durect

Key Opinion Leader Discussion:

Larsucosterol & Alcohol-associated Hepatitis

May 16th, 2023

Agenda

- Introduction / Welcome
  - Jim Brown, DVM
- What is AH?
  - Paul Gaglio, MD
- Larsucosterol: Addressing the AH Treatment Gap
  - Brett Fortune, MD
- Larsucosterol and the Phase 2b AHFIRM Trial
  - Norman Sussman, MD
- Larsucosterol Commercial Opportunity
  - Keith Lui
- Q&A

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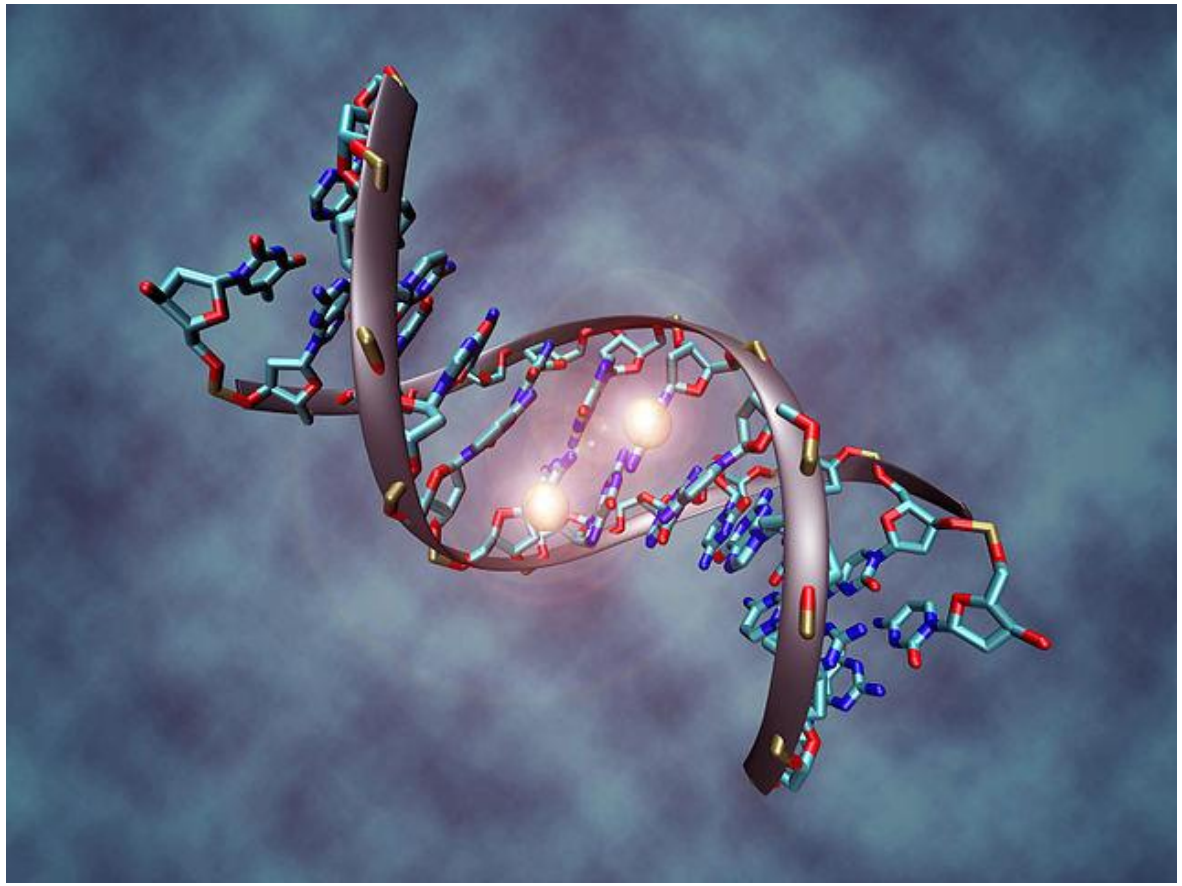
Introduction

Jim Brown, DVM
President and
Chief Executive Officer

Harnessing the Power of Epigenetics



- **Epigenetics** focuses on altering gene expression without changing DNA sequences
  - These changes can be inherited and/or environmental
  - Disease states can change epigenetics
  - Epigenetic changes can manifest as disease
- Examples of such changes are DNA methylation and histone modification
  - **Larsucosterol** acts by reducing DNA hypermethylation

Larsucosterol Overview

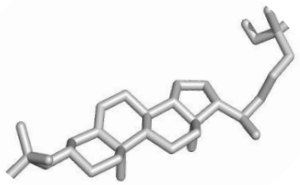
Lead Compound in DURECT's Epigenetic Modulator Program

Modulator of DNA methylation

- New class of therapeutics
- Endogenous sulfated oxysterol
- Highly conserved across all 7 species studied to date

Clinical safety

- Well tolerated at all doses
- More than 500 subjects dosed in multiple Phase 1 & 2 studies



Larsucosterol
5-cholesten-3β, 25-diol 3-sulfate (25HC3S)

Role in cellular functions

- Stabilizes mitochondria
- Reduces lipotoxicity
- Reduces inflammation
- Improves cell survival and tissue regeneration

Broad therapeutic potential

- MOA[1] supports investigating larsucosterol for the treatment of multiple acute organ injury and chronic diseases
- Phase 1b NASH data suggest broad activity

[1] MOA = Mechanism of Action

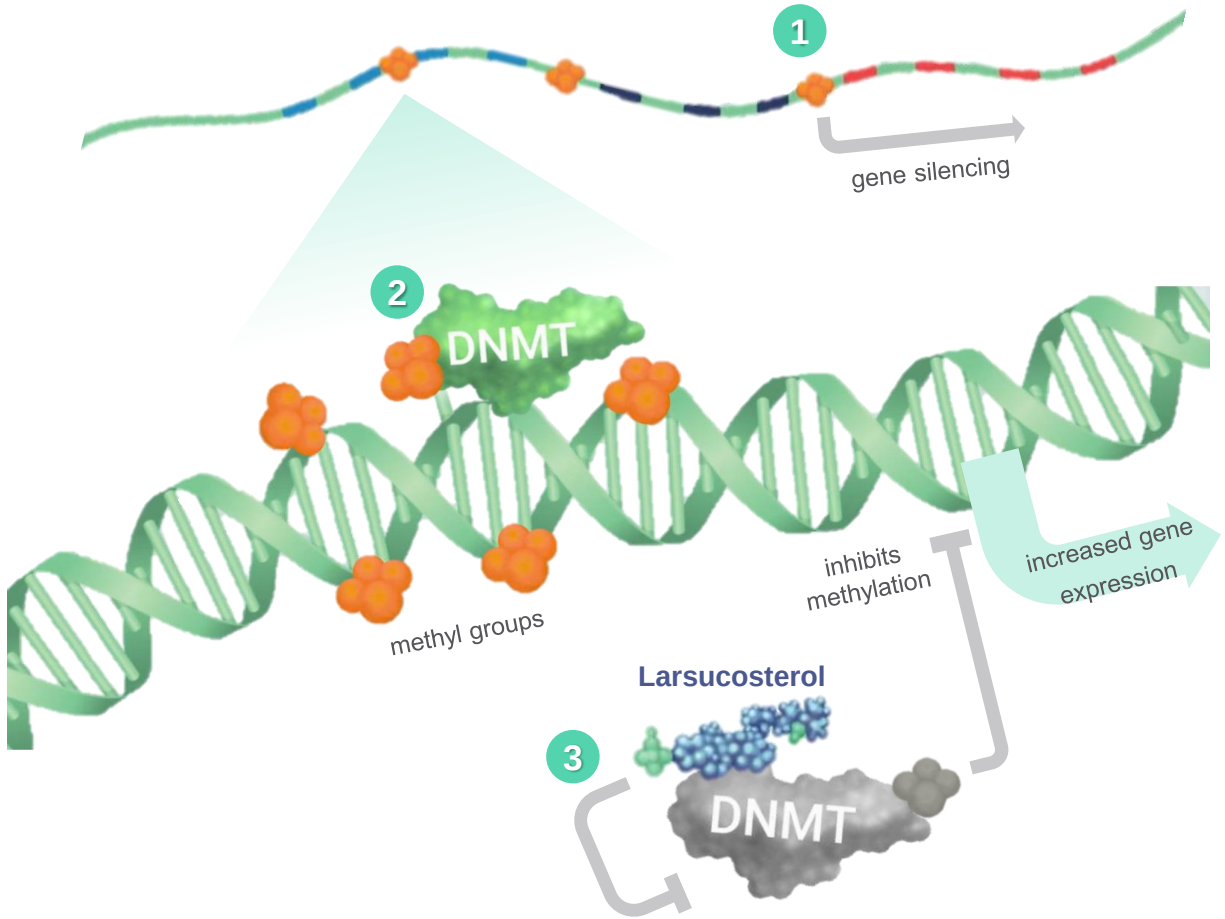
Larsucosterol Has Been Studied in Broad Range of Indications

Compelling data in all animal models

Clinical Trials	Acute Organ Injury Models	Chronic Disease Models
AHFIRM Phase 2b AH[1] n≈300/200 larsucosterol	Acetaminophen / Alcohol Injury Mouse	High Fat Hamster
Phase 2a AH (n=19)	Endotoxin Injury Mouse	High Fat Mouse
Phase 2a Psoriasis (n=25)	Acute Pancreatitis Rat	STAM™ NASH
Phase 1b NASH (n=69)	Brain Ischemic Injury Rat	Bile Duct Ligation Rat
Additional Clinical Trials (combined n>200)	Renal Ischemic Injury Rat	Leptin Deficient Rat

[1] Ongoing trial. AH = Alcohol-associated Hepatitis.

Mechanism of Action Leverages Epigenetics to Impact Disease



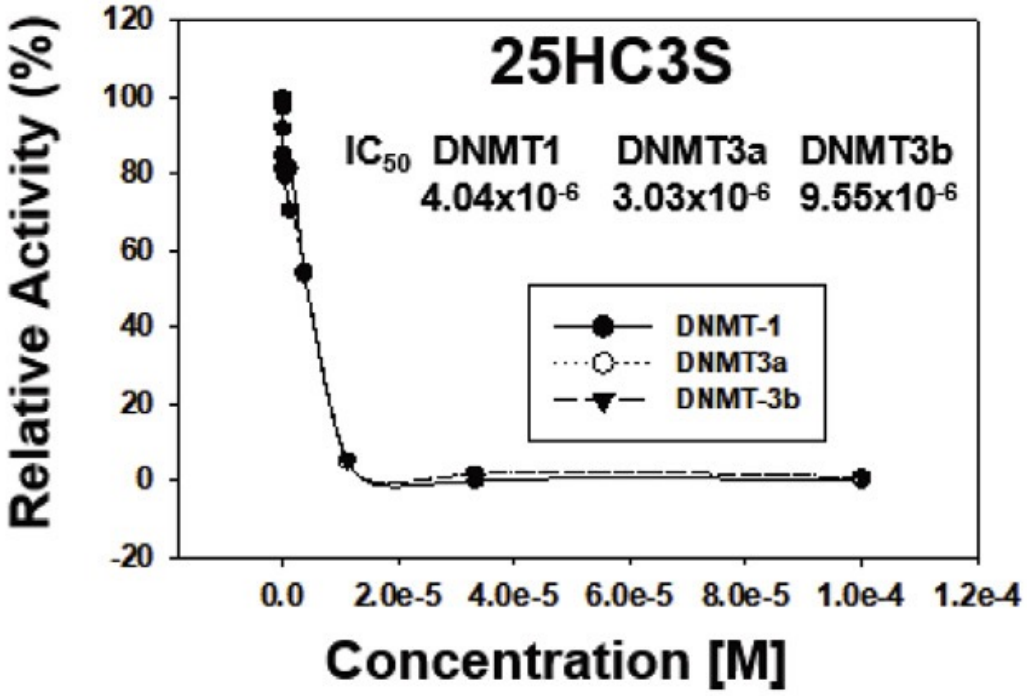
1 **Epigenetic Dysregulation in AH Patients**
Aberrant DNA hypermethylation is associated with many diseases including severe AH

2 **Epigenetic Regulators Modulate Gene Expression**
DNA methyltransferases (DNMTs) are one such regulator that add methyl groups to certain regions of DNA, generally reducing gene expression

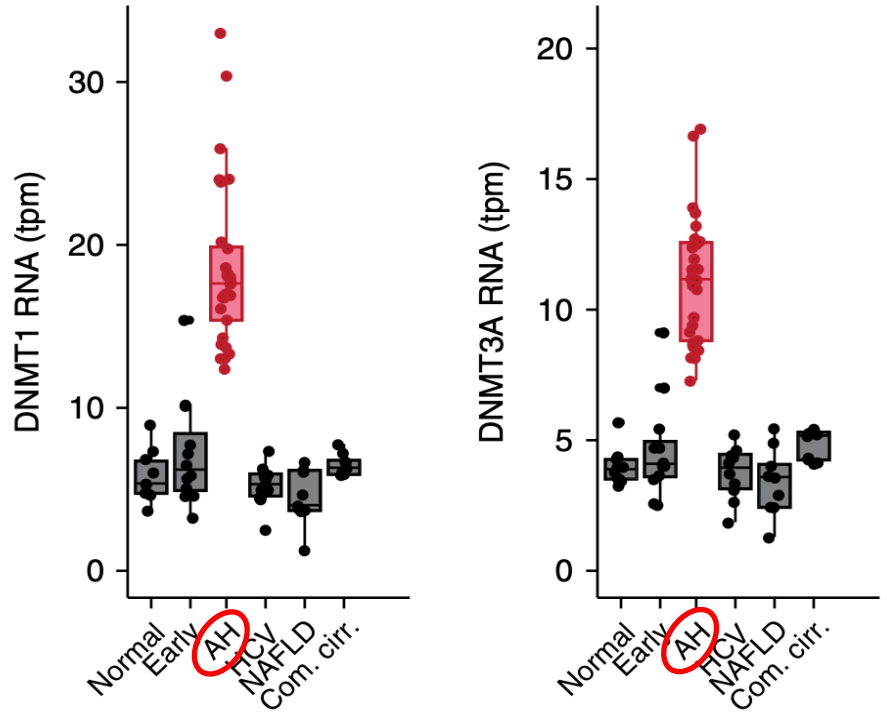
3 **Larsucosterol Inhibits DNMTs**
By inhibiting DNMTs (1, 3a, & 3b), larsucosterol reduces DNA hypermethylation, which modulates important cell signaling pathways

Inhibition of DNMT-1, 3a & 3b Aligns with AH

Liver samples from patients with severe AH have increased expression of DNMT-1 & 3a



Wang Y et al. 2021, Journal of Lipid Research, 62:1-14



Argemi et al. 2019. Nature Communications, 10: 3126

Note: in this paper, larsucosterol is referred to as 25HC3S

What Is AH?

Paul Gaglio, MD
Director of Hepatology Outreach, Columbia

Dr. Paul J. Gaglio: Biography and Disclosures

- Paul J. Gaglio, MD, FACP, AGAF, FAASLD, Professor of Medicine (in Surgery)
  - Director of Hepatology Outreach at NY-Presbyterian Hospital, Columbia University Irving Medical Center
  - Former Medical Director of Adult Liver Transplantation at the Montefiore Medical Center, Columbia Presbyterian Hospital, and the Tulane University Medical Center
  - Education & Training:
    - Bachelor's in Biology/Physiology from Rutgers College
    - MD from UMDNJ-New Jersey Medical School
    - Internship and Residency at Mount Sinai Medical Center
    - Fellowship in Digestive Disease/Liver Transplantation at New Jersey Medical School
  - Fellow of the American College of Physicians, the American Gastroenterological Association, and the American Association for the Study of Liver Diseases

Disclosures: Advisory Board for Gilead, AbbVie, Salix, Mallinckrodt, & Intercept

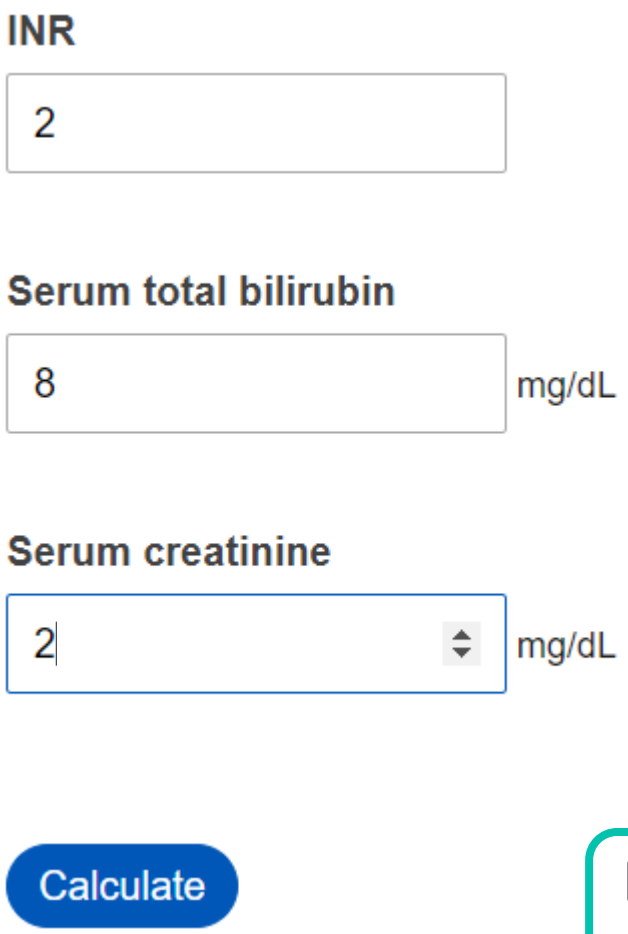
What Is AH?

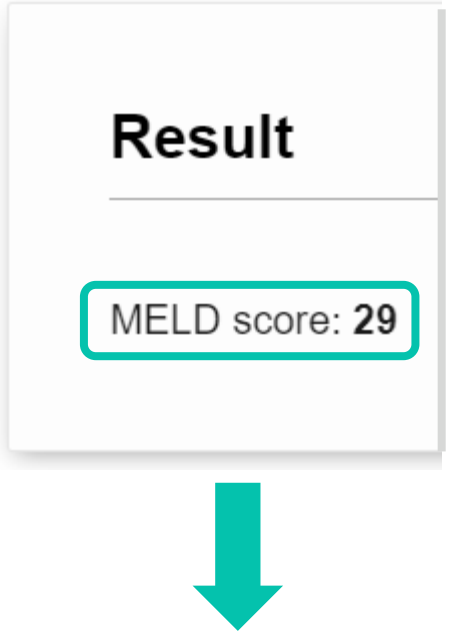
- A typical patient with alcohol-associated hepatitis (AH)
- What is excessive drinking?
  - AH is usually associated with very heavy drinking
- AH as a distinct clinical entity with a high mortality
  - Multiple causes of death including sepsis and liver failure
- Methods of assessing AH severity
- Current therapeutic options

Case Presentation – A Sample Patient Journey

- 40 year old man, transferred from an outside hospital with jaundice and concern for liver failure
- Past medical history includes type 2 DM, hyperlipidemia, BMI 31
- Labs at transfer: MELD 29 (Model for End-stage Liver Disease)
- Lives with his wife and three children
- Denies prior heavy alcohol consumption until 6 months ago
  - He increased alcohol use due to "stress at work"
  - He consumes approximately 1 bottle of wine each evening and one bottle of wine plus 3-4 mixed drinks on weekends
    - ~50 "units" of alcohol per week

Higher MELD Scores Correlate with Increased Mortality





Expected 90-day mortality: 45-58%

Components of MELD Score

- INR – blood clotting
  - Factors are made by the liver
- Bilirubin – yellow pigment derived from red blood cells
  - Causes jaundice
- Creatinine – measure of kidney function

MayoClinic.org

NIAAA Definitions for Adults of Drinking Age

Moderate

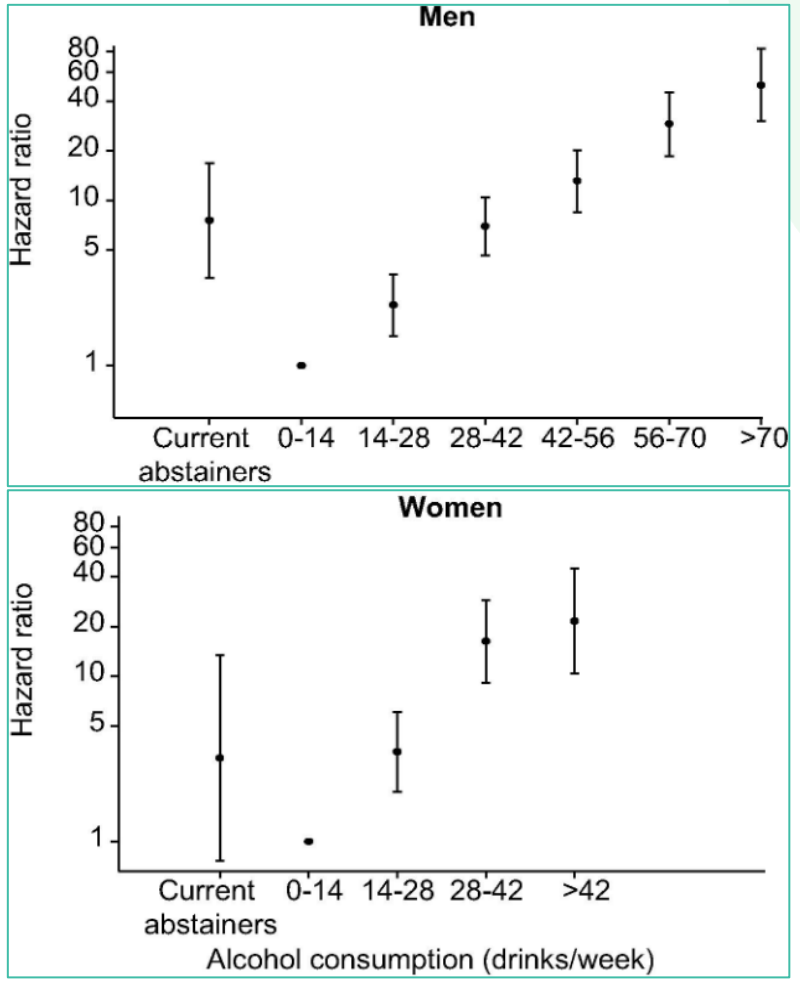
- Men: 2/day (≤14/week)
- Women: 1/day (≤7/week)

Heavy

- Men: 4/day or >14/week
- Women: 3/day or >7/week

Binge: Blood alcohol ≥0.08%

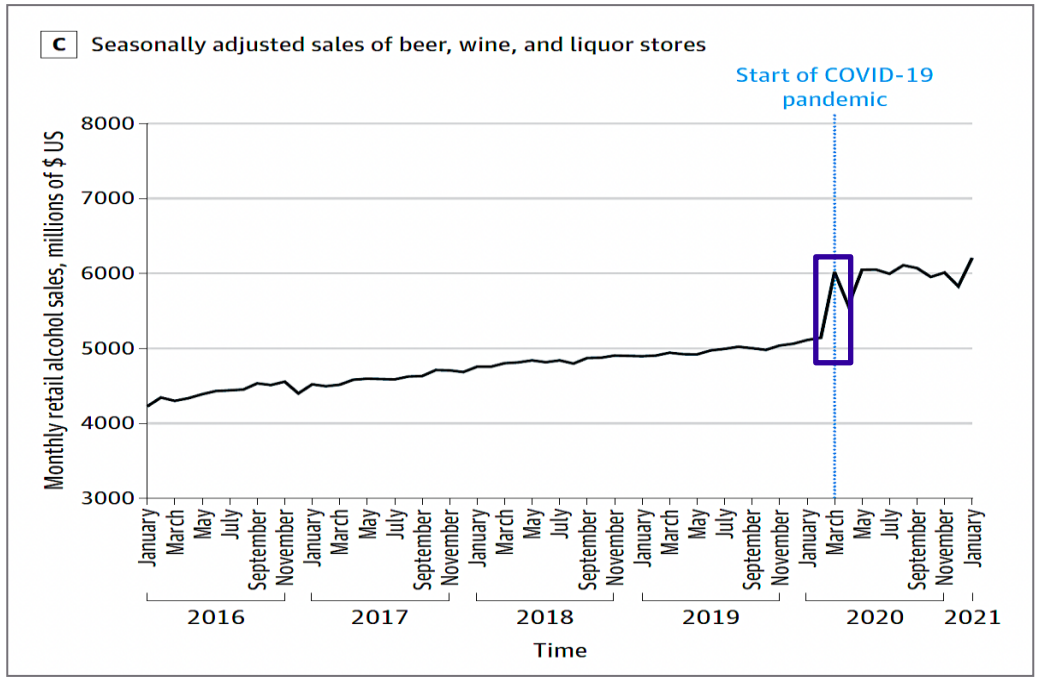
- Men: ≥5 drinks in ~2 hours
- Women: ≥4 drinks in ~2 hours



Asgaard, G et al. J Hep 2015; 62:1061-1067

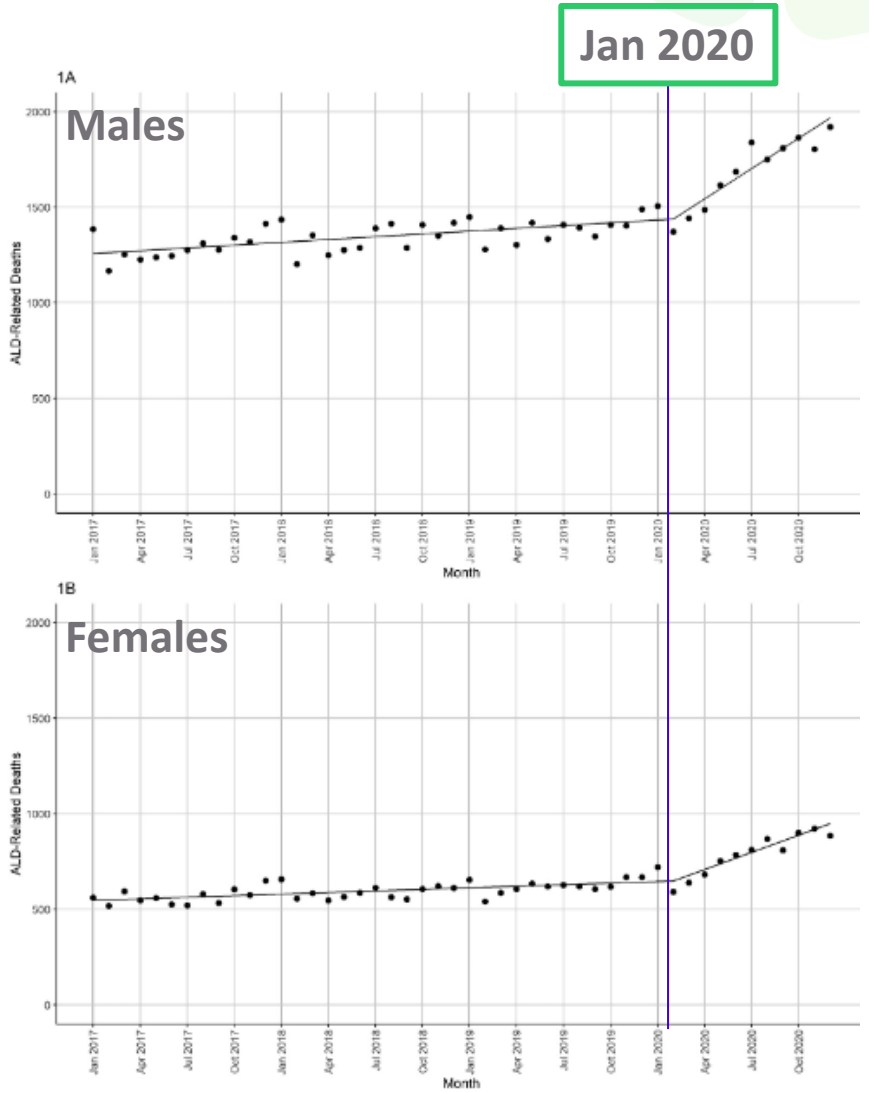
Alcohol Sales and Alcohol-Related Deaths Rising Steadily

Exacerbated by Covid/Quarantine



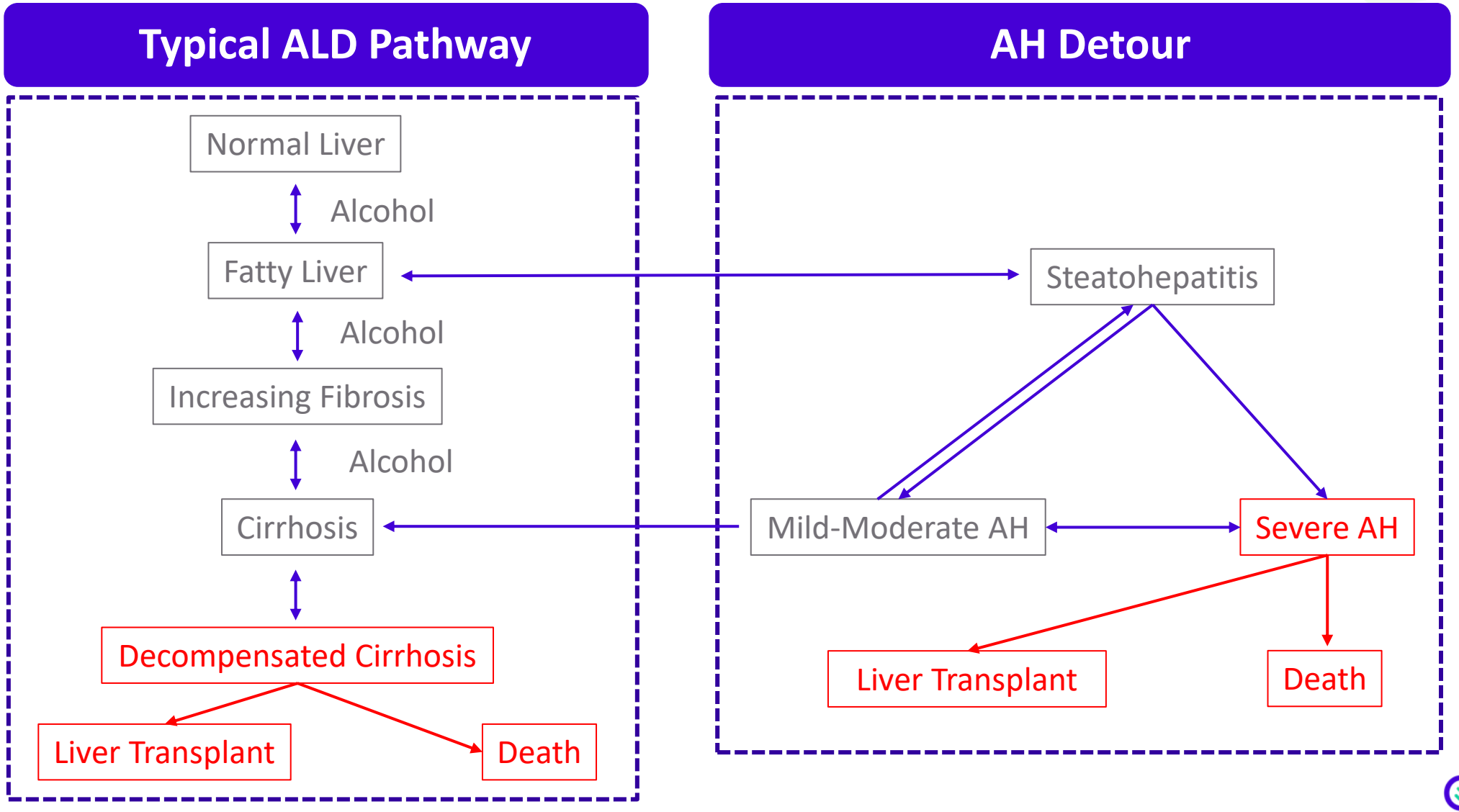
Anderson MS, et al. JAMA Open 2021

National monthly retail alcohol sales 2016-2021 for purchases from beer, wine, and liquor stores from the US Census Bureau Monthly Retail Trade Report

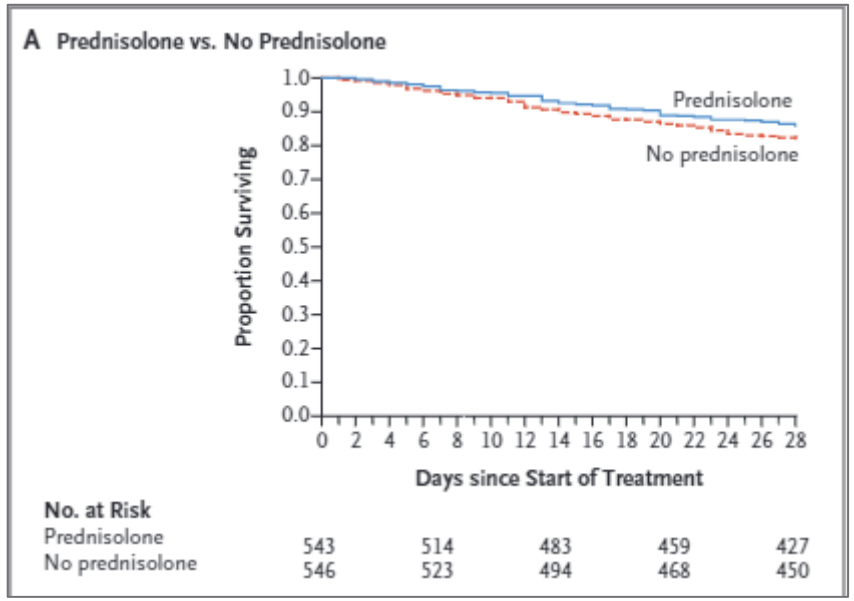


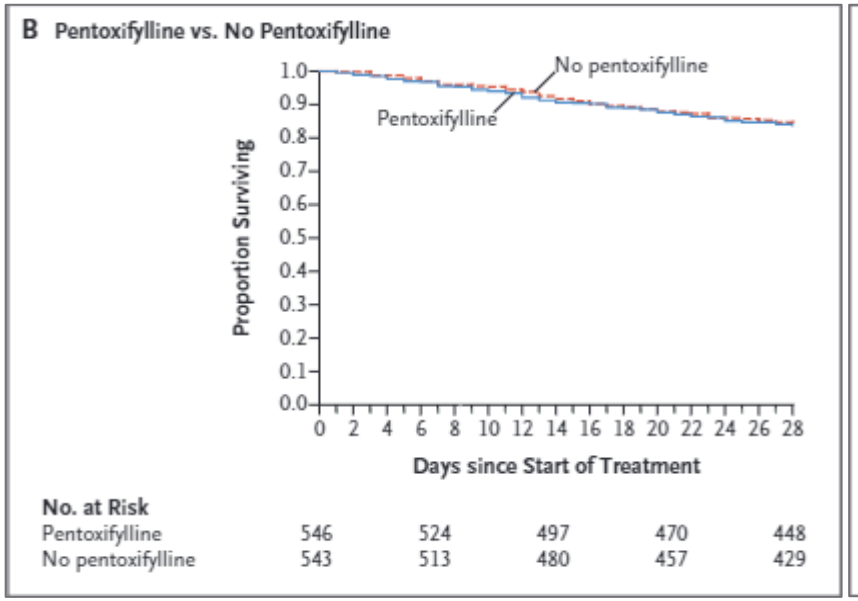
Deutsch-Link, S et al. Clin Gastro and Hep 2022;20:2142–2144

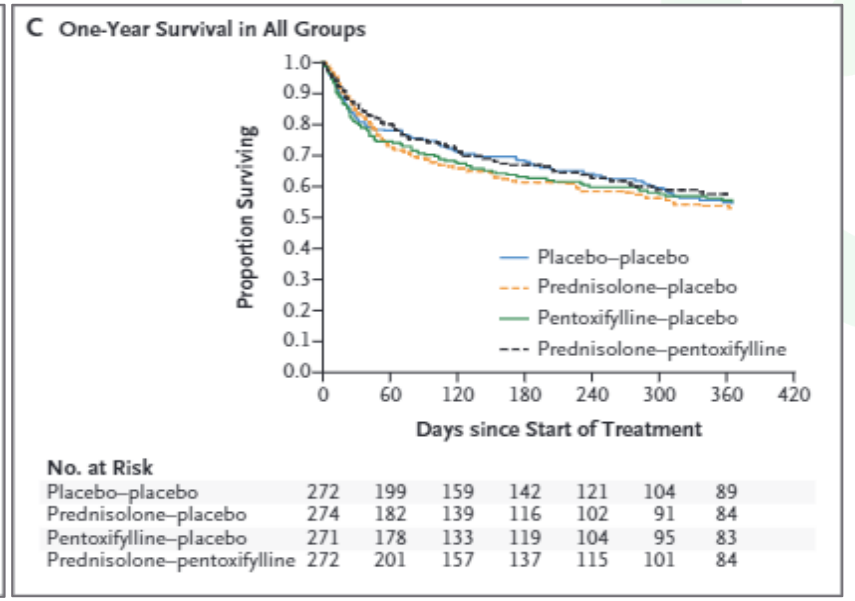
AH is a Detour



AH is Associated with Heavy Drinking and a Serious Risk of Death







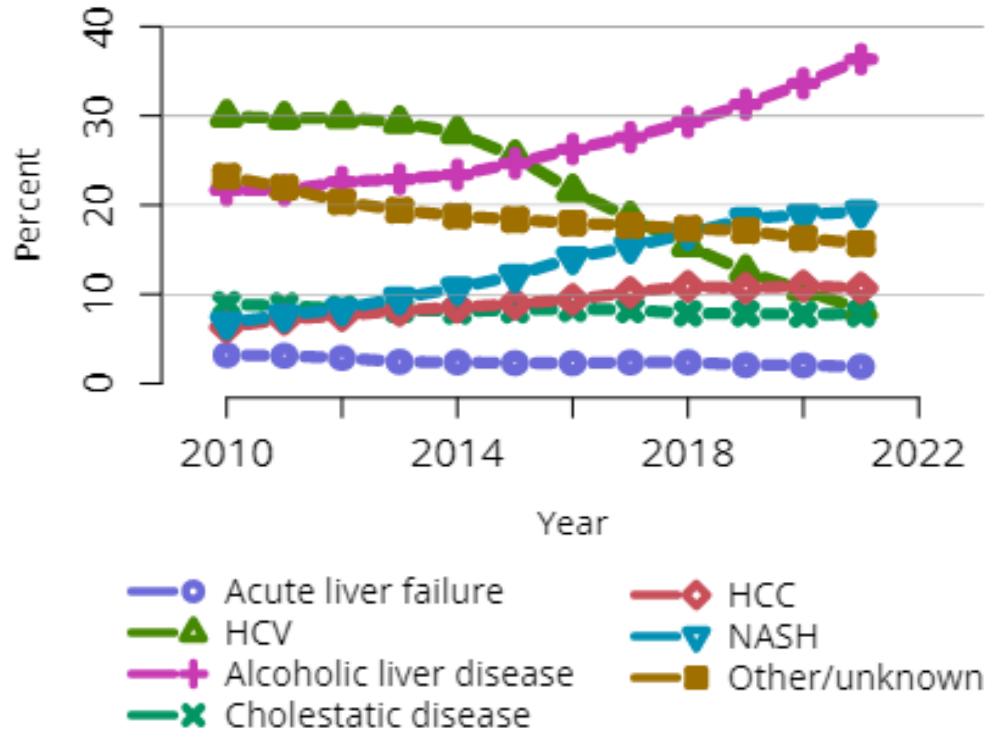
Age	49 yrs	**Maddrey**	63
Male	60%	**MELD**	21
EtOH (F)	150 g/day	**GAHS**	8.4
EtOH (M)	200 g/day	**Mortality (28/90)**	16%/30%

Thursz M et al. N Engl J Med 2015; 372:1619-28

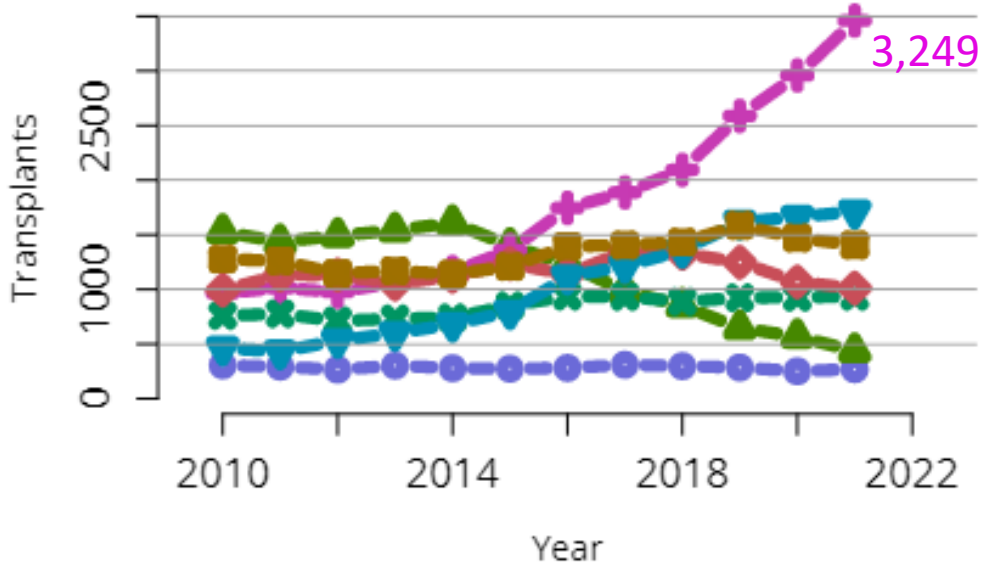
18

Alcohol is Currently the Leading Cause for Liver Transplantation

Transplant Listing by Diagnosis



Liver Transplants by Diagnosis



~8,700 adult liver transplants in 2021
Insufficient to meet patient needs

Kwong AJ et al. OPTN/SRTR Annual Data Report, 2021

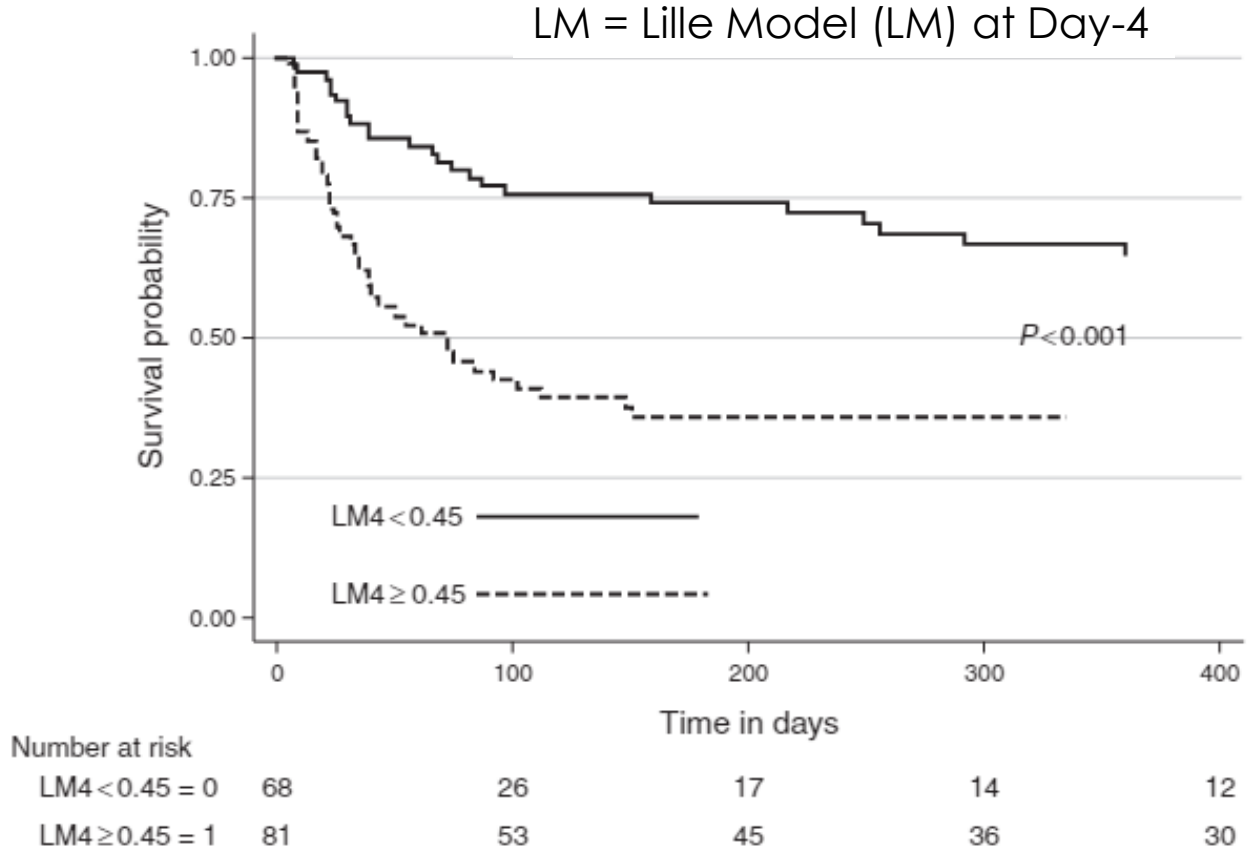
Case Presentation – Patient Journey (continued)

- Blood and urine cultures negative at time of admissions
- CXR was normal
- Patient was eligible for prednisolone
  - Started prednisolone, B-vitamins, zinc, and nutrition
  - Lille score at day 4 did not improve – stopped prednisolone
- Presented to our multidisciplinary liver transplantation committee
  - Deemed to be a candidate for liver transplantation
- Transferred to ICU day 5 for hepato-renal syndrome
- Liver became available and he underwent liver transplantation

Lille Score at Day-4 Predicts AH Survival at 6 Months

Based primarily on declining bilirubin

Age		Years
Bilirubin Day 0		mg/dL
Albumin Day 0		g/dL
Creatinine Day 0		mg/dL
Protime Day 0		sec
Bilirubin Day 4		mg/dL



Garcia-Saenz-de-Sicilia et al. Am J Gastroenterol 2017; 112:306-315

Conclusions

- AH is a detour from usual alcohol-associated liver disease
- AH usually occurs in very heavy drinkers
- MELD and Lille scores predict risk of death
  - **30-50% mortality in severe cases of AH**
- Steroids may be used in severe cases
  - Frequently contraindicated
  - Not FDA-approved
  - **No effect on survival at 90 days**
- Liver transplantation may rescue a few at-risk patients
  - Only ~8,700 adult liver transplants for all indications in U.S.[1]
  - **Most patients are ineligible and many on transplant waiting list die each year**

[1]Kwong AJ et al. OPTN/SRTR Annual Data Report, 2021

Larsucosterol: Addressing the AH Treatment Gap

Brett Fortune, MD
Montefiore Medical Center

Dr. Brett Fortune: Biography and Disclosures

- Brett E. Fortune, MD, MSc, FAASLD, Associate Professor of Medicine
  - Associate Professor of Medicine at Albert Einstein College of Medicine
  - Medical Director, Liver Transplant Program at Montefiore Einstein Center for Transplantation
  - Associate Editor of *Liver Transplantation*
  - Active member of AASLD and AST
    - Past Chair of Public Health SIG
    - Steering Committee, Portal HTN SIG, Financial, Comm/Tech, Liver Intestine COP
  - Investigator on the AASLD CQC, ALTA study
  - Formerly on the NIH funded Liver Cirrhosis Network
  - Education & Training:
    - Fellowships in Gastroenterology and Transplant Hepatology at the University of Colorado

Disclosures: Consultant for W.L. Gore and Associates

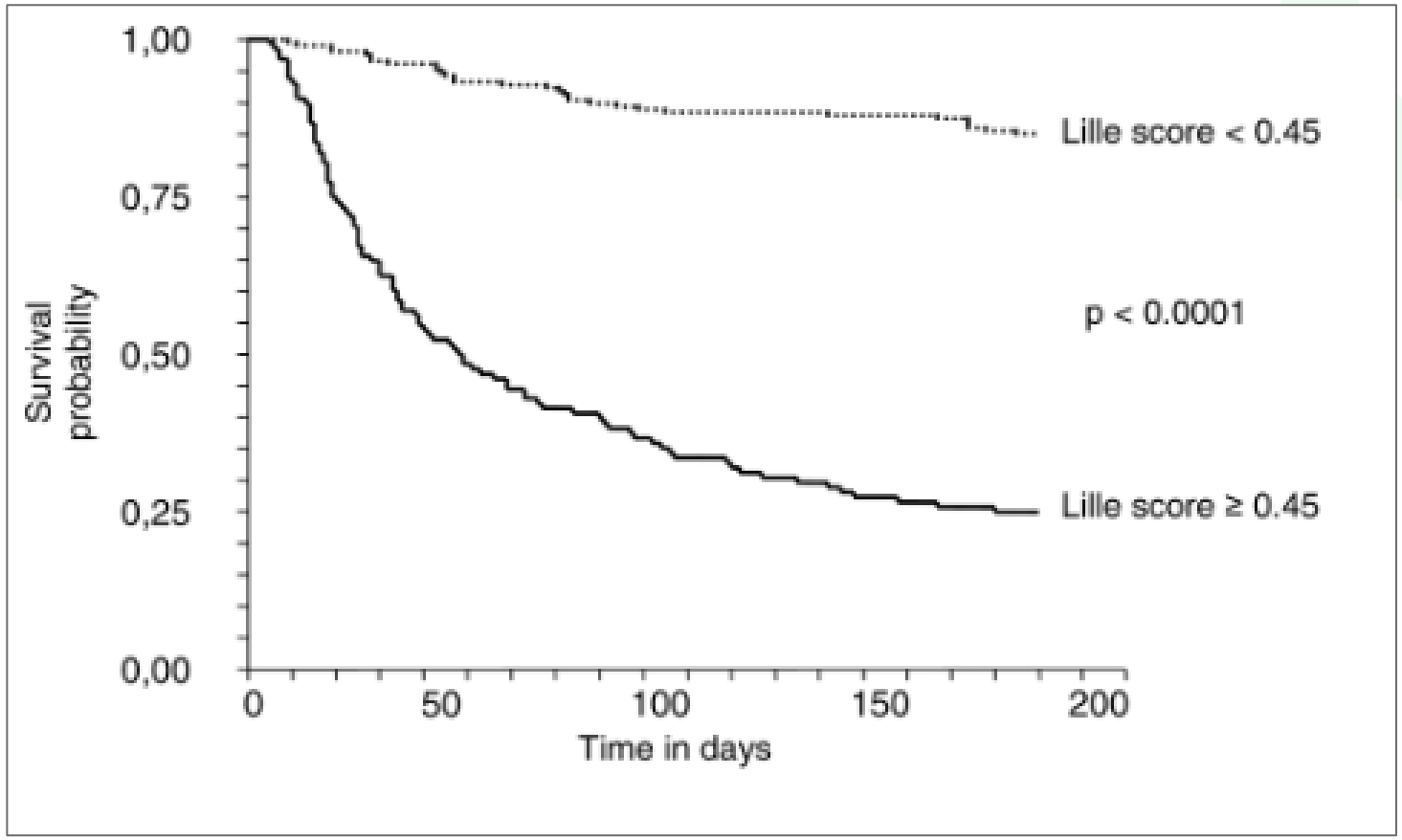
Current State of AH Treatment Options

- AH is potentially survivable
  - Need a therapeutic agent that improves odds for patients
- Steroids are controversial
  - Many contraindications and no long-term benefit
- Transplants benefit patients
  - Many patients are not eligible
  - Availability insufficient for qualified patients
- Declining bilirubin is the most important prognostic finding
  - Key element in the Lille score

Lille Score – Predicts AH Survival at 6 Months

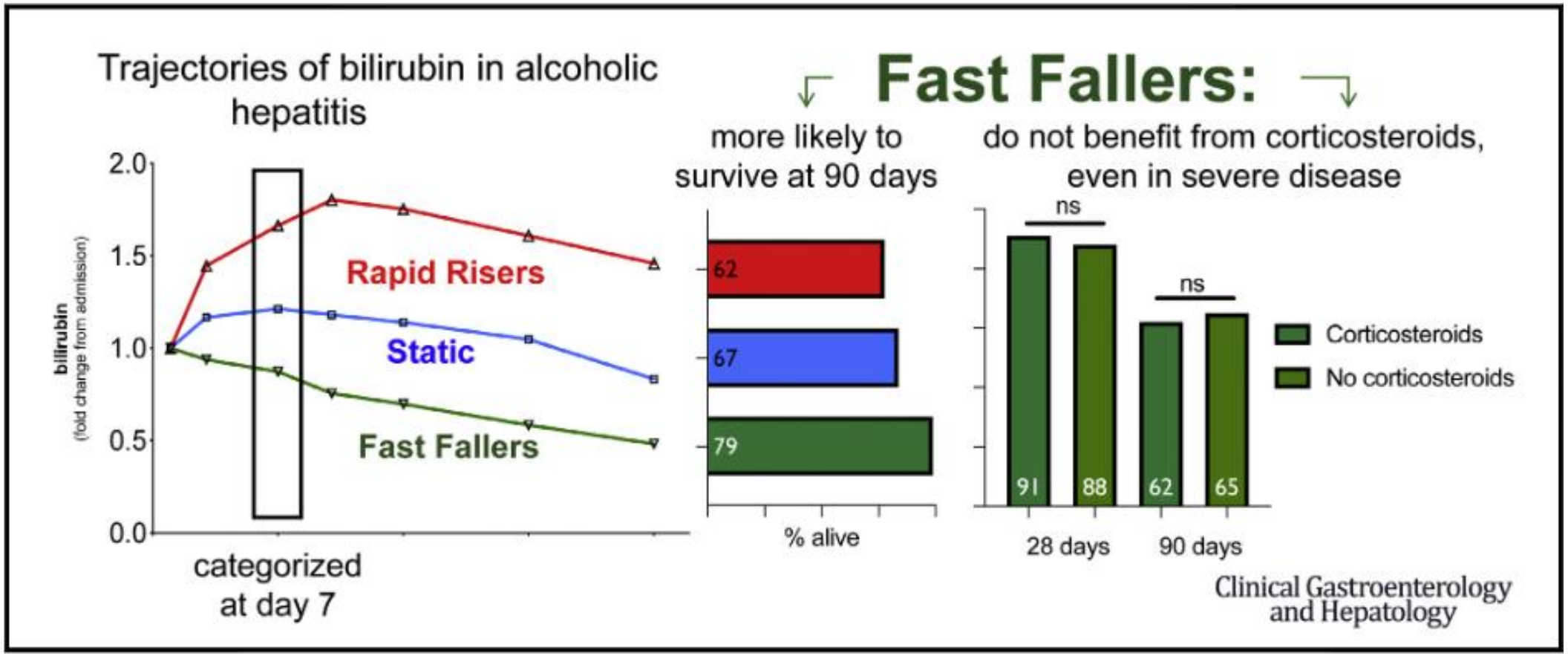
Based primarily on declining bilirubin day 0-7

Age		Years
Bilirubin Day 0		mg/dL
Albumin Day 0		g/dL
Creatinine Day 0		mg/dL
Protime Day 0		sec
Bilirubin Day 7		mg/dL



Louvet A et al. Hepatology 2007; 45:1348-1354

Decreasing Bilirubin Predicts AH Survival Irrespective of Steroids



Parker R et al. Clin Gastro Hepatol (2022); 20:e289–e297

Would an Effective Therapeutic Help with AH Management?

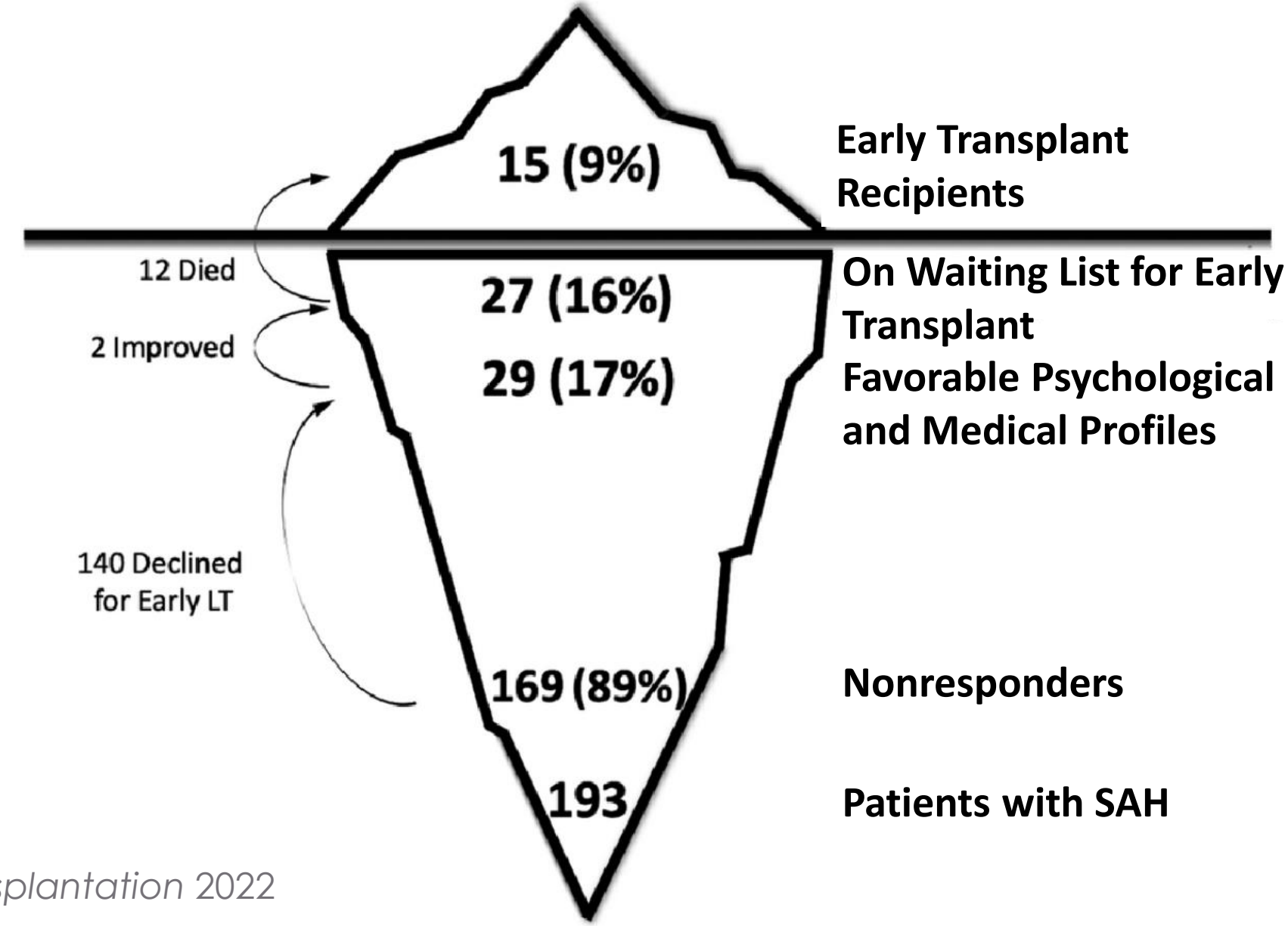
Transplant Is Not an Option for Most Severe AH (SAH) Patients

Only a minority respond to current SAH therapy

For nonresponders: Very few patients make it to liver transplant

Only 16% were wait listed for transplant

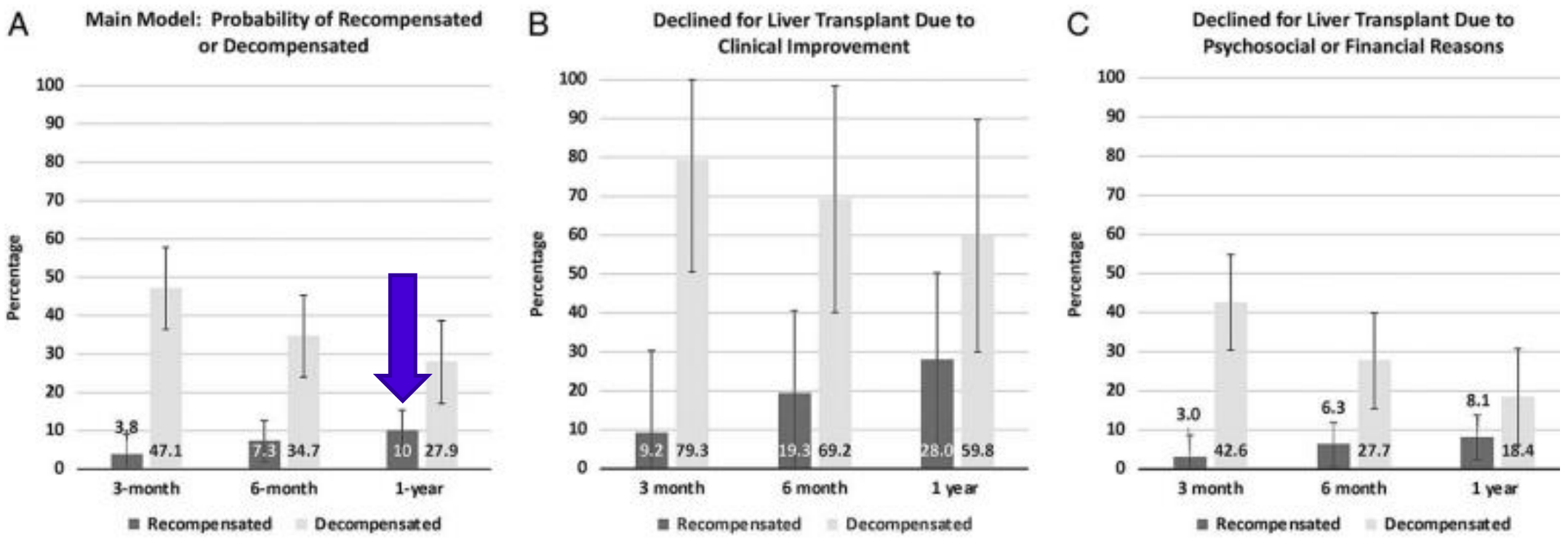
Likely overestimates transplant access



Im G, et al. *Liver Transplantation* 2022

Nonresponding Patients Declined for Transplant Are Unlikely to Regain Normal Liver Function and Have High Mortality

- 49% died after 6 months, only 10% had recompensation at 1 year



Hsu C, et al. ACCELERATE-AH group. *Hepatology* 2023

Would We Like an Effective SAH Therapeutic? – YES!!!

- SAH is a potentially survivable condition but lacks an effective treatment
  - Among nonresponders, liver transplant is the only curative option but rarely available to SAH patients

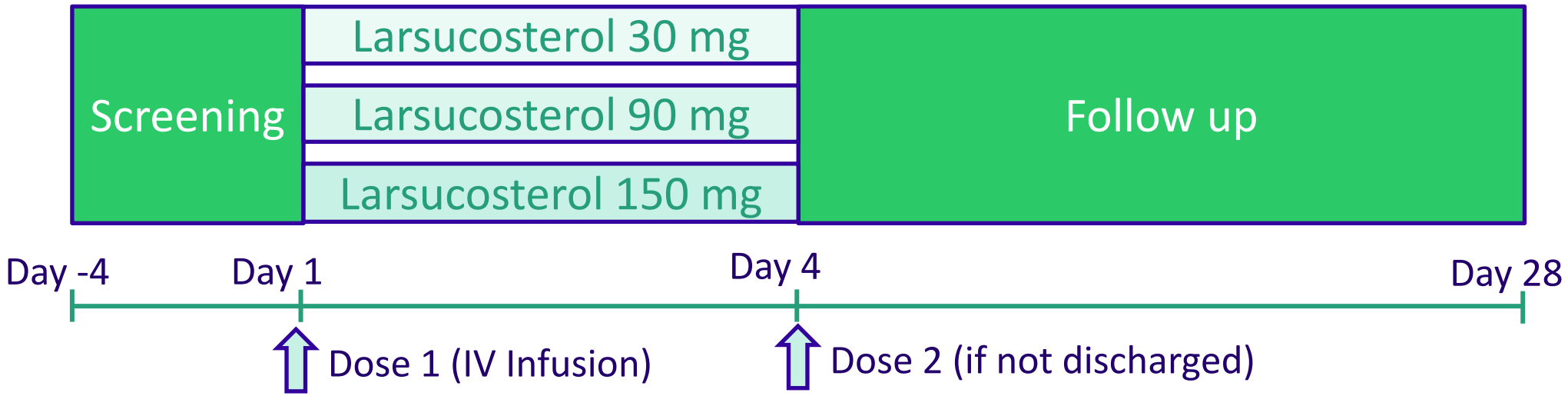
- An effective treatment for SAH would:
  - Improve short-term and (ideally) long-term transplant-free survival
  - Increase likelihood of hepatic recompensation
  - Reduce healthcare resource utilization
    - Reducing readmissions, costs
  - Have favorable safety profile for patients with advanced liver disease

Phase 2a: Evaluation of Larsucosterol in Patients with Moderate/Severe Alcohol-Associated Hepatitis

Key Inclusion Criteria

Moderate AH: MELD 11-20
Severe AH: MELD 21-30

Study Design



Endpoints

Primary

- Safety & tolerability
- Liver biochemistry (including MELD & Lille scores)

Larsucosterol: Summary of Phase 2a Trial in AH

100% Survival (19/19) in Open Label Phase 2a Trial in Patients with Moderate to Severe AH

- Improved key biomarkers and prognostic indicators
  - Reduced bilirubin and MELD scores
  - 89% response rate based on Lille score
- Well tolerated across all dose levels with no drug-related SAEs

Hassanein T, et al. Safety and efficacy of DUR-928: A potential new therapy for acute alcoholic hepatitis. Late-breaking oral presentation at 70th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting™, 2019

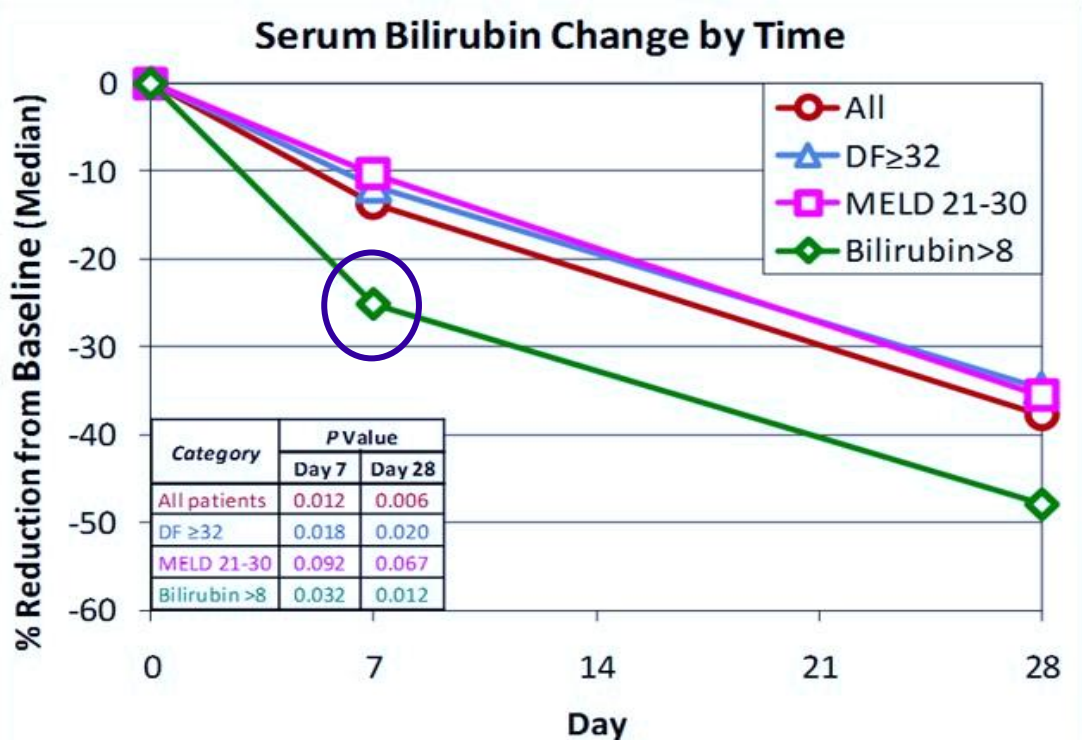
Phase 2a: Majority of Patients Discharged After One Dose

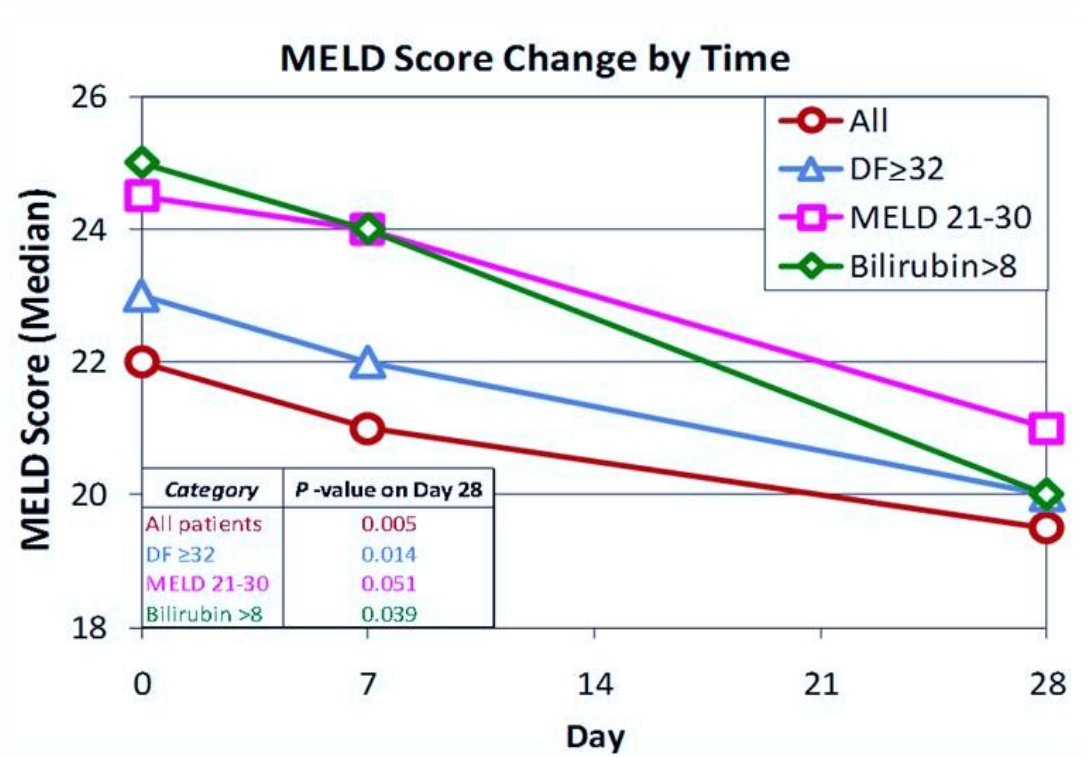
Potential Pharmacoeconomic Benefit as Measured by Time to Discharge

Number (%) of patients who were discharged in ≤ 4 days after receiving a single dose of larsucosterol	
All patients (n=19)	14/19 (74%)
Severe patients (MELD 21-30) (n=12)	8/12 (67%)

Phase 2a: Reduction in Bilirubin & MELD

More Pronounced Effect in Patients with Higher Bilirubin

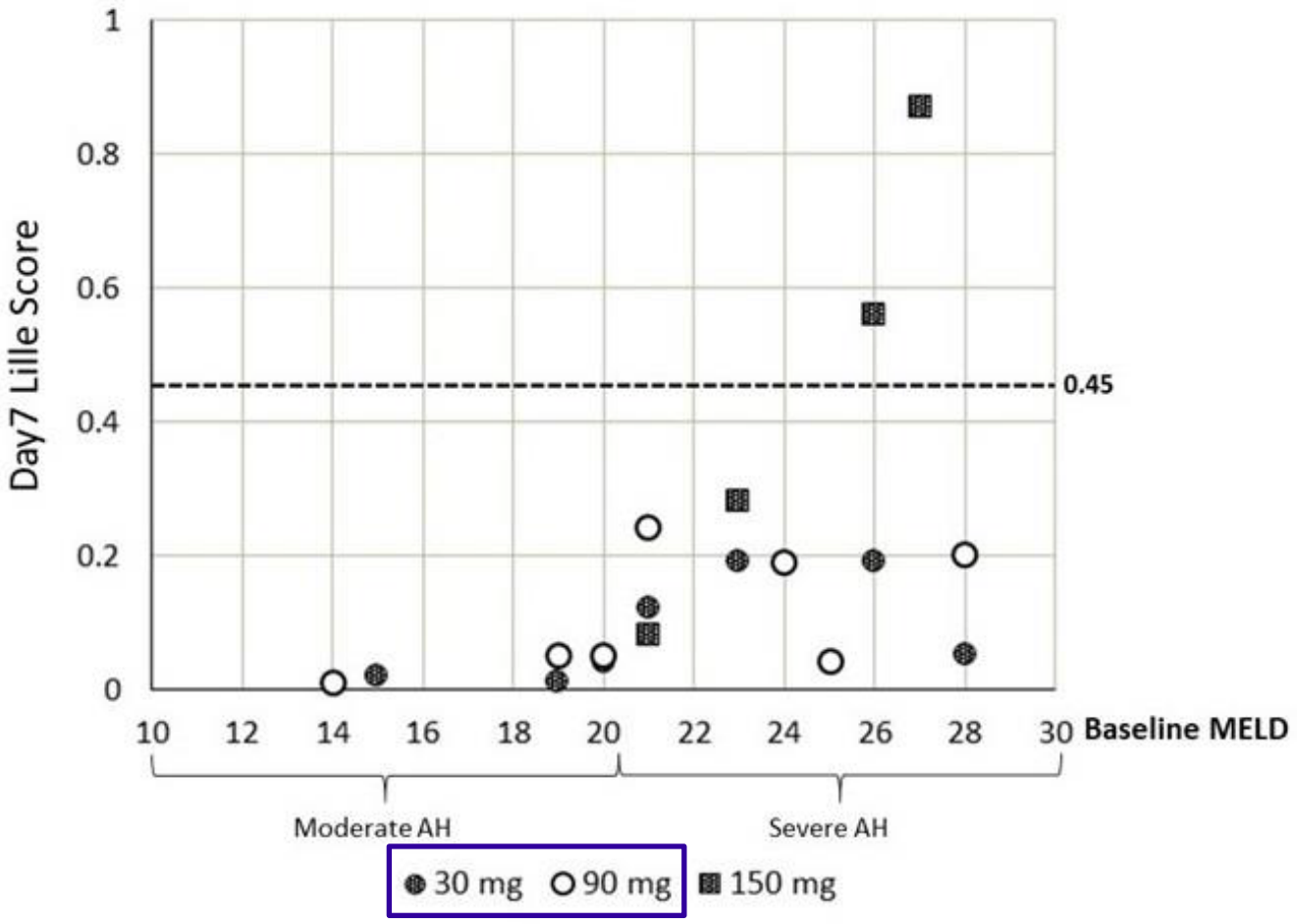


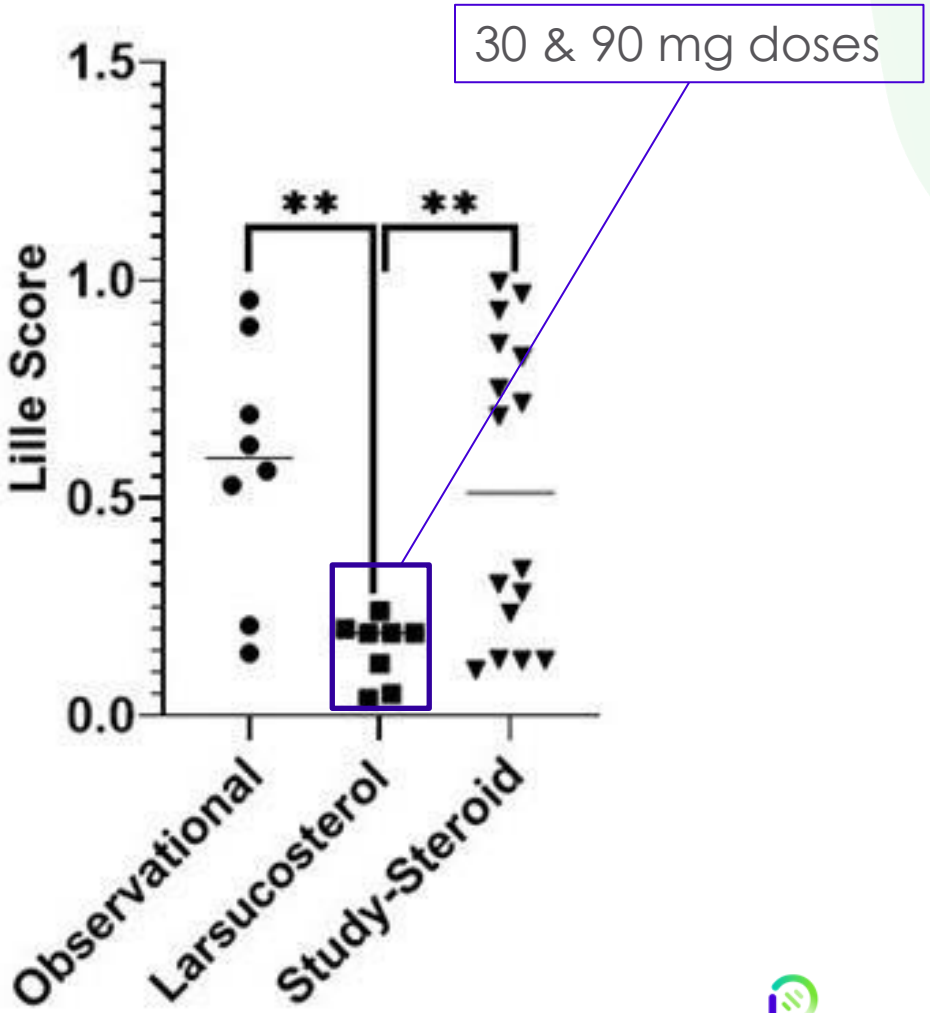


One of 19 patients did not return for the follow-up visits on Day 7 and Day 28; all data were analyzed based on those who completed visits.

Lille Score – The Best Early Predictor of Survival

Larsucosterol Subjects had Lower Lille Scores – Best for 30 & 90 mg Doses





Hassanein T et al. Am J Gastro (in press)

*** Represents p<0.01 by T-test; Non-head-to-head comparison*

Summary

- All subjects in the larsucosterol arms survived
- 30 & 90 mg are in the optimal therapeutic range
  - 150 mg may be outside the optimal range
- Biochemical and clinical outcomes support further development of this drug
- A randomized, double-blind, placebo-control trial (AHFIRM) is in progress

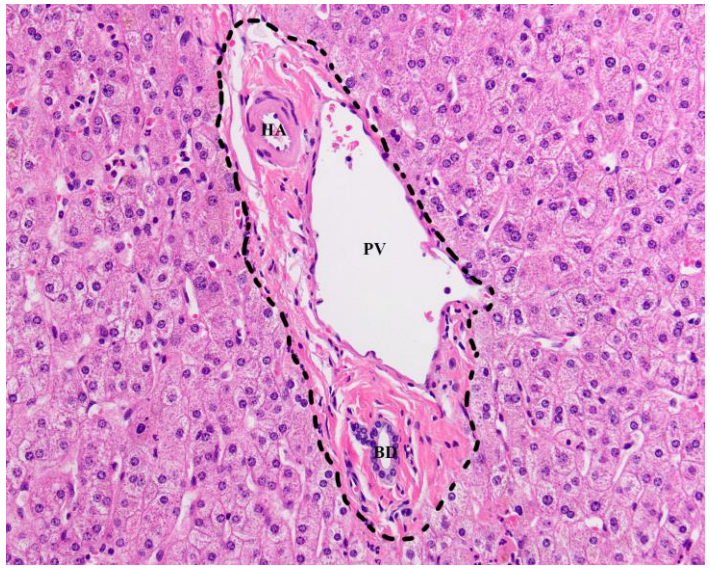
Larsucosterol and the Phase 2b AHFIRM trial

Norman L. Sussman, MD, FAASLD
Chief Medical Officer

What We Know About AH

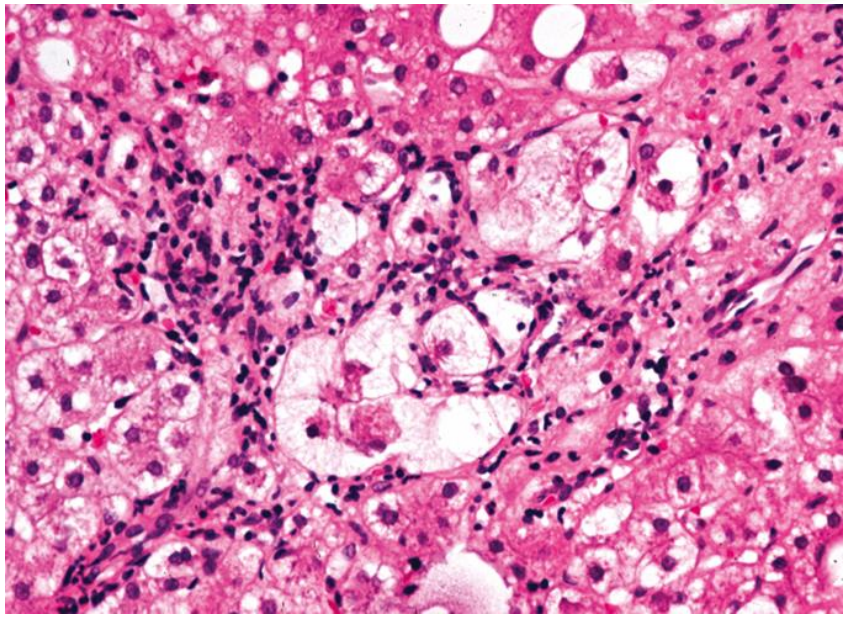
- A serious acute disease with a high risk of death
  - Average 30% mortality at 90 days
- Incidence was increasing prior to the COVID-19 pandemic
  - Trend exacerbated at the time of lock-down
- The demographic is shifting to younger patients and a higher percentage of women
- No satisfactory therapeutic agent after decades of study
  - Evidence to date suggests larsucosterol could be the first approved therapeutic for AH

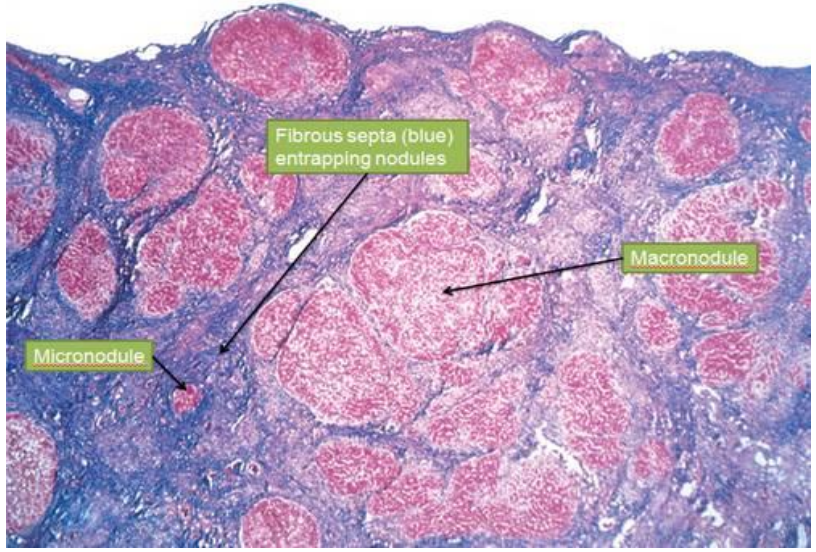
Histologic Changes in Alcohol Associated Liver Disease



Normal

AH





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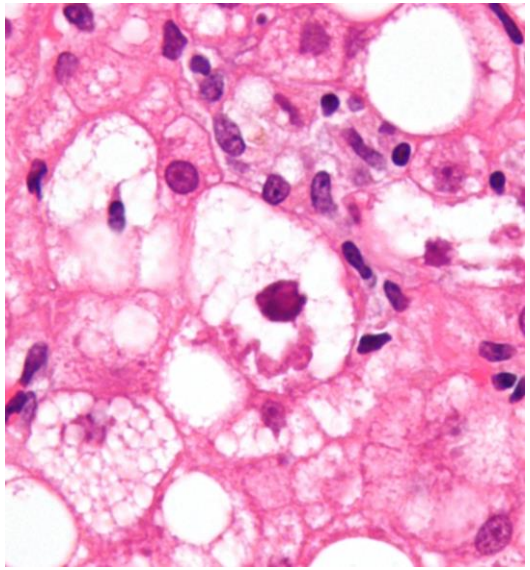


Larsucosterol Clinical Progress

- Phase 2a provided the impetus for a randomized, placebo-control trial
  - Improved biochemical profile
  - 100% survival

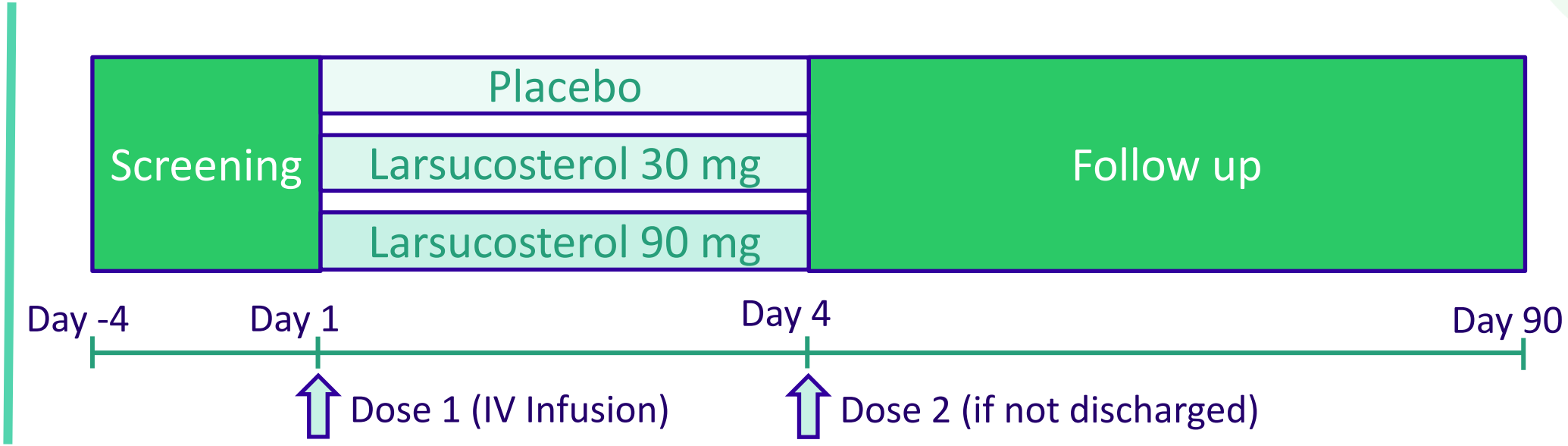
- **Phase 2b AHFIRM:** Subjects with **A**lcoholic **H**epatitis to Evaluate Sa**F**ety Eff**I**cacy of La**R**sucosterol Treat**M**ent
  - Key differences from Phase 2a
    - Restricted to SAH patients
    - Double-blind, randomized, placebo-control trial

AHFIRM – Larsucosterol Phase 2b Trial for AH

Key Inclusion Criteria

Severe AH: MDF ≥ 32, MELD 21-30
300 subjects randomized 1:1:1 into two treatment groups vs. SoC

Study Design



- Multinational
  - US, EU, UK, Australia
- **Full enrollment expected in 2Q23**

AHFIRM – Larsucosterol Phase 2b Trial for AH

Primary Endpoint

- 90-day event rate (death or liver transplantation)

Key Secondary Endpoints

- 90-day mortality
- 28-day event rate (death or liver transplantation)
- 28-day mortality

AHFIRM Trial – Anticipated Next Steps

- Completion of Enrollment (2Q23)
- Last Patient Visit
  - ~90 days following completion of enrollment (3Q23)
- Top-Line Results
  - ~8-12 weeks following last patient visit (4Q23)
  - Initial results for primary and key secondary endpoints
- Potential NDA filing following positive results

Larsucosterol Commercial Opportunity

Keith Lui
SVP, BD, Commercial, Medical Affairs

AH Imposes High Economic Burden on US Healthcare System

- ~158,000 U.S. hospitalizations per year[1]
- AH hospitalizations increased by approximately 5.5% per year between 2015 and 2019[2]
- 86% of hospitalized AH patients are insured[2]

Each hospitalization episode with AH:

[1] https://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp
[2] Marlowe, N., Lam, D., Krebs, W., Lin, W. & Liangpunsakul, S. (2022) Prevalence, co-morbidities, and in-hospital mortality of patients hospitalized with alcohol-associated hepatitis in the United States from 2015 to 2019. Alcoholism: Clinical and Experimental Research.

Primary Research with Multiple Hospital Stakeholders Informs AH Market Landscape, Strategy and Access Considerations

ClearView Healthcare Partners

Stakeholder Descriptions

Academic and community board-certified KOLs, hospitalists, and physicians with **significant experience** treating AH patients

Medical directors from national and regional MCOs, covering a mix of Commercial and Medicare lives

Hospital P&T experts (e.g., **hospital chief pharmacists**) and **hospital economic stakeholders** (e.g., VP finance, CFO)

DRG Coder Experts who manage the process and challenges associated with reimbursement for AH patients

Defined Terms:
KOL: Key Opinion Leader; MCO: Managed Care Organization; DRG: Diagnosis-related Group; P&T: Pharmacy & Therapeutics.

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High Unmet Needs for AH Included the Need for More Effective Therapies That Reduce Mortality and Reducing Continual Alcohol Use

Key AH Unmet Needs

Unmet Need	Degree of Need	Description	Physician Perspectives
Pharmacotherapies that Reduce Mortality		• Physician feedback and literature convey steroids have no significant effect on 90-day mortality • Most physicians highlighted the need for **a more effective pharmacotherapy** aimed at **reducing overall AH mortality** rates	*"We need something which can reduce long-term mortality, steroids are not great and have a whole host of side effects." – HVP*
Preventing Alcohol Use Post-discharge		• 30 – 50% of AH patients drink alcohol following discharge, with low compliance with support programs • No drugs for AUD have been studied in AH; there is a high need for therapies to treat the underlying use disorder	*"We do not prescribe anything other than steroids, and the unmet need lies after discharge in treating AUD." – HVP*
Pharmacotherapy For Mild/Moderate Patients		• Currently physicians have nothing to offer mild/moderate patients but indicated there would be clinical benefit in catching these patients early in their disease trajectory	*"Right now all we have is supportive care for mild/moderate patients and to tell them to stop drinking." – KOL*
Pharmacotherapy Not Subject to Low Patient Compliance		• Given low patient compliance and follow-up after discharge, issues with a 28-day steroids course are common • Physicians highlighted an **acute inpatient drug** with a **short treatment course** would be of great benefit for these patients	*"A common problem is the need to continue steroids after discharge, as compliance is low we often don't know if they finish." – HVP*

Defined Terms:
MDF: Maddrey Discriminant Function; AUD: Alcohol Use Disorder; Function; HVP: High-Volume Physician for AH.
Source: Physician Interviews; ClearView Analysis.

Key: Low High

Value Drivers Differed Across Stakeholders, Highlighting Importance of Tailored Framing of Larsucosterol Value Proposition

Larsucosterol Value Drivers

Reduction in Mortality

Physicians prioritize **mortality** as the **most important endpoint**, and nearly all found larsucosterol's significant reduction in **90-day mortality or liver transplant** rate clinically meaningful

Hospital Cost Offset Economics

Reducing costly **length of inpatient stays** and **30-day readmissions** is key for offsetting drug costs and securing favorable hospital formulary inclusion

Reduction in Healthcare System Cost Burden

Hospital economics and payer stakeholders will likely use **reduction in 30-day readmissions** to assess impact on per-patient cost burden, while **reduction in AH liver transplants** supports cost-benefit to the overall healthcare system

Stakeholder Interviews; ClearView Analysis.

Larsucosterol AH Launch Strategic Imperatives (SI) and Goals

	SI1	SI2	SI3	SI4	SI5
	Shape the AH Market	**Build the Brand**	**Define Patient Access**	**Drive Rapid Adoption**	**Maximize Long-Term Value**
Launch Goals	Build awareness of DURECT as a leader in AH R&D and educate on the impact of epigenetic dysregulation and larsucosterol's potential value	Establish larsucosterol as the revolutionary advancement in the treatment of AH	Ensure early and comprehensive access through bold regulatory, clinical, and value / access strategies	Create a tailored, comprehensive commercial and corporate infrastructure strategy to drive optimal value	Build, fortify and defend larsucosterol in AH and future indications

Larsucosterol Launch Preparation and Commercial Infrastructure Development Are Underway

Key Initiatives Ongoing		2023 Launch Readiness Objectives
Outlining clear company-wide **launch requirements**	»	Ensure **critical activities** are launch-ready
Tailoring our **go-to-market approach** and **aligning cross-functional** launch plans	»	**Inform near-term decisions** on where and how we invest in building commercialization capabilities
Identifying and collaborating early with key stakeholders	»	**Understand needs** and develop **long-term** relationships, commitment, and trust
Developing an **in-depth understanding** of the disease area, customers, and market landscape	»	Design and **clearly differentiate** larsucosterol programs to best meet customers' needs

Early planning allows time to build capabilities and mitigate risks and delays, while being mindful of other organizational priorities

Thank You!

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Q&A