non-responder.

CC-52

Regulatory Steatohepatitis Primary Endpoint Not Statistically Significant
(ITT_old Population, N=931)

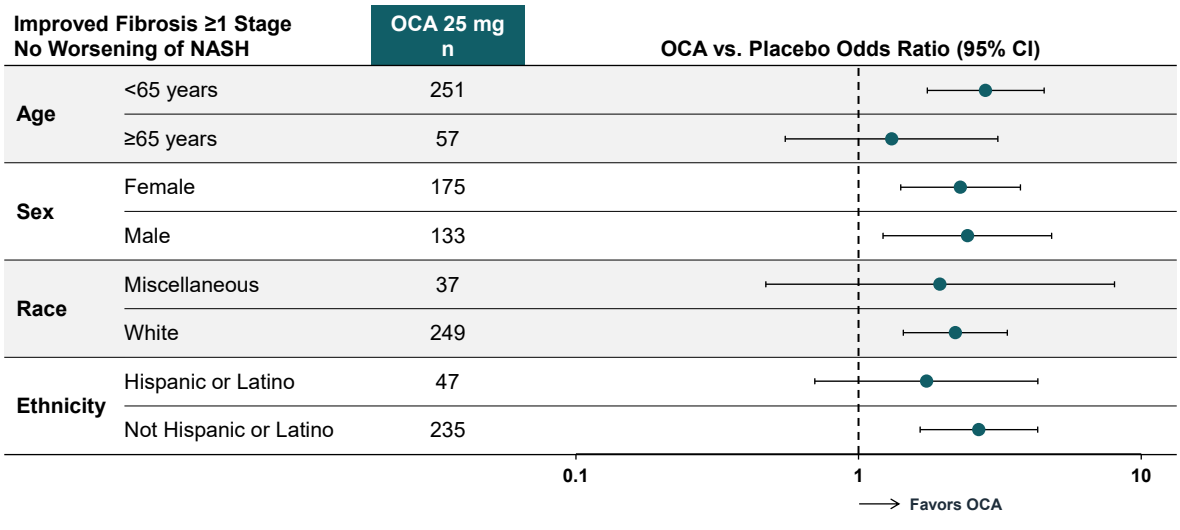
Steatohepatitis Primary: NASH resolution, no worsening of fibrosis at Month 18



Missing M18 biopsy imputed as non-responder.

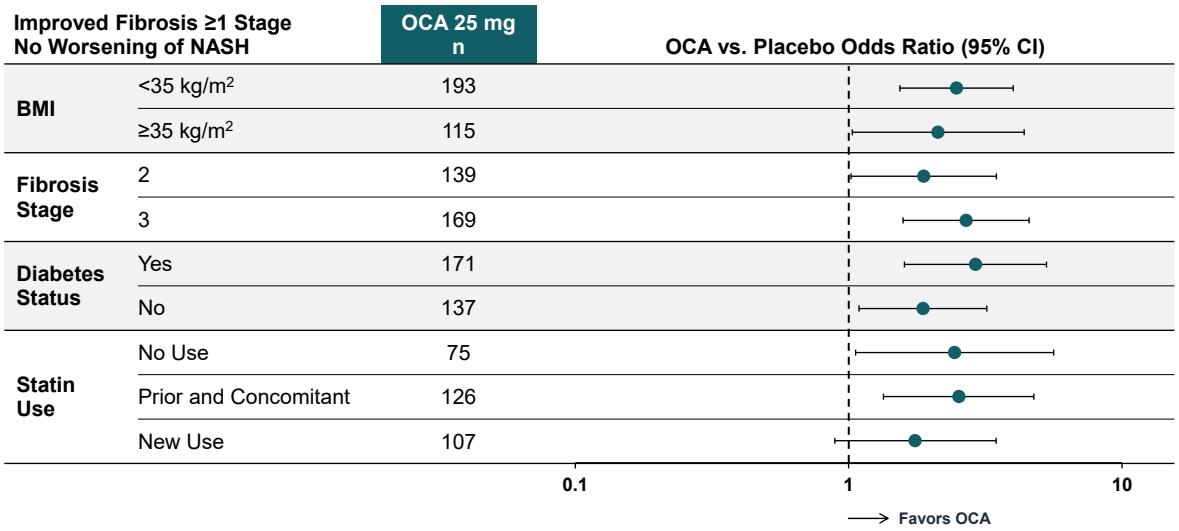
CC-53

Anti-Fibrotic Benefit Consistent Across Baseline Demographics
(ITT_old Population, N=931)



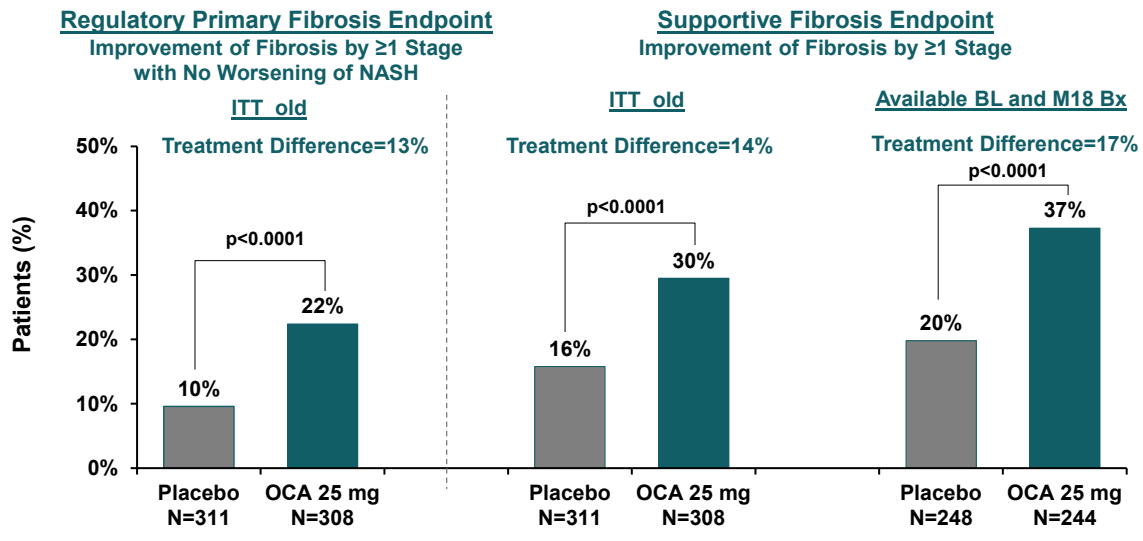
CC-54

Anti-Fibrotic Benefit Consistent Across Baseline Disease Characteristics (ITT_old Population, N=931)



CC-55

Proportion of Fibrosis Responders Higher on OCA

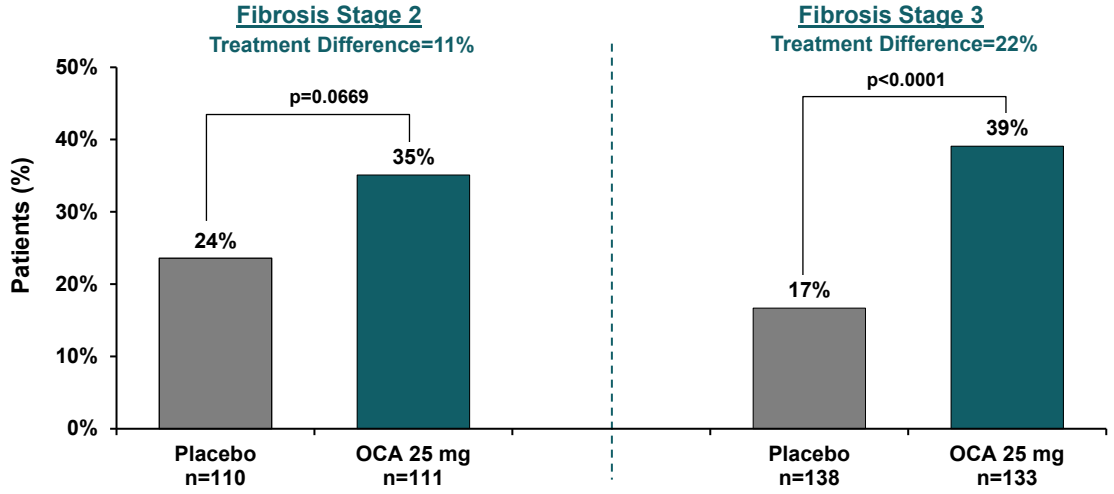


ITT_old: Missing M18 biopsy imputed as non-responder. Bx=Biopsy

CC-56

Robust Response for Baseline Fibrosis Stages 2 and 3
(ITT_old Population, Available Baseline and Month 18)

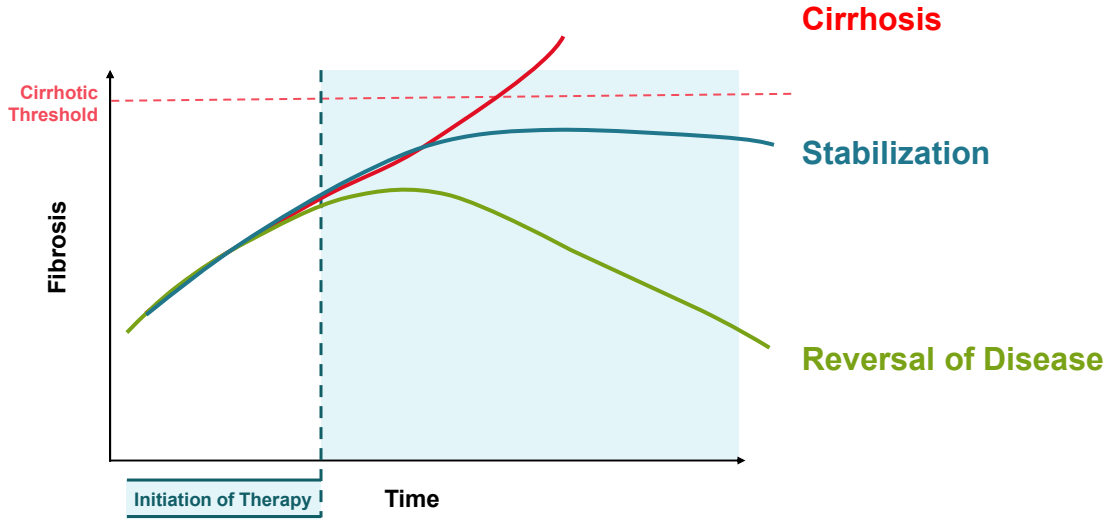
Improvement ≥1 stage of fibrosis at Month 18



N is number of patients with both baseline and post-baseline biopsy.

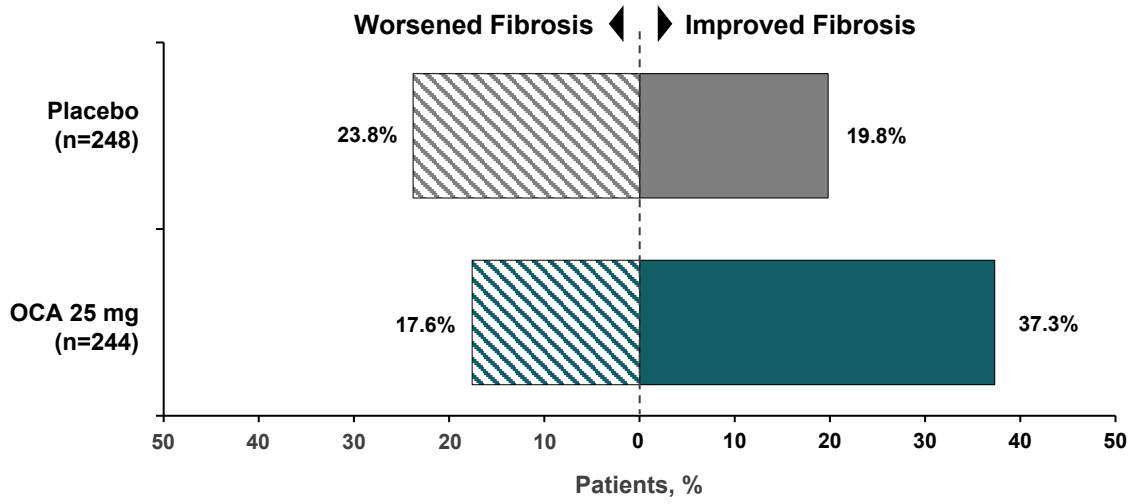
CC-57

Goal of Therapy is To Prevent Progression to Cirrhosis



CC-58

Fewer Patients on OCA 25 mg had Fibrosis Progression
(ITT_old Population, Available Baseline and Month 18)

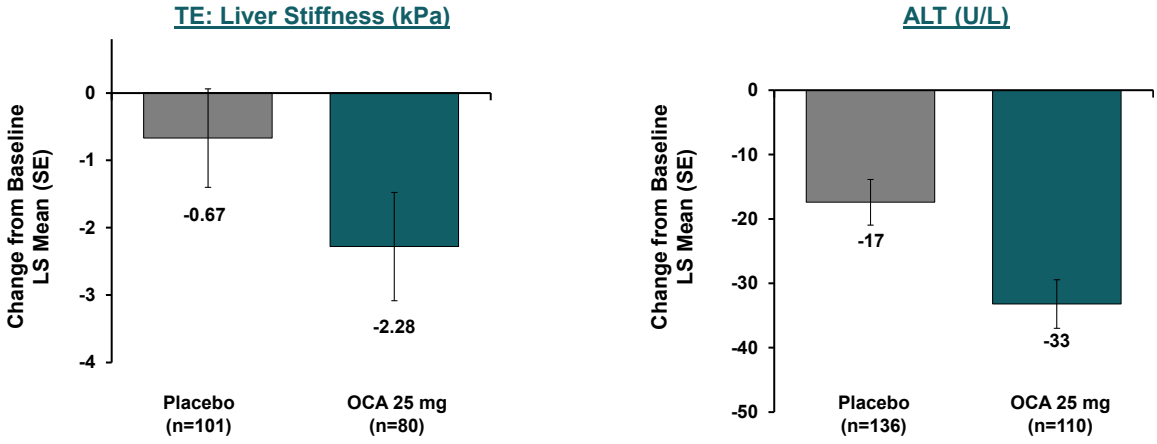


N is number of patients with both baseline and post-baseline biopsy.

CC-59

Evidence of Benefit Beyond Histology
(ITT_old Population, Available Baseline and Month 18)

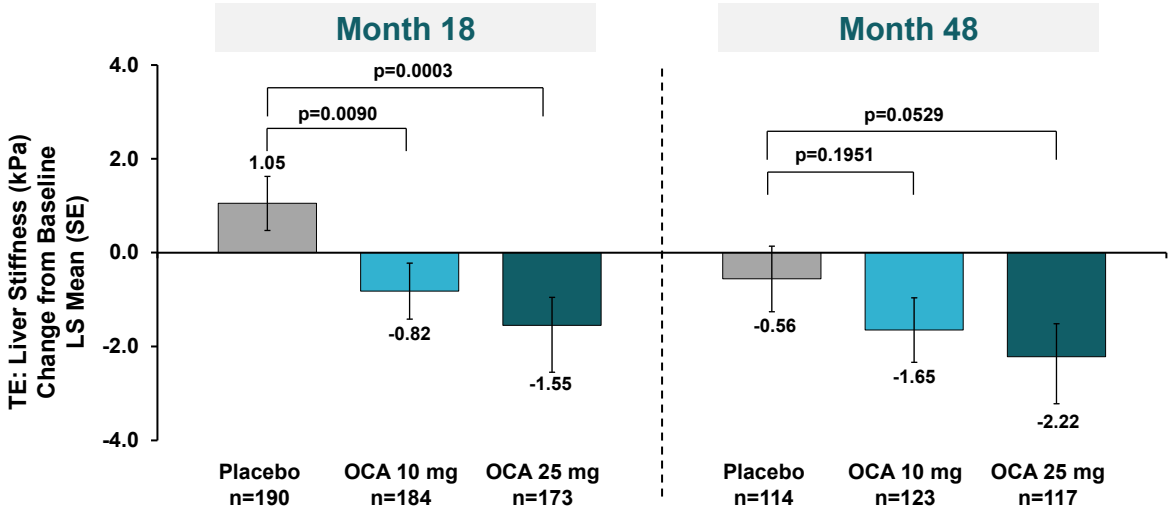
Patients with No Change in Fibrosis Stage at Month 18



N is number of patients with both baseline and post-baseline biopsy.

CC-60

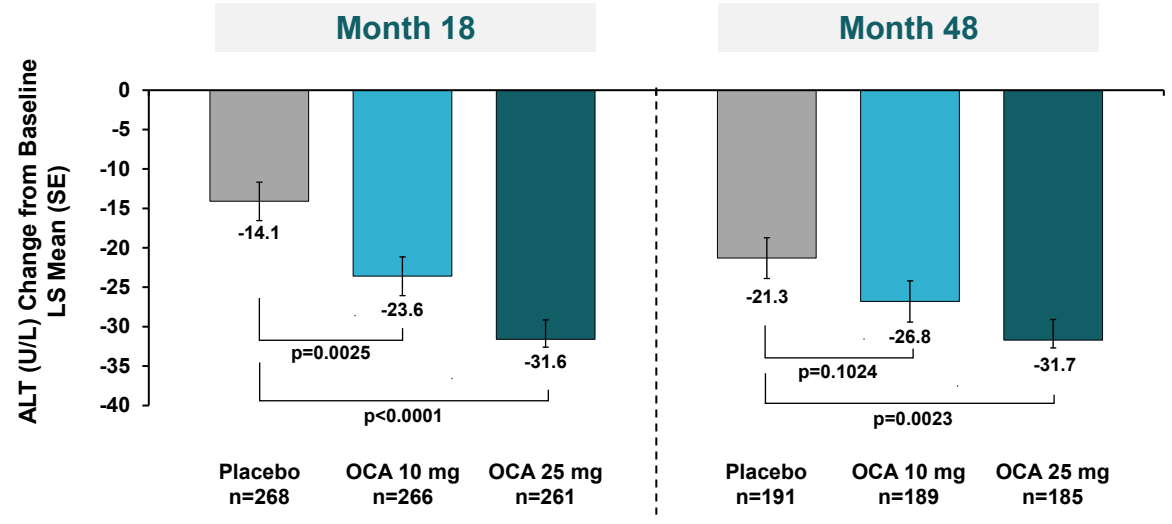
OCA Improves Liver Stiffness Measurements
(ITT_old Population, N=931)



Treatment n values represent patients with TE assessments at baseline and Month 18 or Month 48.

CC-61

OCA Improves Liver Biochemistries
(ITT_old Population, N=931)



Treatment n values represent patients with ALT assessments at baseline and Month 18 or Month 48.

CC-62

Totality of Data Confirm Anti-fibrotic Effect of OCA 25 mg

- Statistically significant anti-fibrotic effect for OCA 25 mg on stringent regulatory endpoint in Original Analysis
  - Primary Endpoint: Fibrosis improvement ≥1 stage with no worsening of NASH
- Treatment effect at Month 18 confirmed by the Consensus Method
  - Clinically meaningful because fibrosis stage is the strongest predictor of clinical outcomes
- Regulatory Primary endpoint underestimates benefit
  - Captures only full-stage reversal of fibrosis
- OCA benefit supported by multiple non-invasive tests (NITs)
  - Improvements in patients on OCA with stabilization or halting of progression, without a full stage change in fibrosis

CC-63

Intercept

OCA Safety

Sangeeta Sawhney, MD
Vice President, Clinical Development
Intercept Pharmaceuticals

CC-64

Safety Topics

1. **Safety Population**
2. **Overall Safety Profile**
3. **Key Safety Topics:**
   - **Hepatic Safety**
   - **Gallstone Related Events**
   - **Cardiovascular Safety**
     (including impact of lipids and glycemic markers)
   - **Renal Events**
4. **Risk Management Plan**
5. **Summary**

CC-65

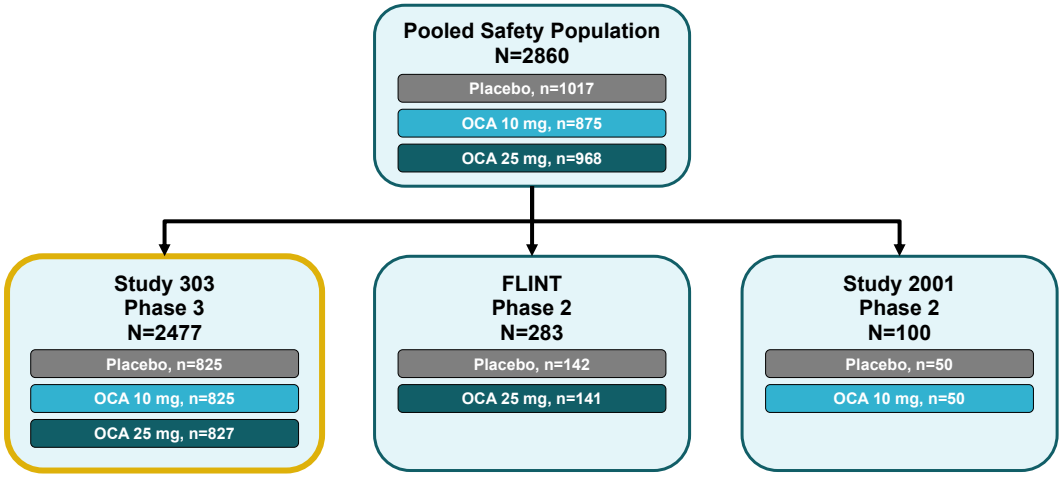
Safety Topics

1. **Safety Population**
2. **Overall Safety Profile**
3. **Key Safety Topics:**
   - **Hepatic Safety**
   - **Gallstone Related Events**
   - **Cardiovascular Safety**
     (including impact of lipids and glycemic markers)
   - **Renal Events**
4. **Risk Management Plan**
5. **Summary**

CC-66

Pooled Safety Population

- 2860 patients from 3 long-term, placebo-controlled clinical trials in pre-cirrhotic NASH



CC-67

Long-Term Exposure Up to 6 Years (Study 303)

- Long-term exposure up to 6 years
- 3-fold increase in safety exposure since the original NDA submission
- Median exposure of 39 months
- ~700 patients with ≥4 years of exposure to OCA

CC-68

Safety Data Presentation

- Data for all adverse events is presented as treatment-emergent
  - Onset date after initiating investigational product + 30 days from last dose
- Data for CV events is presented as on-study
  - Onset date after initiation of investigational product up to the data snapshot

CC-69

Patients with Pre-cirrhotic NASH have Many Comorbidities (Study 303)

	Placebo N=825 n (%)	OCA 10 mg N=825 n (%)	OCA 25 mg N=827 n (%)
Type 2 diabetes mellitus	466 (56.5)	477 (57.8)	482 (58.3)
Obesity	535 (64.8)	528 (64.0)	533 (64.4)
Hypertension	554 (67.2)	549 (66.5)	537 (64.9)
Hypercholesterolemia* (LDL ≥100 mg/dL)	473 (58.2)	464 (57.1)	487 (59.6)
Cardiac disorders	103 (12.5)	107 (13.0)	108 (13.1)
Cholelithiasis	159 (19.3)	149 (18.1)	160 (19.3)
Renal and urinary disorders	186 (22.5)	210 (25.5)	186 (22.5)

*Percentages are based on non-missing data

CC-70

Safety Overview
(Study 303)

	Placebo N=825 n (%)	OCA 10 mg N=825 n (%)	OCA 25 mg N=827 n (%)
TEAEs	**766 (92.8)**	**795 (96.4)**	**807 (97.6)**
TEAEs Leading to Tx Discontinuation	93 (11.3)	102 (12.4)	179 (21.6)
Severe TEAEs	174 (21.1)	182 (22.1)	240 (29.0)
SAEs	181 (21.9)	204 (24.7)	216 (26.1)
Deaths	8 (1.0)	9 (1.1)	10 (1.2)

CC-71

Pruritus Events Did Not Negatively Impact QOL
(Study 303)

	Placebo N=825 n (%)	OCA 10 mg N=825 n (%)	OCA 25 mg N=827 n (%)
Pruritus TEAEs	221 (26.8)	289 (35.0)	**476 (57.6)**
Serious	0	0	**5 (0.6)**
Leading to IP Discontinuation	8 (1.0)	14 (1.7)	**100 (12.1)**
Severe	3 (0.4)	10 (1.2)	**57 (6.9)**
Leading to Death	0	0	**0**

CC-72

SAEs (Study 303)

Preferred Term	Placebo N=825 n (%)	OCA 10 mg N=825 n (%)	OCA 25 mg N=827 n (%)
SAEs	181 (21.9)	204 (24.7)	216 (26.1)
Acute kidney injury	1 (0.1)	5 (0.6)	10 (1.2)
Cholecystitis acute	0	1 (0.1)	6 (0.7)
Pruritus	0	0	5 (0.6)
Urinary tract Infection	0	1 (0.1)	5 (0.6)
Diabetes mellitus	0	0	5 (0.6)

CC-73

Adverse Events Leading to Death: No Clear Treatment Related Pattern for Underlying Etiology (Study 303)

System Organ Class	Placebo N=825 n (%)	OCA 10 mg N=825 n (%)	OCA 25 mg N=827 n (%)
TEAEs Leading to Death	**8 (1.0)**	**9 (1.1)**	**10 (1.2)**
Cardiac disorders	1 (0.1)	2 (0.2)	2 (0.2)
Infections and infestations	2 (0.2)	1 (0.1)	4 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.2)	3 (0.4)	2 (0.2)
General disorders and administration site conditions	0	0	1 (0.1)
Hepatobiliary disorders	0	0	1 (0.1)
Psychiatric disorders	2 (0.2)	1 (0.1)	0
Injury, poisoning and procedural complications	0	1 (0.1)	0
Renal and urinary disorders	0	1 (0.1)	0
Gastrointestinal disorders	1 (0.1)	0	0

CC-74

Off-Treatment Adverse Events Leading to Death: No Clear Treatment Related Pattern for Underlying Etiology (Study 303)

System Organ Class	Placebo N=825 n (%)	OCA 10 mg N=825 n (%)	OCA 25 mg N=827 n (%)
Off-Treatment AEs Leading to Death	**2 (0.2)**	**2 (0.2)**	**4 (0.5)**
Respiratory, thoracic and mediastinal disorders	0	1 (0.1)	2 (0.2)
Cardiac disorders	0	0	1 (0.1)
Renal and urinary disorders	0	0	1 (0.1)
Infections and infestations	0	1 (0.1)	0
Gastrointestinal disorders	1 (0.1)	0	0
Vascular disorders	1 (0.1)	0	0

CC-75

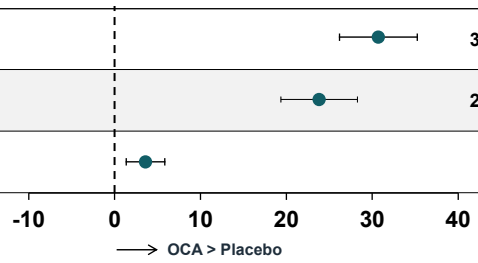
Safety Topics

1. Safety Population
2. Overall Safety Profile
3. **Key Safety Topics:**
   - **Hepatic Safety**
   - **Gallstone Related Events**
   - **Cardiovascular Safety** (including impact of lipids and glycemic markers)
   - **Renal Events**
4. Risk Management Plan
5. Summary

CC-76

Risk Difference of AESIs (Study 303)

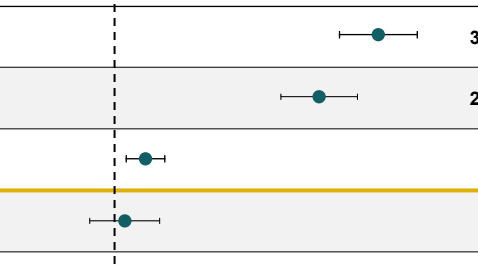
AESI	Incidence, n (%) Placebo N=825	OCA 25 mg N=827	Risk Difference (95% CI)
Pruritus	221 (26.8)	476 (57.6)	**30.7** (26.18, 35.24)
Dyslipidemia	193 (23.4)	390 (47.2)	**23.8** (19.36, 28.27)
Gallstone-Related Events	33 (4.0)	63 (7.6)	**3.6** (1.36, 5.85)



CC-77

Risk Difference of AESIs (Study 303)

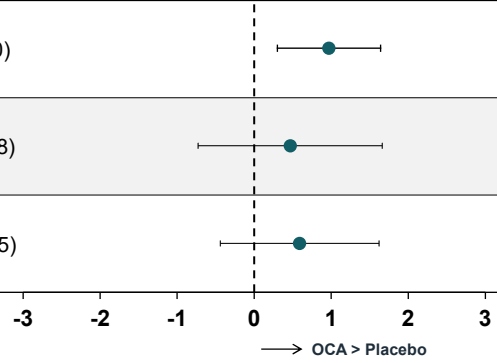
AESI	Incidence, n (%) Placebo N=825	OCA 25 mg N=827	Risk Difference (95% CI)
Pruritus	221 (26.8)	476 (57.6)	**30.7** (26.18, 35.24)
Dyslipidemia	193 (23.4)	390 (47.2)	**23.8** (19.36, 28.27)
Gallstone-Related Events	33 (4.0)	63 (7.6)	**3.6** (1.36, 5.85)
Hyperglycemia	190 (23.0)	201 (24.3)	**1.2** (-2.90, 5.25)
Urolithiases	32 (3.9)	28 (3.4)	**-0.6** (-2.35, 1.25)
Pancreatitis	7 (0.8)	8 (1.0)	**0.1** (-0.80, 1.02)



CC-78

Risk Difference of Adjudicated Events (Study 303)

AESI	Incidence, n (%) Placebo N=825	OCA 25 mg N=827	Risk Difference (95% CI)
Adjudicated Hepatic: Potential Liver Injury ≥ Moderate in Severity and ≥ Possibly Related to IP	0	8 (1.0)	**1.0** (0.30, 1.64)
On-Study Adjudicated CV: Core MACE	11 (1.3)	15 (1.8)	**0.5** (-0.73, 1.66)
Adjudicated Renal: Acute Kidney Injury	7 (0.8)	12 (1.5)	**0.6** (-0.44, 1.62)



CC-79

Safety Topics

1. Safety Population
2. Overall Safety Profile
3. **Key Safety Topics:**
   - **Hepatic Safety**
   - Gallstone Related Events
   - Cardiovascular Safety (including impact of lipids and glycemic markers)
   - Renal Events
4. Risk Management Plan
5. Summary

CC-80

Background on the 2017 Hepatic Safety Amendment in Study 303

- 2 serious events reported in 2017, leading to the amendment
  - Study 209: 1 fatal event in a patient with cirrhosis at BL on OCA 25 mg
  - Study 303: 1 liver transplant in a patient on OCA 25 mg
- Implementation of the amendment led to marked decrease in hepatic events, especially the most severe events
- Approximately 50% of patients in Study 303 enrolled post 2017 Safety Amendment

CC-81

Monitoring Measures Implemented in 2017 Hepatic Safety Amendment (Study 303)

Pre-Amendment

- AE and SAE monitoring at each visit
- Safety labs at each visit
  - Serum chemistry, hematology, coagulation
  - Glycemic control measures
  - Lipoprotein analysis

Post-Amendment

- AE and SAE monitoring at each visit
- Safety labs at each visit
- Investigator and patient education to recognize clinical signs or symptoms of liver injury/impairment
- Specific liver lab thresholds
  - ALT
  - Total Bili / Direct Bili
  - ALP
- IP interruption if suspicion of liver injury

Proposed label consistent with monitoring and frequency in 2017 amendment

CC-82

DILI Assessment in Study 303

- All events reviewed by independent committee in a blinded, rigorous manner
  - DILI was defined as a liver injury caused by medications, herbs, etc leading to abnormal liver tests or liver dysfunction with the reasonable exclusion of other etiologies
  - "Possible" relationship was defined as a probability of 25-49%, "Probable" as 50-74%, and "Highly-Likely" as 75-100%
- Must characterize DILI in setting of chronic progressive liver disease
- Monitoring for hepatic events and drug interruption post 2017 safety amendment inform the proposed label

CC-83

Safety Amendment Effective in Decreasing Rate of Moderate to Severe Hepatic Events (Study 303)

	Pre-Amendment		Post-Amendment	
	Placebo N=501 n (EAIR) (95% CI)	OCA 25 mg N=502 n (EAIR) (95% CI)	Placebo N=825 n (EAIR) (95% CI)	OCA 25 mg N=827 n (EAIR) (95% CI)
Total Safety Follow-Up, Patient-Years	407	401	2605	2375
Patients with ≥1 Potential DILI Event	29 (7.13) (4.82, 10.07)	36 **(8.98)** (6.37, 12.21)	89 (3.42) (2.75, 4.19)	103 **(4.34)** (3.55, 5.24)
Patients with ≥1 Potential DILI Event Considered ≥ Moderate in Severity and ≥ Possibly Related to IP	0	6 **(1.5)** (0.55, 3.23)	0	3 **(0.13)** (0.03, 0.37)

CC-84

FDA Review of 12 Cases (Table 12)

FDA #	Dose	Pattern	Blinded HSAC Adjudication	Unblinded FDA Review	Month, Comments
2	10 mg	Cholestatic	Probable	Probable	M1, Event resolved D/C IP
3	25 mg	Cholestatic	Probable	Probable	M1, Event resolved D/C IP
9	**25mg**	**Mixed/Chol**	**Probable**	**Possible**	**M1, Event resolved D/C IP**
1	25 mg	Cholestatic	Possible	Probable	M5, Liver Transplant
10	25 mg	Cholestatic	Possible	Possible	M8, Event resolved D/C IP
12	**25 mg**	**Cholestatic**	**Possible**	**Unlikely**	**M9, Event resolved D/C IP**
6	25 mg	Cholestatic	Possible	Possible	M13, Event resolved D/C IP
11	**25 mg**	**Mixed**	**Possible**	**Unlikely**	**M13, Event resolved D/C IP**

CC-85

FDA Review of 12 Cases (Table 12)

FDA #	Dose	Pattern	Blinded HSAC Adjudication	Unblinded FDA Review	Month, Comments
2	10 mg	Cholestatic	Probable	Probable	M1, Event resolved D/C IP
3	25 mg	Cholestatic	Probable	Probable	M1, Event resolved D/C IP
9	**25mg**	**Mixed/Chol**	**Probable**	**Possible**	**M1, Event resolved D/C IP**
1	25 mg	Cholestatic	Possible	Probable	M5, Liver Transplant
10	25 mg	Cholestatic	Possible	Possible	M8, Event resolved D/C IP
12	**25 mg**	**Cholestatic**	**Possible**	**Unlikely**	**M9, Event resolved D/C IP**
6	25 mg	Cholestatic	Possible	Possible	M13, Event resolved D/C IP
11	**25 mg**	**Mixed**	**Possible**	**Unlikely**	**M13, Event resolved D/C IP**
7	25 mg	Cholestatic	Possible	Possible	M15, Gallstone related, Event resolved D/C IP (and steroids)
4	25 mg	Cholestatic	Unlikely	Poss.-Probable	M20, Gallstone related, Fatal
5	10 mg	Hepatocell.	Possible	Possible	M30, Gallstone related, Event resolved
8	10 mg	Cholestatic	Possible	Possible	M30, Gallstone related, Event resolved D/C IP

CC-86

Safety Topics

1. Safety Population
2. Overall Safety Profile
3. **Key Safety Topics:**
   - Hepatic Safety
   - **Gallstone Related Events**
   - Cardiovascular Safety (including impact of lipids and glycemic markers)
   - Renal Events
4. Risk Management Plan
5. Summary

CC-87

Gallstone Related TEAEs (Study 303)

	Placebo N=825 n (%)	OCA 10 mg N=825 n (%)	OCA 25 mg N=827 n (%)
Gallstone Related TEAEs	33 (4.0)	44 (5.3)	63 (7.6)
Cholelithiasis	26 (3.2)	32 (3.9)	50 (6.0)
Cholecystitis	3 (0.4)	4 (0.5)	6 (0.7)
Cholecystitis acute	0	1 (0.1)	6 (0.7)
Biliary colic	2 (0.2)	0	6 (0.7)
Cholecystitis chronic	1 (0.1)	1 (0.1)	4 (0.5)
Bile duct stone	1 (0.1)	3 (0.4)	3 (0.4)
Cholangitis	1 (0.1)	1 (0.1)	3 (0.4)
Serious	6 (0.7)	8 (1.0)	21 (2.5)
Leading to Tx Discontinuation	1 (0.1)	4 (0.5)	3 (0.4)

CC-88

Pancreatitis TEAEs
(Study 303)

	Placebo N=825 n (%)	OCA 10 mg N=825 n (%)	OCA 25 mg N=827 n (%)
Pancreatitis TEAEs	7 (0.8)	5 (0.6)	8 (1.0)
Leading to death	1 (0.1)	0	0

CC-89

Safety Topics

1. Safety Population
2. Overall Safety Profile
3. **Key Safety Topics:**
   - Hepatic Safety
   - Gallstone Related Events
   - **Cardiovascular Safety** (including impact of lipids and glycemic markers)
   - Renal Events
4. Risk Management Plan
5. Summary

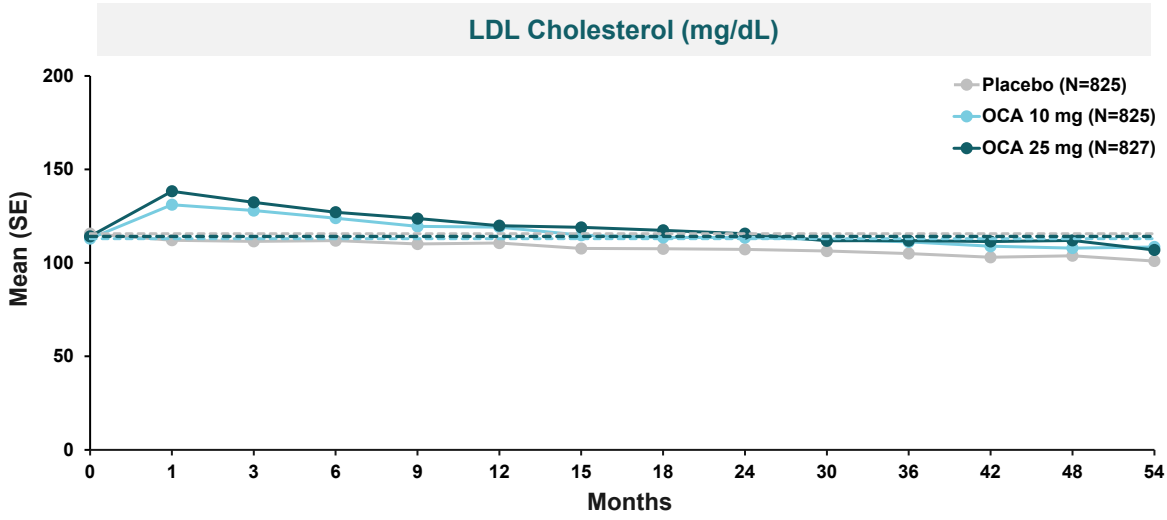
CC-90

No Clear Signal for Excess Cardiovascular Risk Observed to Date

- Risk factor assessment
  - Early, transient increases in LDL and HbA1c
  - No change in SBP or HR
- Study 303: Independently adjudicated MACE
- No imbalance in rates of positively adjudicated events between treatment groups
- While no definitive conclusions can be drawn, no apparent excess CV risk observed with OCA to date
- Treat LDL and HbA1C per clinical guidelines

CC-91

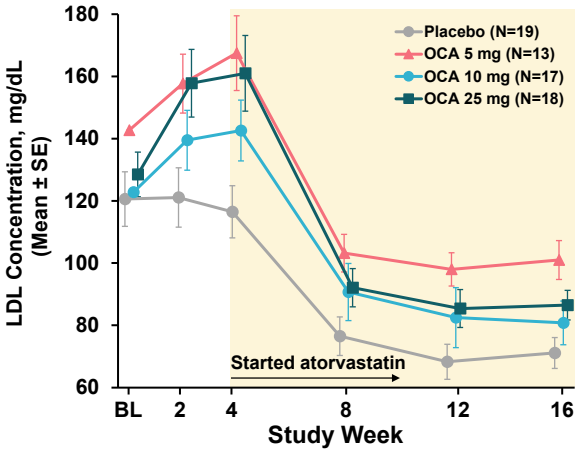
Transient Increase in LDL Cholesterol with Return to Near Baseline at Month 18 (Study 303)



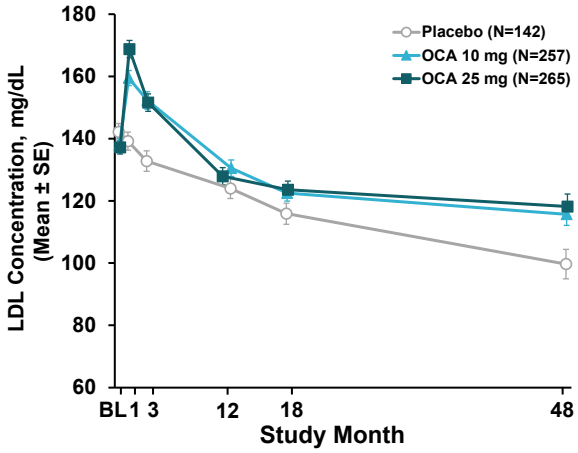
CC-92

Modest Increase in LDL Managed with Standard Lipid Lowering Therapy

Study 209
Efficacy Evaluable Population (N=67)



Study 303: New Statin Use



CC-93

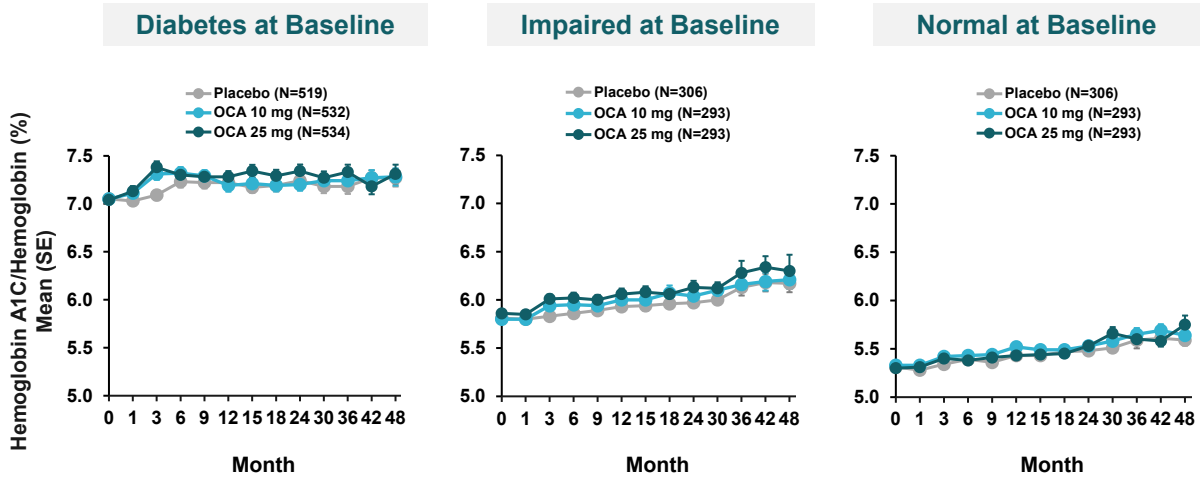
No Difference in Clinically Significant Hyperglycemia Events (Study 303)

	Placebo N=825 n (%)	OCA 10 mg N=825 n (%)	OCA 25 mg N=827 n (%)
Hyperglycemia TEAEs	190 (23.0)	223 (27.0)	201 (24.3)
Serious	2 (0.2)	5 (0.6)	11 (1.3)
Diabetes mellitus*	0	0	5 (0.6)
Diabetes mellitus inadequate control*	1 (0.1)	2 (0.2)	3 (0.4)
Diabetic ketoacidosis	1 (0.1)	2 (0.2)	2 (0.2)
Leading to Tx Discontinuation	0	1 (0.1)	0
Leading to Death	0	0	0

* In patients with Diabetes Mellitus at baseline

CC-94

No Clinically Significant Difference in Glycemic Control (Study 303)



CC-95

On-Study Adjudicated MACE (Study 303)

	Placebo N=825 n (%)	OCA 10 mg N=825 n (%)	OCA 25 mg N=827 n (%)
Core MACE	11 (1.3)	5 (0.6)	15 (1.8)
4-Point MACE	13 (1.6)	9 (1.1)	18 (2.2)
5-Point MACE	16 (1.9)	9 (1.1)	18 (2.2)

CC-96

On-Study Adjudicated MACE by ASCVD Risk[1] (Study 303)

10-Year ASCVD Risk < 20%	Placebo N=572 n (%)	OCA 10 mg N=541 n (%)	OCA 25 mg N=522 n (%)
Core MACE	4 (0.7)	1 (0.2)	5 (1.0)
4-Point MACE	6 (1.0)	1 (0.2)	8 (1.5)
5-Point MACE	8 (1.4)	1 (0.2)	8 (1.5)

10-Year ASCVD Risk ≥ 20%	Placebo N=90 n (%)	OCA 10 mg N=105 n (%)	OCA 25 mg N=121 n (%)
Core MACE	6 (6.7)	2 (1.9)	8 (6.6)
4-Point MACE	6 (6.7)	4 (3.8)	8 (6.6)
5-Point MACE	6 (6.7)	4 (3.8)	8 (6.6)

1. ASCVD risk assessment: *Circulation.* 2019;140(11):e596

CC-97

Safety Topics

1. Safety Population
2. Overall Safety Profile
3. **Key Safety Topics:**
   - Hepatic Safety
   - Gallstone Related Events
   - Cardiovascular Safety (including impact of lipids and glycemic markers)
   - **Renal Events**
4. Risk Management Plan
5. Summary

CC-98

No Clear Signal for AKI with OCA

- Comprehensive evaluation
  - Adverse events
  - Lab biomarkers
  - Study 303: Adjudicated events
- Low rate of AKI overall, numerically higher for OCA 25 mg
- Labeling recommends monitoring of renal function

CC-99

Safety Topics

1. Safety Population
2. Overall Safety Profile
3. Key Safety Topics:
   - Hepatic Safety
   - Gallstone Related Events
   - Cardiovascular Safety
     (including impact of lipids and glycemic markers)
   - Renal Events
4. **Risk Management Plan**
5. **Summary**

CC-100

Comprehensive Hepatic Risk Management Plan

Identify Patients and Prescribers

- Exclude patients unlikely to benefit
  - Minimal fibrosis
- OR at higher risk
  - Cirrhosis
  - Evidence of portal hypertension
  - Decompensated cirrhosis or a prior decompensation event
- Prescribers limited to hepatologists and gastroenterologists

CC-101

Comprehensive Hepatic Risk Management Plan

Identify Patients and Prescribers

- Exclude patients unlikely to benefit
  - Minimal fibrosis
- OR at higher risk
  - Cirrhosis
  - Evidence of portal hypertension
  - Decompensated cirrhosis or a prior decompensation event
- Prescribers limited to hepatologists and gastroenterologists

Educate Patients and Prescribers

- Prompt interruption for acute intercurrent illness or hospitalization
- Stopping rules
- Access and education through specialty pharmacy

CC-102

Comprehensive Hepatic Risk Management Plan

Identify Patients and Prescribers

- Exclude patients unlikely to benefit
  - Minimal fibrosis
- OR at higher risk
  - Cirrhosis
  - Evidence of portal hypertension
  - Decompensated cirrhosis or a prior decompensation event
- Prescribers limited to hepatologists and gastroenterologists

Educate Patients and Prescribers

- Prompt interruption for acute intercurrent illness or hospitalization
- Stopping rules
- Access and education through specialty pharmacy

Monitor & Manage

- Monitor liver tests
  - At initiation
  - Month 1
  - Every 3 months for first 18 months
  - Every 6 months thereafter
- Drug interruption
- Stopping rules for permanent discontinuation

CC-103

Drug Interruption and Stopping Rules

- **Promptly interrupt treatment for:**
  - Acute intercurrent illness
  - Signs or symptoms of hepatic impairment
  - Lab parameters
    - Total bilirubin ≥ 2x ULN
    - ALT > 5x ULN or ≥ 300 U/L
    - ALP > 2x ULN
    - Persistent thrombocytopenia
    - INR >1.5

- **Stopping rules for permanent discontinuation**
  - Safety
    - Liver injury without alternative etiology
  - Futility
    - Progression to cirrhosis
    - Evidence of worsening fibrosis

CC-104

Management of Gallstones

Contraindication

- Symptomatic gallstone disease

Monitor & Manage

- Interrupt OCA in patients with symptoms
- Patients may resume OCA after complete resolution of event

CC-105

Management of Cardiovascular and Renal Safety

Cardiovascular

- Monitor lipids and glycemic markers at initiation and treat per clinical guidelines

Renal

- Monitor renal function parameters, including blood creatinine, as clinically appropriate

CC-106

Continuation of PBC Measures and Enhanced PV Proposals

- Continuation of PBC measures
  - Drug prescribed by GI and Hepatology Practices
  - Education of NASH care team
  - Patient information and education
  - Specialty pharmacy network
- Enhanced Pharmacovigilance proposals
  - Patient support or assistance programs
  - Website: Safety-related information, including risk management and educational tools for patients and healthcare providers
  - Patient Registry

CC-107

Safety Conclusions

- OCA safety profile is well-characterized, based on large placebo-controlled, long-term exposure data
  - Consistent with MOA
  - Consistent with background comorbidities in patients with NASH
  - Recognition and management of safety events within scope of gastroenterologist and hepatologist practice
  - Can be managed with existing practice guidelines
- Commitment to education and training of prescribers

CC-108

Clinical Perspective

Arun Sanyal, MD
Professor of Medicine
VCU School of Medicine
Chair of NIDDK NASH Clinical Research Network Steering Committee

CC-109

Situation Today for Patients with NASH

- More patients presenting with clinically significant fibrosis
- Without approved treatment options, many patients progress to cirrhosis and eventually decompensation
  - Diet and lifestyle are usually ineffective
  - Liver transplant not an option for many patients
- Urgency for new treatment to prevent progression to cirrhosis and its complications

CC-110

Typical Patient with NASH

Presentation of Pre-Cirrhotic Fibrosis

- 55-year-old patient in clinic for past 10 years
- Past medical history: CHF, T2DM
- Multiple weight loss attempts
- Progressive increase in liver stiffness to 14 kPa
- Stage 3 fibrosis

No therapy to offer

Wait and watch

Up to 25% probability of progression to cirrhosis in as little as 2-4 years

CC-111

Typical Patient with NASH

Presentation of Pre-Cirrhotic Fibrosis

- 55-year-old patient in clinic for past 10 years
- Past medical history: CHF, T2DM
- Multiple weight loss attempts
- Progressive increase in liver stiffness to 14 kPa
- Stage 3 fibrosis

No therapy to offer

Wait and watch

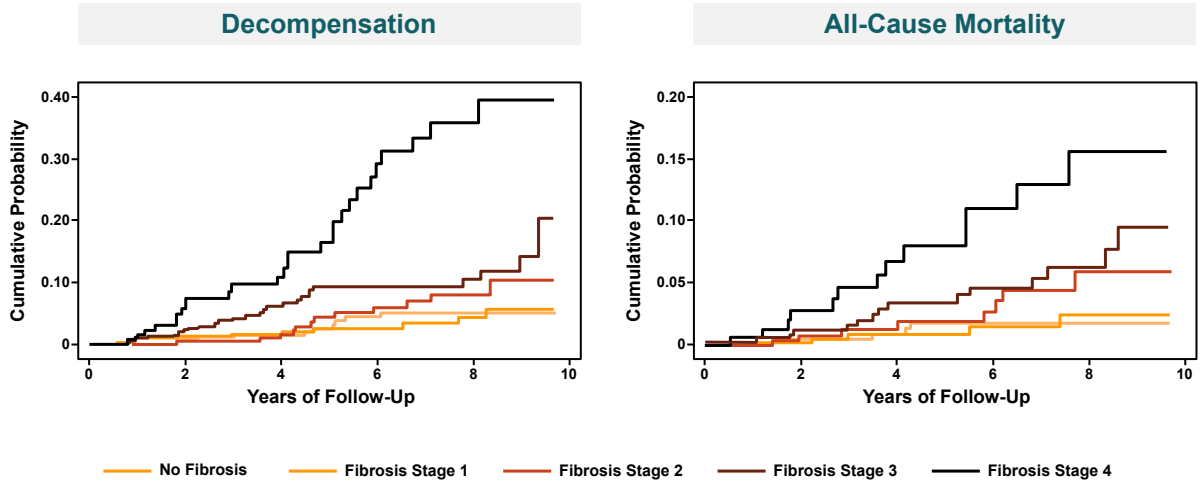
Up to 25% probability of progression to cirrhosis in as little as 2-4 years

Progression to Cirrhosis

- Platelet count = 100,000
- Liver stiffness = 25 kPa
- eGFR = 55
- Risk of decompensation
- Unlikely to qualify for liver transplant

CC-112

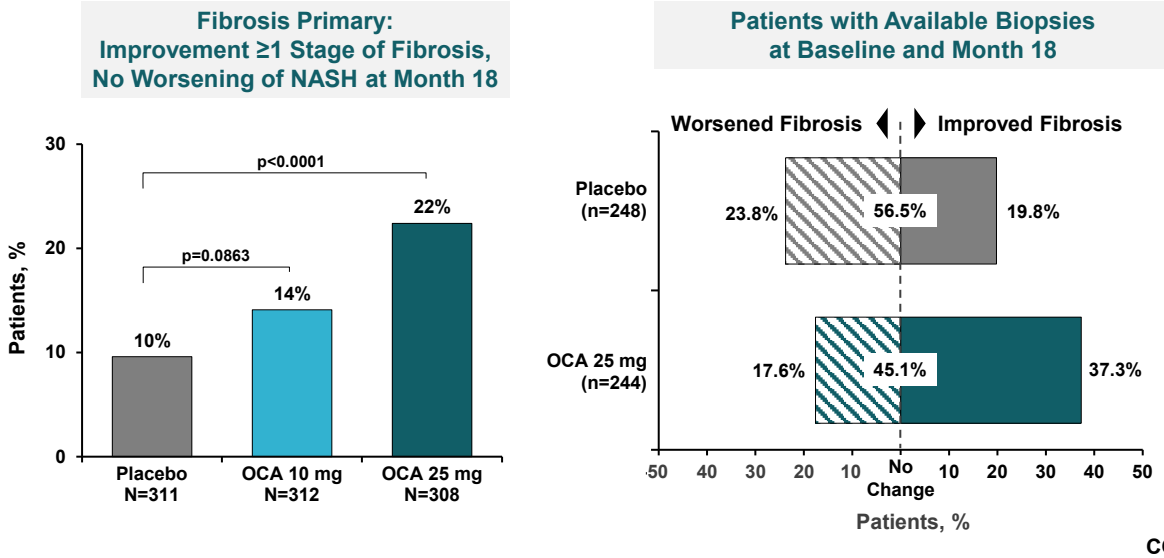
Fibrosis is the Strongest Predictor of Negative Outcomes



Adapted from Sanyal AJ, et al. *N Engl J Med*. 2021;385(17):1559–1569.

CC-113

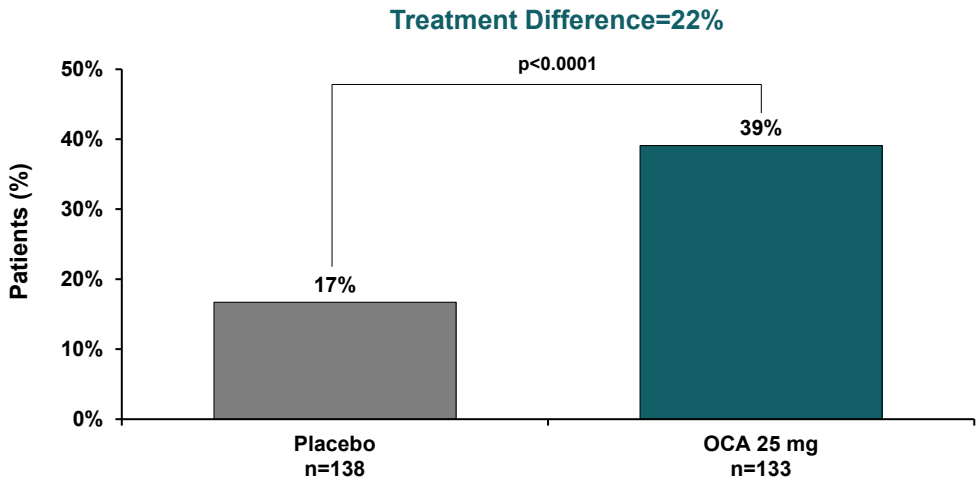
Clinical Assessment of Efficacy: Fibrosis



CC-114

Robust Response for Fibrosis Stage 3
(ITT_old Population, Available Baseline and Month 18)

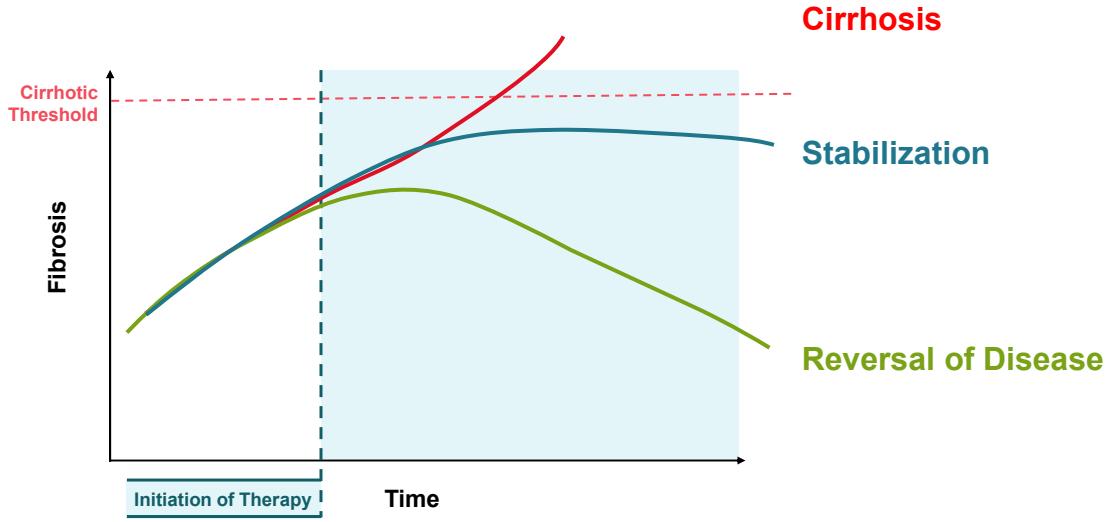
Improvement ≥1 stage of fibrosis at Month 18



N is number of patients with both baseline and post-baseline biopsy.

CC-115

OCA Can Bend the Curve Away from Progression to Cirrhosis



CC-116

Addressing FDA Concerns Regarding Operationalization

- Patient selection
- Hepatotoxicity
  - Monitoring for DILI
  - Monitoring for progression to cirrhosis
- Management of other TEAEs
  (e.g., increased LDL-C and worsening glucose intolerance)

CC-117

Monitoring for DILI

Topic	Clinical Practice
Frequency and Duration of Monitoring	▪ Management of NASH is lifelong ▪ Routine, 6-month follow-up typical; greater frequency feasible if needed ▪ Allows identification of asymptomatic elevation of liver chemistry

2017 Safety Amendment	▪ Interruption of drug when:
	  ▪ Liver chemistry criteria are met
	  ▪ Acute intercurrent illness

Difficult to Distinguish DILI from Typical Fluctuations	▪ Small lab excursions are common but rarely represent DILI ▪ Clinically significant elevations in liver enzymes, bilirubin, and INR more relevant ▪ Suspected DILI requires discontinuation of all possibly-offending drugs ▪ DILI identification is a core competence of hepatologist/gastroenterologist
Liver Biopsy	▪ Rarely required, unless severe liver dysfunction persists despite drug discontinuation

CC-118

Monitoring for Progression to Cirrhosis

Topic	Clinical Practice
Standard Schedule is Infeasible	▪ Routine follow-up is standard clinical practice
NITs Lack Predictive Value	▪ 2023 AASLD guidance states NITs can reliably identify patients who have progressed to cirrhosis ▪ Baveno NIT criteria for assessment of clinically significant portal hypertension
Sub-specialty Care Required	▪ Hepatologists, gastroenterologists, and others under their supervision will manage and prescribe OCA per labeling

CC-119

Management of Other TEAEs

Topic	Clinical Practice
Metabolic Comorbidities	▪ Comorbidity profile in NASH often warrants multi-disciplinary care and multiple medications as background therapy ▪ Increase in LDL can be managed with statins
Gallstones	▪ Increased background risk of gallstone disease with NASH ▪ Incremental risk with OCA is small ▪ Symptomatic gallstones should be managed before initiating OCA
Pruritus	▪ Early and generally manageable

CC-120

Benefit – Risk Profile is Favorable for Accelerated Approval

- Patients are progressing towards cirrhosis now
- OCA has proven anti-fibrotic benefit and can potentially prevent progression to cirrhosis
- Management of OCA therapy is within the scope of GI/Hepatology
- Totality of evidence supports accelerated approval of OCA

CC-121

Intercept

Application for Accelerated Approval:
Obeticholic Acid (OCA) for the Treatment of Adult Patients with Pre-cirrhotic Liver Fibrosis due to Nonalcoholic Steatohepatitis (NASH)

Backup Slides Displayed

CC-122

Parameters for Noninvasive Assessment for Diagnosis of Cirrhosis

AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease

Mary E. Rinella, MD, Brent A. Neuschwander-Tetri, MD, Mohammad Shadab Siddiqui, MD, Manal F. Abdelmalek, MD, MPH, Stephen Caldwell, MD, Diana Barb, MD, David E. Kleiner, MD, PhD, Rohit Loomba, MD, MHSc

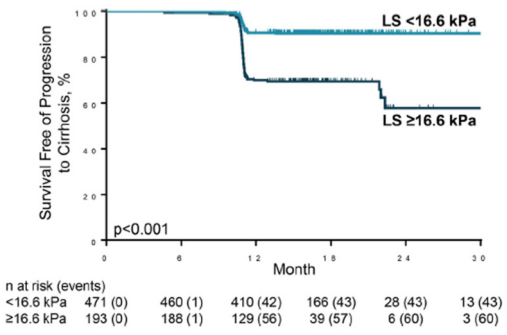
Diagnosis of Cirrhosis (Rule-in or Rule-out)		
CPR	FIB-4	90% specificity cut point for ruling-in and 90% sensitivity for ruling-out cirrhosis, respectively
Serum	ELF	ELF ≥11.3 is associated with increased risk of hepatic decompensation among patients with cirrhosis
Imaging	VCTE	LSM by VCTE ≥20 kPa is associated with cirrhosis, but for ruling out, cirrhosis optimal cut point is <8 kPa
Imaging	MRE	LSM by MRE ≥5 kPa has a very good (approaches 95%) specificity for diagnosis of cirrhosis and is also associated with increased risk of incident hepatic decompensation

AASLD Practice Guidance on the Clinical Assessment and Management of NAFLD (Hepatology 2023)

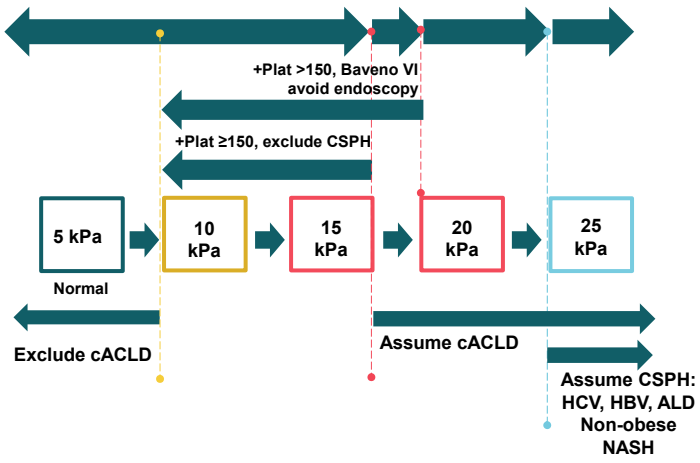
BU-1264

5kPa (and 20%) Increase in Liver Stiffness (TE) is a Strong Independent Predictor for Progression to Cirrhosis

5 kPa (and 20%) Increase in LS Predicts Progression to Cirrhosis[1*]



Liver decompensation and liver-related death[2]



*A ≥5 kPa (and ≥20%) increase in liver stiffness (TE) is a strong and independent predictor for progression to cirrhosis[1]

1. Loomba R et al. Gut 2023. 2. de Franchis R et al. J Hepatol. 2022.

BU-1494

Table 12 – FDA BD: <30 Days

#	OCA Dose	FDA/HSAC Score*	Stage at BL	Days	Clinical Course	Mitigation	Confounders
2	10	3/3	F3	28	49/F, severe pruritus, cholestatic	D/C once jaundiced	Mirtazapine
3	25	3/3	F3	28	63/F, cholestatic	Probable cirrhosis at baseline by NITs (TE >25 kPa, FIB-4=3.3, Platelets <150k)	Methotrexate, mirtazapine
9	25	4/3	F3	28	57/M, mixed pattern	Probable cirrhosis at baseline by NITs (Initial TE=48 kPa)	

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely

BU-2128

Table 12 – FDA BD: 30 Day to 1 Year

#	OCA Dose	FDA/HSAC Score*	Stage at BL	Days	Clinical Course	Mitigation	Confounders
1	25	3/4	F2	150	63/M, N/V, rash, dark urine; cholestatic, D/C'd IP 13 days after initiation of symptoms, liver transplant	Stop drug onset symptoms	Allopurinol, diclofenac, amlodipine
10	25	4/4	F2	176	64/F, cholestatic	Probable cirrhosis at baseline by NITs (FIB-4=4.1, Platelets <150K)	
11	25	5/4	F2	363	59/M, mixed pattern	ETOH contraindicated	Heavy alcohol misuse
12	25	5/4	F3	251	68/M, cholestatic, 2 concomitant courses of amox/clav	Probable cirrhosis at baseline by NITs (FIB-4=4.5, Platelets <150K)	Amox/clav

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely

BU-2129

Table 12 – FDA BD: >1 Year

#	OCA Dose	FDA/HSAC Score*	Stage at BL	Days	Clinical Course	Mitigation	Confounders
4	25	3 or 4/5	F3	530	60/F, cholestatic, in setting of CBD stone, sepsis due to cholangitis	• Cirrhosis by biopsy 2 months before presentation • D/C drug with intercurrent illness and hospitalization	4 days without cholangitis intervention, drug cont'd for 3 weeks post event
5	25	4/4	F1b	912	70/M, cholestatic, in setting of CBD stone	D/C drug with intercurrent illness and hospitalization	
6	25	4/4	F2	408	68/F, cholestatic, hip fracture with repair	D/C drug with intercurrent illness and hospitalization	Cefazolin
7	25	4/4	F3	461	65/F, cholestatic, in setting of CBD stone	Probable cirrhosis (TE=20.9 at BL)	Liraglutide
8	10	4/4	F3	833	59/F, cholestatic, hyponatremia	Drug D/C'd with suspected intercurrent illness	Non-compliance, history of cholelithiasis

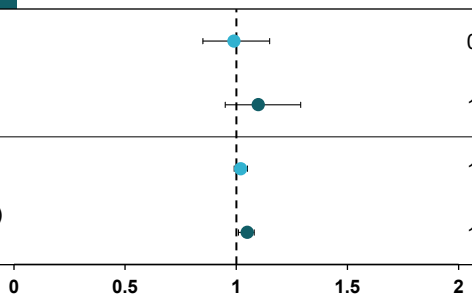
*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely

BU-2130

Gallstone Status at Baseline and Treatment Emergent AESI (Study 303)

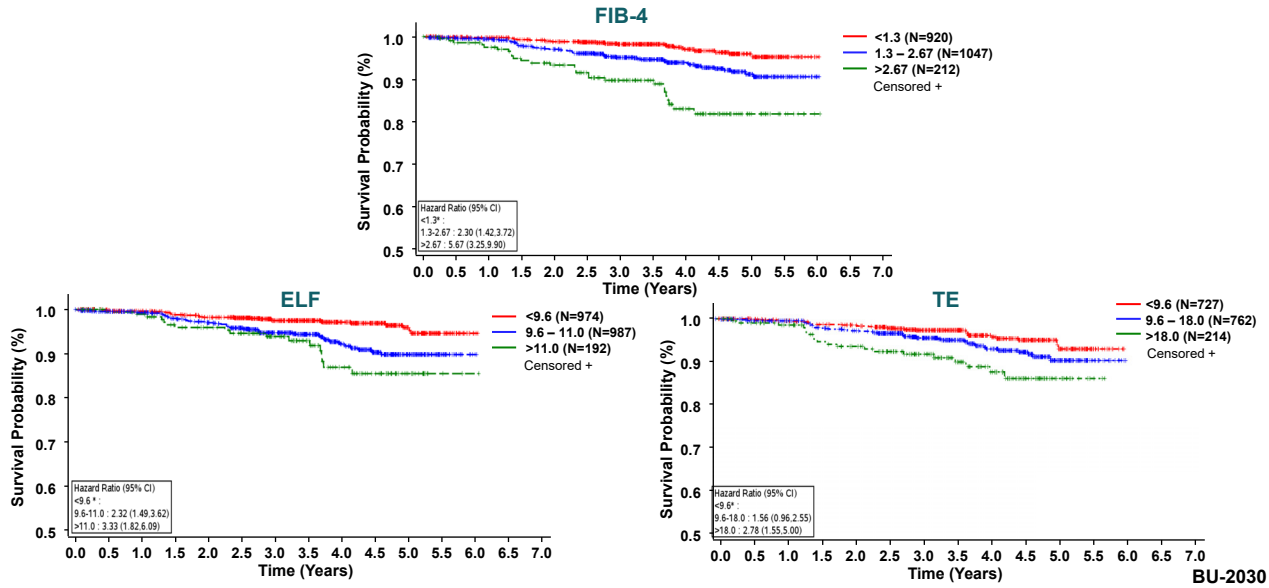
Incidence of Gallbladder/Gallstone-related AESI

Method	Incidence: Placebo	Incidence: OCA 10 mg	Incidence: OCA 25 mg	Relative Risk (95% CI)
Definite Gallstones at Baseline, % (n/N)	12.7% (7/55)	11.1% (5/45)	20.3% (15/74)	0.99 (0.85, 1.15) 1.10 (0.95, 1.29)
No Gallstones or Not Documented at Baseline, % (n/N)	4.6% (26/562)	6.5% (37/566)	8.9% (47/528)	1.02 (0.99, 1.05) 1.05 (1.01, 1.08)



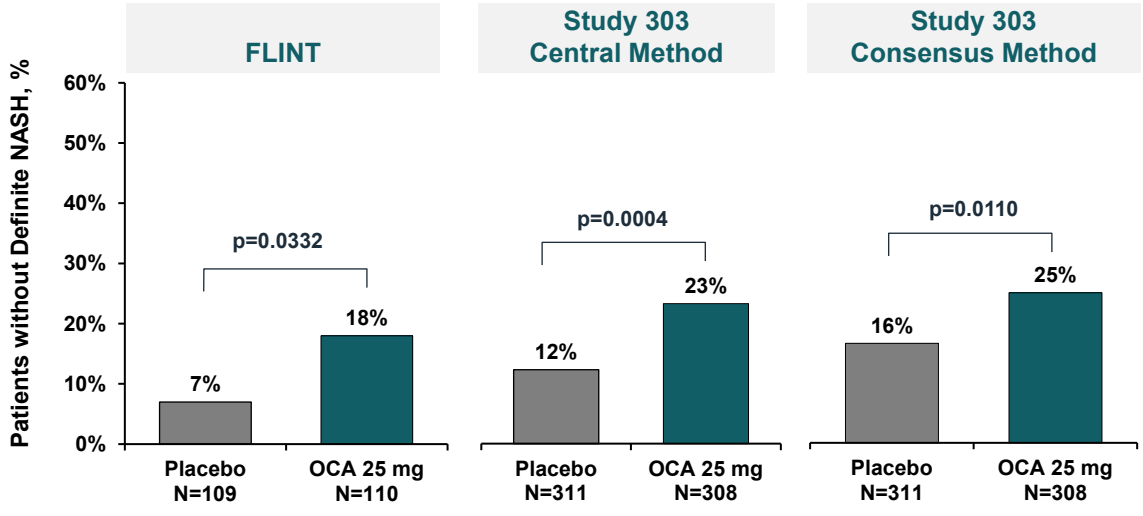
BU-1289

Time to First Hepatic Clinical Outcomes by Baseline
(ITT_all Population: Blinded Data)



BU-2030

Global Pathology Assessment of NASH Resolution
(Study 303: ITT_old, N=931 and FLINT: mITT, N=219)



BU-1341