Unlocking Epigenetic Therapeutics to Revolutionize Medicine

SEPTEMBER 2022

Forward-Looking Statements

The statements in this presentation regarding DURECT's and its collaborative partners' products in development, anticipated product benefits, anticipated product markets, clinical trial results and plans, DURECT's future business plans and projected financial results and DURECT's emergence as an innovative biopharmaceuticals company are forward-looking statements involving risks and uncertainties that can cause actual results to differ materially from those in such forward-looking statements. Potential risks and uncertainties include, but are not limited to, DURECT's (and that of its third-party collaborators', where applicable) abilities to successfully enroll and complete clinical trials, complete the design, development, and manufacturing process development of the product candidates, obtain product and manufacturing approvals from regulatory agencies, manufacture and commercialize the product candidates, and achieve marketplace acceptance of the product candidates, as well as DURECT's ability to fund its growth and operations. Further information regarding these and other risks is included in DURECT's most recent Annual or Quarterly Report on Form 10-K or 10-Q filed with the SEC under the heading "Risk Factors."

Company Highlights

- Harnessing the power of epigenetic regulation
- Larsucosterol: Potential first-in-class treatment for AH
- Potential pivotal trial ongoing with data in 2H 2023
- Compelling Phase 2a data in AH
- Significant unmet need in AH – no approved therapy
- POSIMIR® launch upcoming

Late Stage Pipeline Addressing Significant Market Opportunities

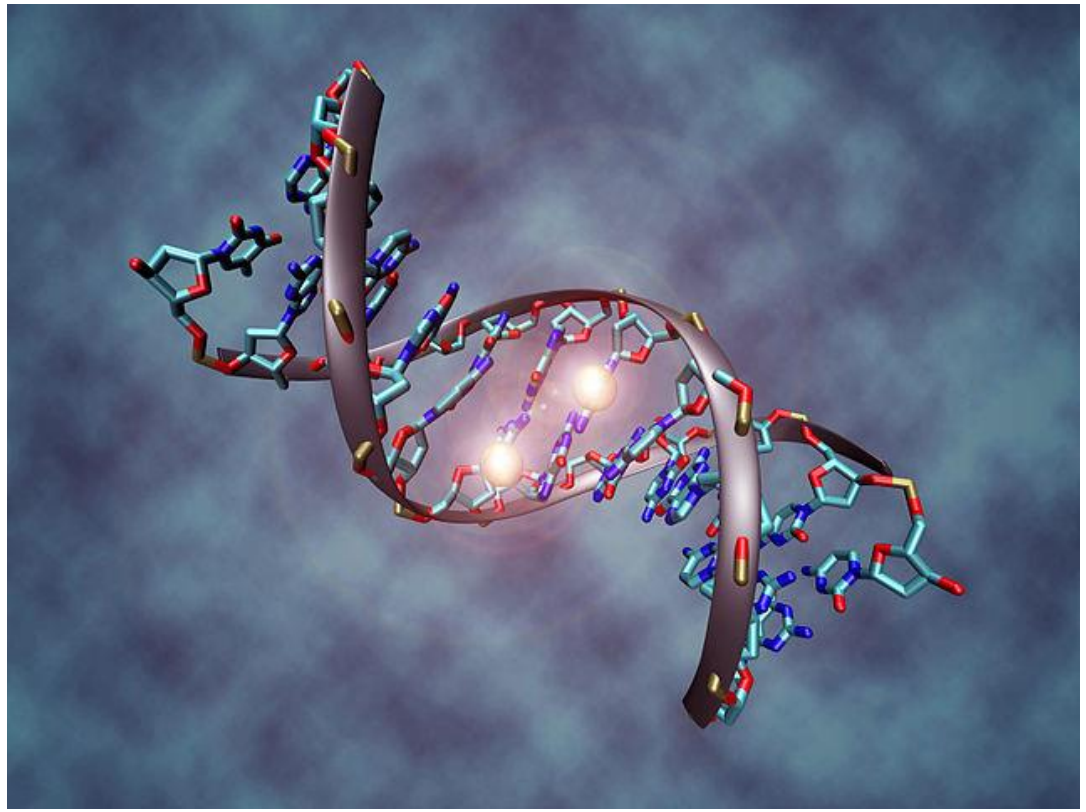
Program	Indication	Phase 1	Phase 2	Phase 3	Approved	Status
Epigenetic Regulator Program						
Larsucosterol (DUR-928)	Alcohol-Associated Hepatitis (AH)					Enrolling Phase 2b AHFIRM Trial Topline data expected 2H 2023
	Non-Alcoholic Steatohepatitis (NASH)					Positive Phase 1b topline data
Partnered Program						
POSIMIR® (bupivacaine solution)	Post-surgical pain[1]					U.S. rights licensed to Innocoll Launch upcoming

[1] Indicated for post-surgical analgesia for up to 72 hours following arthroscopic subacromial decompression

Larsucosterol

Overview & Mechanism of Action

What is Epigenetics?



- **Epigenetics** is a process of gene modulation – DNA methylation and acetylation are two examples
  - Epigenetic changes control gene expression without changing the DNA blueprint
  - Epigenetic changes can be inherited and/or environmental
  - Many diseases are associated with DNA hypermethylation
- **Larsucosterol** reduces DNA hypermethylation and may therefore benefit patients with certain diseases

Larsucosterol Overview

Lead Compound in DURECT's Epigenetic Regulator Program

Modulator of DNA methylation

New class of therapeutics

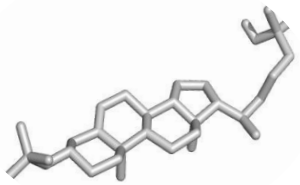
Endogenous sulfated oxysterol

Highly conserved across all 7 species studied to date

Clinical safety

Well tolerated at all doses

More than 350 subjects dosed in multiple completed Phase 1 & 2 studies



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

Role in cellular functions

Stabilizes mitochondria

Reduces lipotoxicity

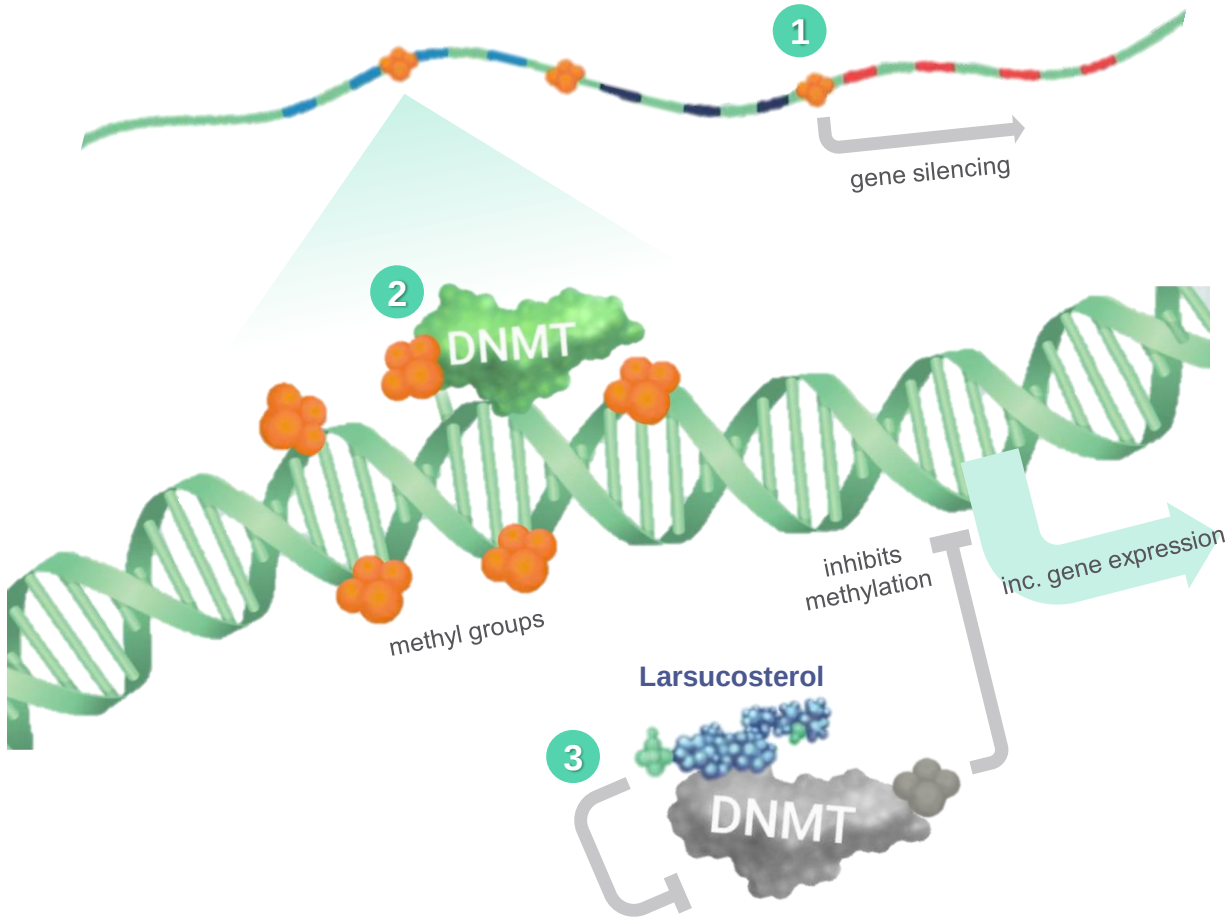
Reduces inflammation

Improves cell survival and tissue regeneration

Broad therapeutic potential

MOA supports investigating larsucosterol for the treatment of multiple acute organ injury and chronic diseases

Mechanism of Action Leverages Epigenetics to Impact Disease



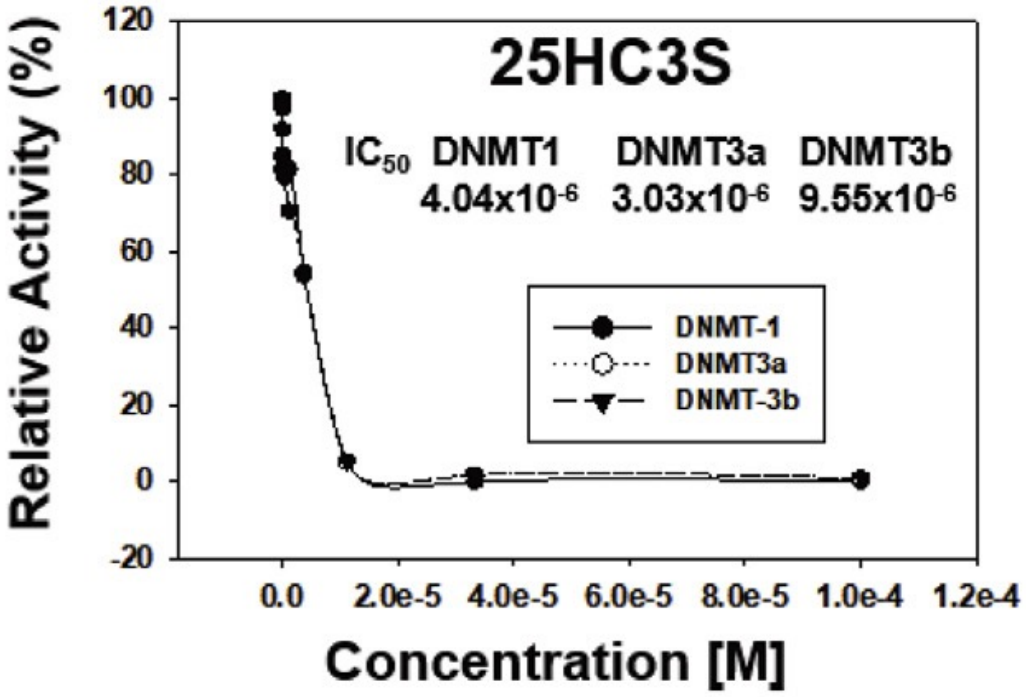
1. **Epigenetic Dysregulation in AH Patients**
   Aberrant DNA hypermethylation is associated with many diseases including severe AH

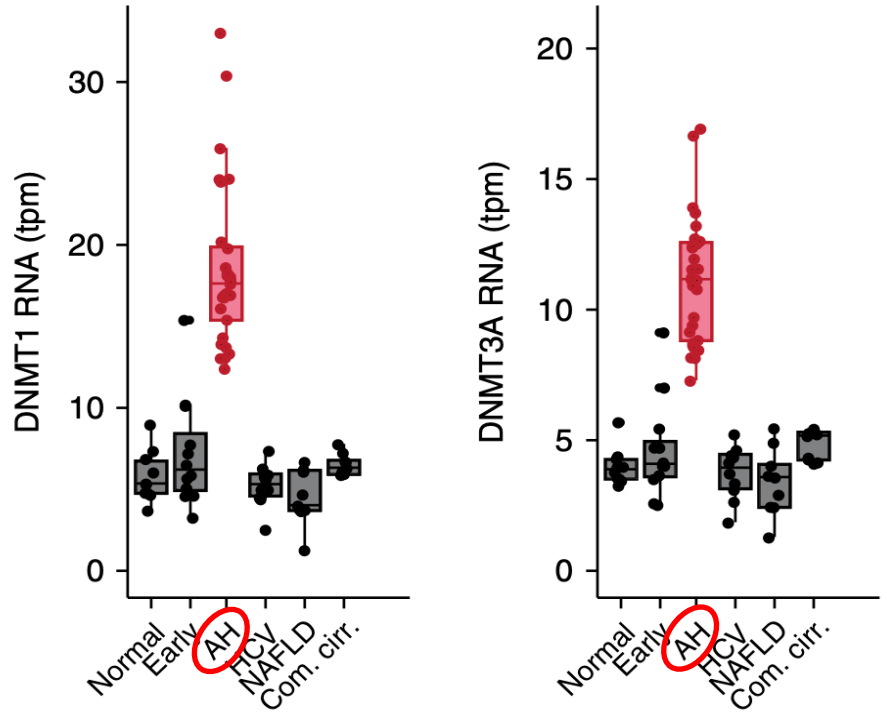
2. **Epigenetic Regulators Modulate Gene Expression**
   DNA methyltransferases (DNMTs) are one such regulator that add methyl groups to certain regions of DNA, generally reducing gene expression

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



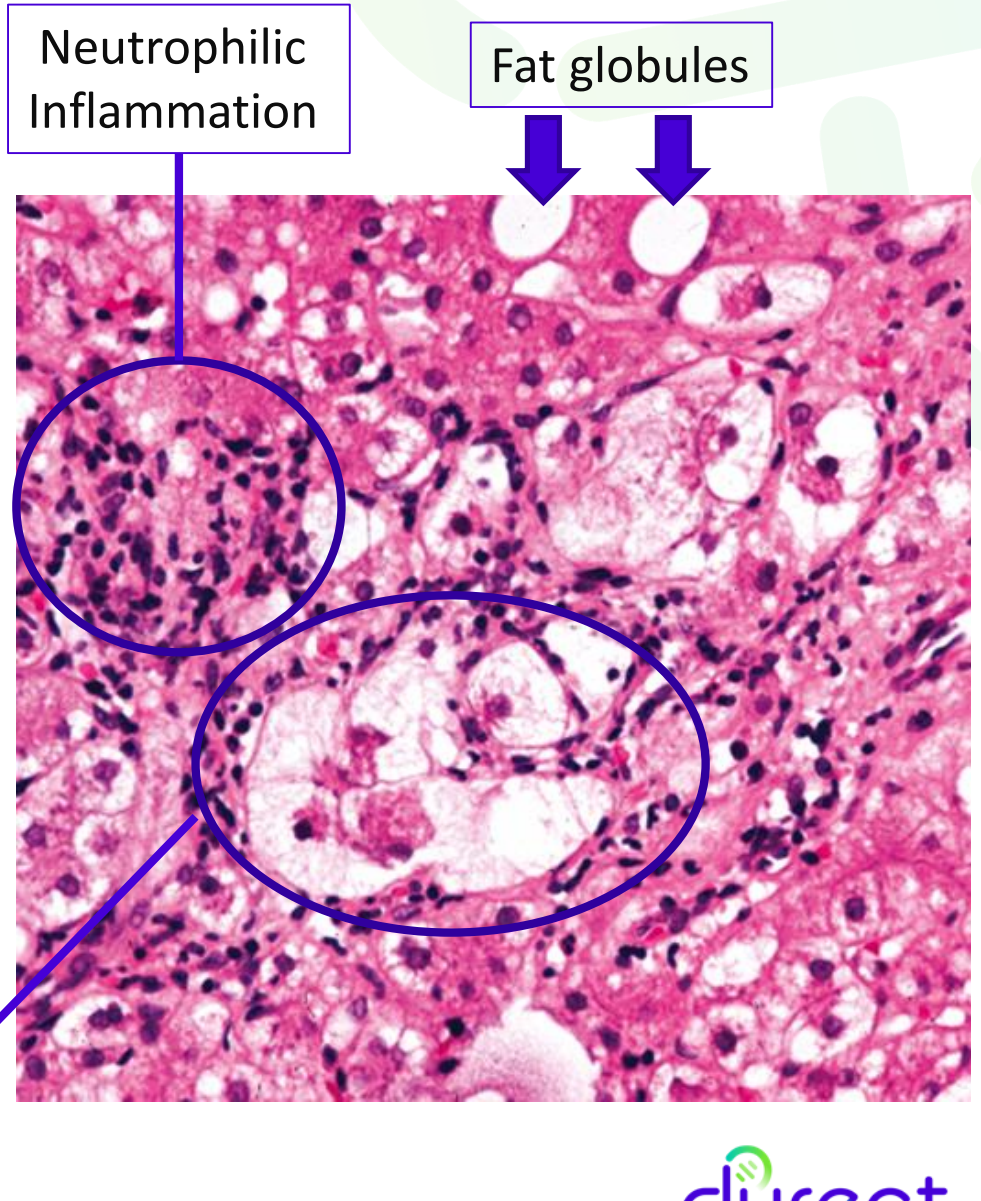


References:
Wang Y et al. 2021, Journal of Lipid Research, 62:1-14 *Note: in this paper, larsucosterol is referred to as 25HC3S*
Argemi et al. 2019. Nature Communications, 10: 3126; https://doi.org/10.1038/s41467-019-11004-3

Larsucosterol
Potential in Alcohol-associated Hepatitis

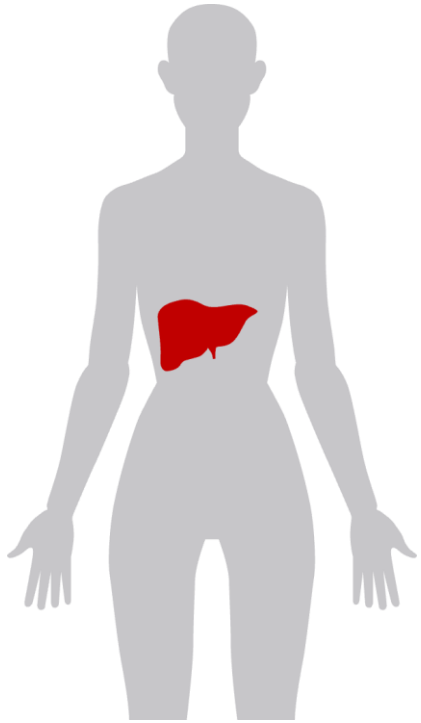
What is Alcohol-associated Hepatitis?

- A subset of alcohol-associated liver disease (ALD)
- May occur suddenly after binge drinking episode
- Characterized by jaundice and severe inflammation – SIRS (Systemic Inflammatory Response Syndrome)
- SIRS causes a sepsis-like state that may progress to multi-organ failure and ultimately death
  - 28-day mortality rate: ~26%[1]
  - 90-day mortality rate: ~30%[1]



Reference:
[1] Hughes E, Hopkins LJ, Parker R (2018). PLoS ONE 13(2): e0192393

AH Lacks Effective Treatment Options with No Approved Therapy

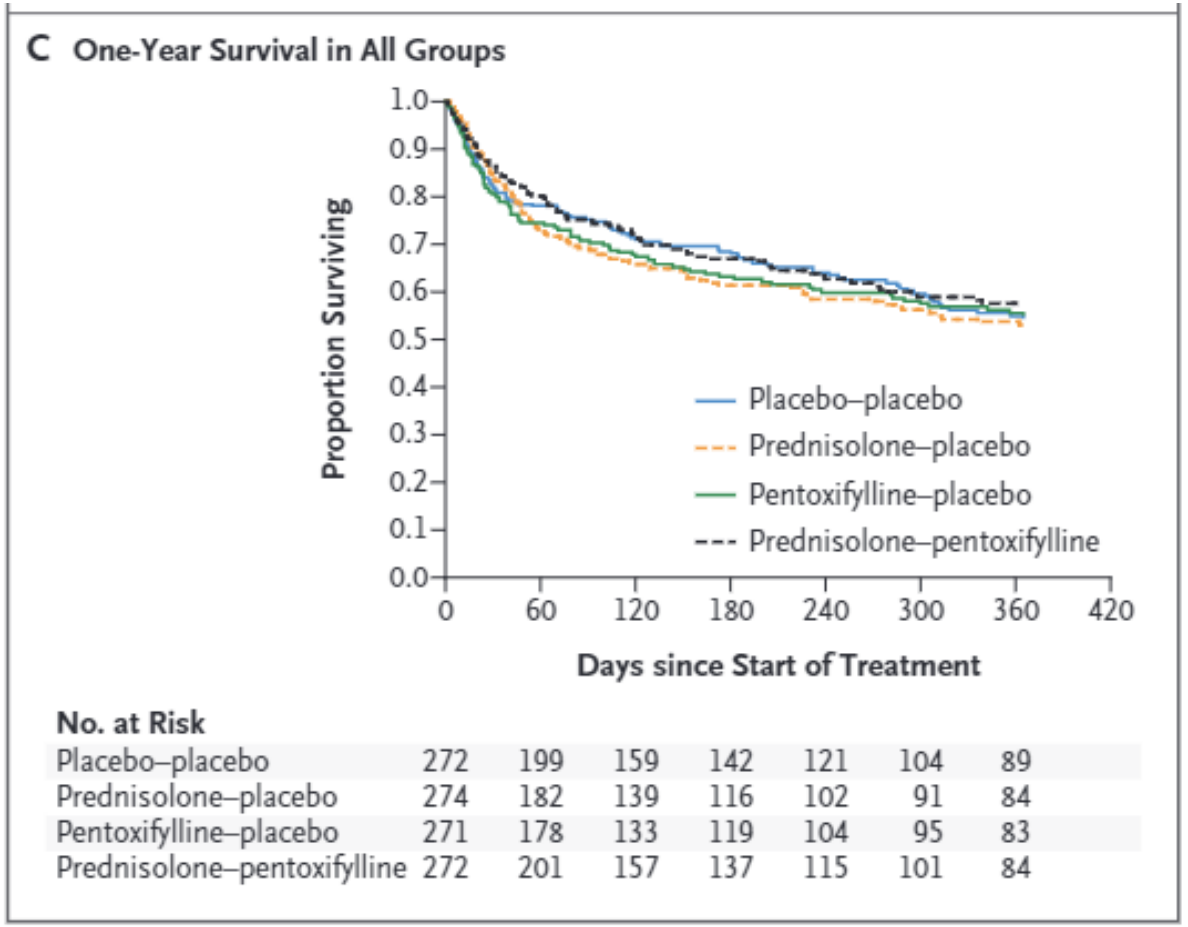


- Corticosteroids used off label despite no long-term survival benefit and increased risk of infection[1]
  - Fewer than 50% of AH patients are eligible for corticosteroids[2]
- Stopping alcohol consumption is not sufficient in many patients[3]
- Liver transplants becoming more common for AH[4]
  - Insufficient organs to treat all patients
  - Life-altering procedure
  - Liver transplant costs >$875,000[5]
- **Larsucosterol could be the first drug approved for AH**

"There's a clear lack of treatment options out there – prednisolone doesn't work; we're still giving it because that's what we've been taught to do … I'd want to see something that works that isn't a steroid, doesn't cause infection, and doesn't need to be taken every day" – Gastroenterologist

References:
[1] Thursz M, et al. 2015, *NEJM*, 372: 1619-1628; [2]Singal AK, et al. 2018, J Hepatol, 69: 534-543; [3] Singal AK, et al. 2014, Clin Gastroenterol Hepatol., 12:555-564; [5]Bentley TS and Ortner NJ 2020, U.S. organ and tissue transplant: cost estimates, discussion, and emerging issues (Milliman Research Report, 2020)

STOPAH Trial Showed No Long-term Survival Benefit from Steroids or Pentoxifylline



No. at Risk							
Placebo–placebo	272	199	159	142	121	104	89
Prednisolone–placebo	274	182	139	116	102	91	84
Pentoxifylline–placebo	271	178	133	119	104	95	83
Prednisolone–pentoxifylline	272	201	157	137	115	101	84

References:
Thursz M, et al. NEJM (2015) 372: 1619-1628

AH Imposes High Economic Burden on Healthcare System

- ~137,000 U.S. hospitalizations per year[1]
- AH hospitalizations increased by approximately 4.8% per year between 2015 and 2018[2]

Each hospitalization episode with AH diagnosis for patients who:	Average length of stay[2]	Average total charges during hospital stay[2]
Died during the hospitalization	9 days	$147,000
Were discharged	6 days	$53,000

- 86% of hospitalized AH patients are insured[1]

References:
[1] Marlowe et al., Alcohol Clin Exp Res. 2022, http://doi.org/10.1111/acer.14896;
[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.

Larsucosterol
Phase 2a Trial in AH

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

- Patients received up to two doses of larsucosterol on Day 1 and Day 4 (if still hospitalized)
  - Multiple dose levels studied: 30mg, 90mg and 150mg
- Showed improvement in key biomarkers and prognostic indicators
  - Reduction in bilirubin and Model for End-stage Liver Disease (MELD) scores
  - 89% response rate based on prognostic indicator of mortality (Lille score)
- Well tolerated across all dose levels with no drug-related SAEs

Larsucosterol AH Phase 2a Trial Results Presented at The Liver Meeting® 2019

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

- Oral late-breaking presentation delivered by Dr. Tarek Hassanein[1]
  - ‘Best of The Liver Meeting’ summary slide presentation
  - In the alcohol-associated liver disease category
- Poster presentation comparing to Univ. Louisville historical control[2]

References:
[1] 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
[2] McClain C, et al. DUR-928 therapy for acute alcoholic hepatitis: A pilot study. Poster session presented at AASLD The Liver Meeting®; 2019 November 10.

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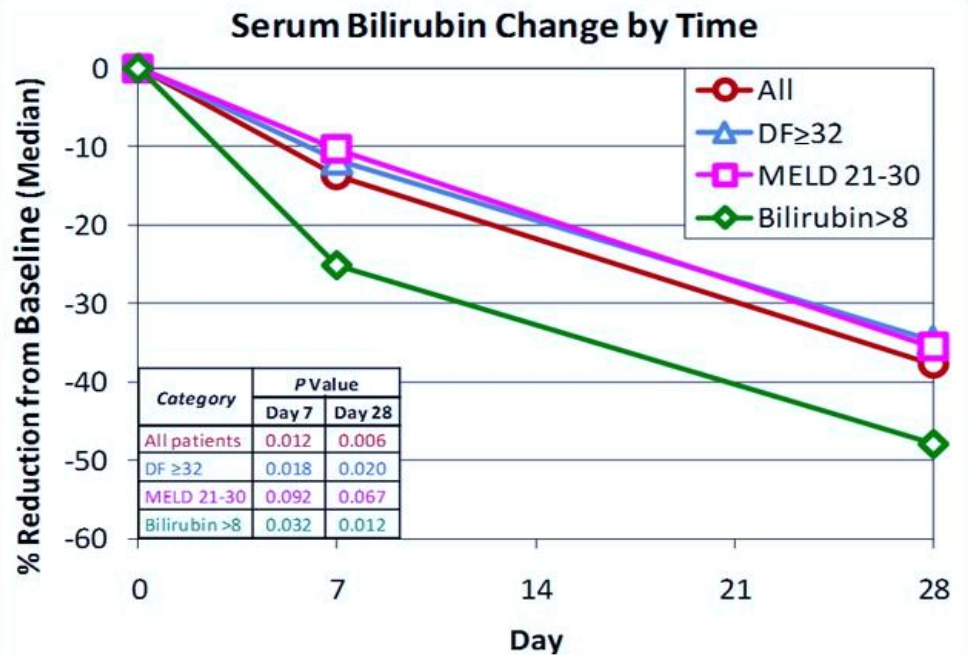
Phase 2a: Majority of Patients Discharged After One Dose

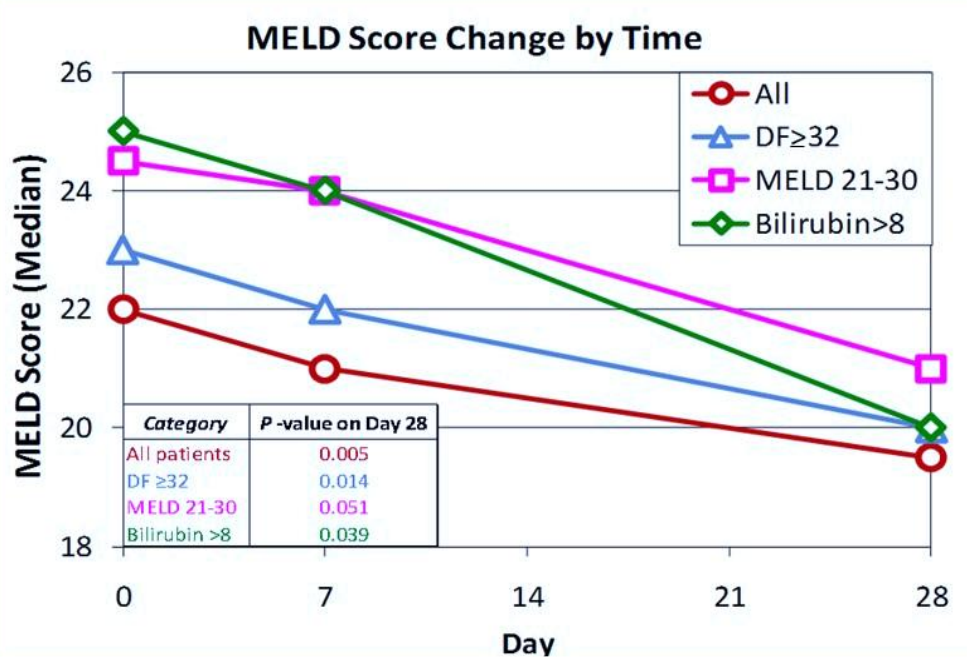
Potential Pharmacoeconomic Benefit as Measured by Time to Discharge

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 Across Patient Categories

More Pronounced Effect in Patients with Higher Bilirubin



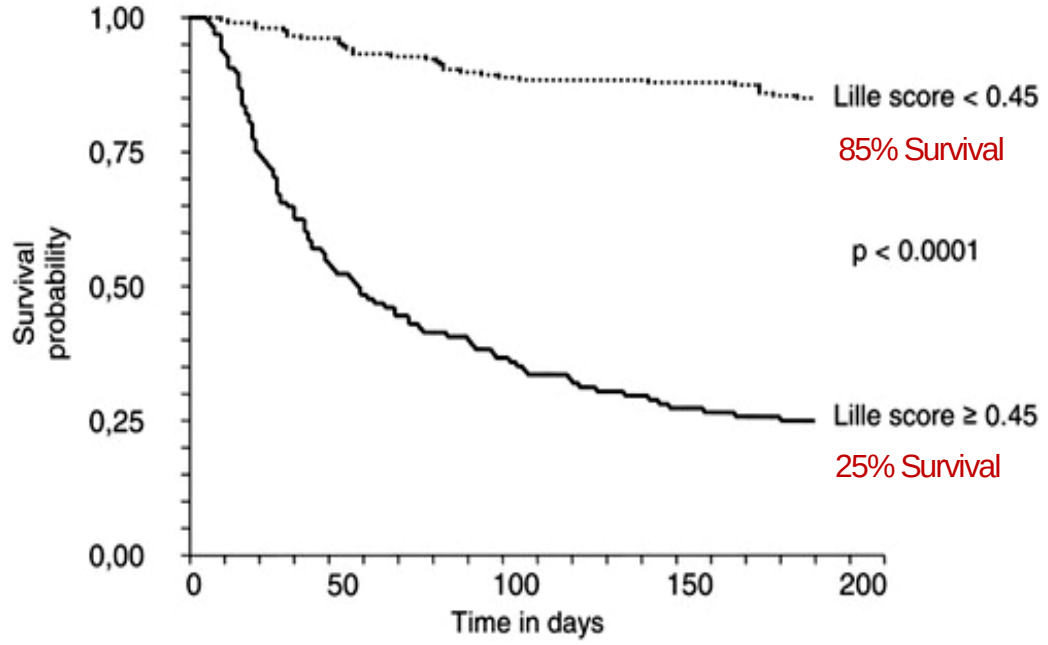


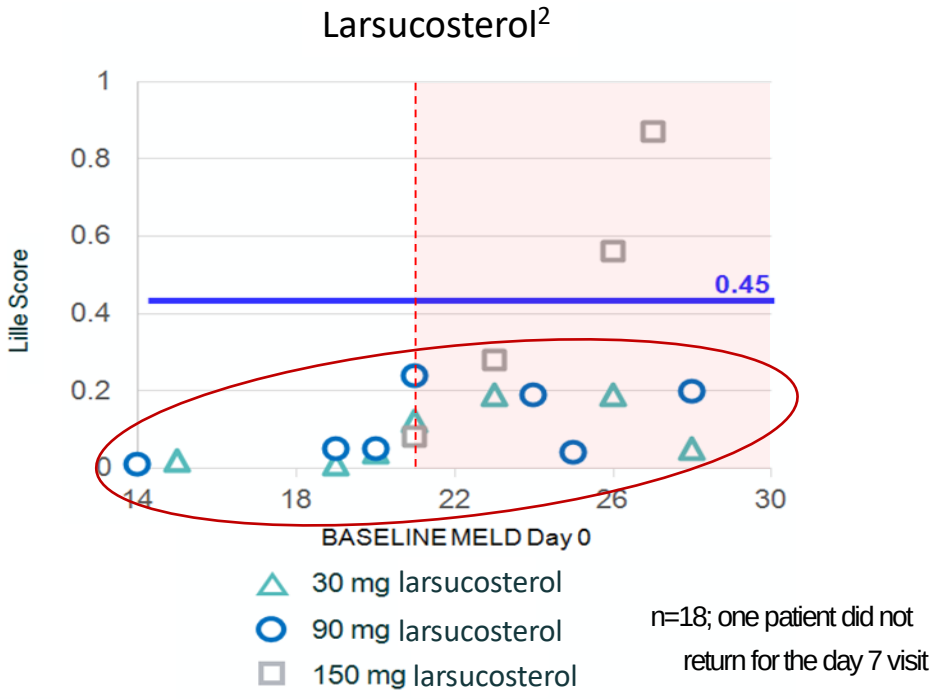
One of 19 patients did not return for the follow-up visits on Day 7 and Day 28; all data were analyzed based on those who completed visits.

Phase 2a: Lille Score Provides Strong Signal for Survival

Composite score that determines response to treatment and risk of death

Larsucosterol treatment resulted in 89% (16/18) response rate by Lille Score (< 0.45)

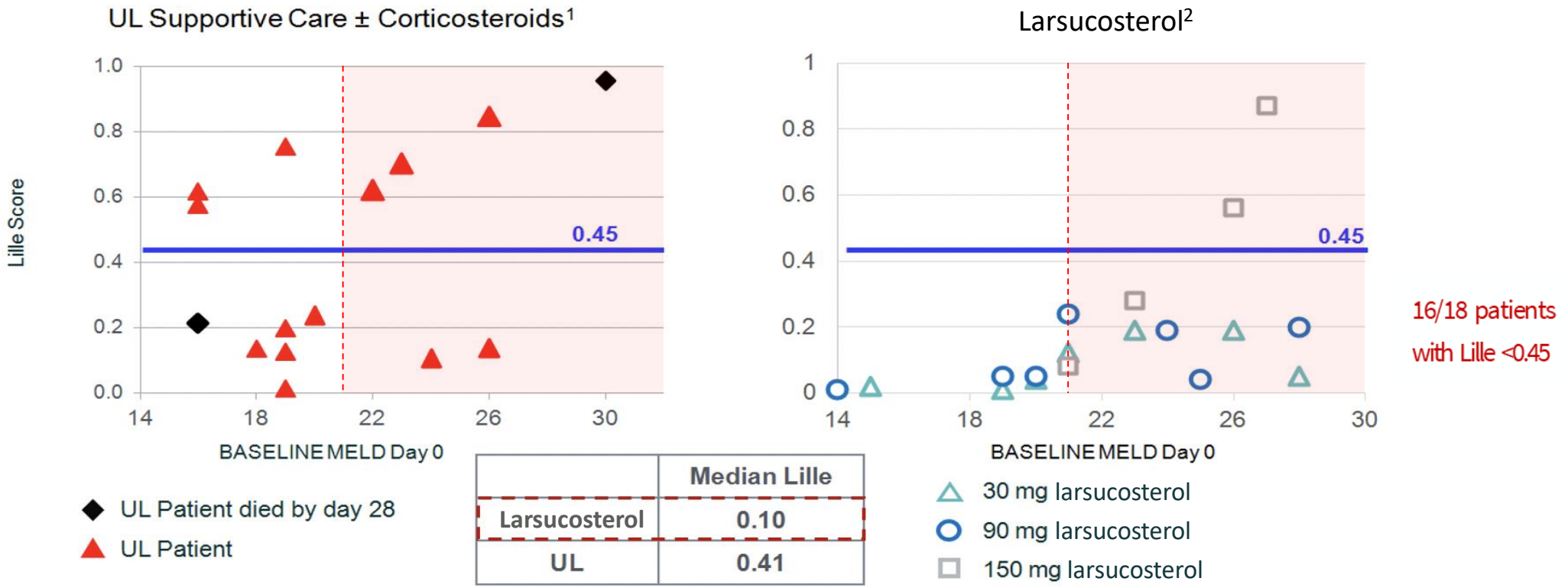




References:
Louvet, A et al. Hepatology 2007; 45:1348-1354

Phase 2a: Lille Score Comparison to UL Historical Control

Larsucosterol treatment had 76% lower median Lille score vs. matched historical control



	Median Lille
Larsucosterol	0.10
UL	0.41

References:

[1]Anonymized data provided by Dr. Craig McClain from the University of Louisville (UL) from his separate Trial, in which 15 AH patients with initial MELD scores ranging from 15-30 received either supportive care alone (n=8) or supportive care with corticosteroids (n=7). Provided as historical control data; [2]n=18 ; one patient did not return for the day 7 visit.

Phase 2a: Larsucosterol Was Well Tolerated Across All Doses

- No Serious Adverse Events attributed to trial drug
- No discontinuations, early withdrawal or termination of trial drug or trial participation due to AEs
- Adverse events possibly related to larsucosterol:
  - 1 occurrence each of moderate generalized pruritus, mild rash, & grade 2 ALP

Larsucosterol

AHFIRM Trial

Phase 2b Trial in **A**lcohol-associated **H**epatitis to Evaluate Sa**F**ety and Eff**I**cacy of La**R**sucosterol Treat**M**ent

Larsucosterol: Potential to be First Approved Therapy for AH

Positive Phase 2a Data Led to Ongoing AHFIRM Trial

- AHFIRM: Phase 2b double-blind, placebo-controlled efficacy trial in 300 severe AH patients
  - Expect to complete enrollment mid-2023 with topline data in 2H 2023
  - Primary endpoint is reduction in mortality or liver transplant at 90 days
- Potential NDA filing if result is positive
  - 42% of new drugs launched in the US in 2018 were approved based on single trial[1]
  - Fast Track Designation

References:
[1] IQVIA Institute, Mar 2019

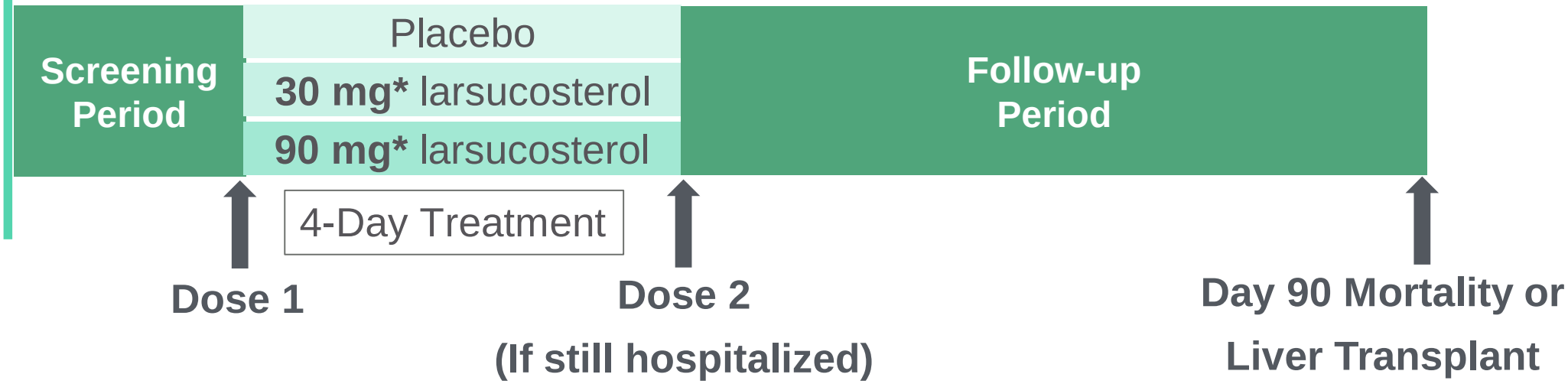
AHFIRM Trial Design Leverages Lessons from Phase 2a Trial

Aim: Demonstrate Safety and Efficacy in Severe AH

Key Inclusion Criteria

- **Severe AH patients** with MDF[1] score ≥ 32 and MELD score 21-30
- **300 subjects** in three groups in a 1:1:1 ratio

Study Design[2]



[1] Maddrey's Discriminant Function

[2] All patients receive supportive care, which for placebo patients may include methylprednisolone capsules at the investigators' discretion. In order to maintain blinding, patients in the two larsucosterol arms receive matching placebo capsules if the investigator prescribes steroids.

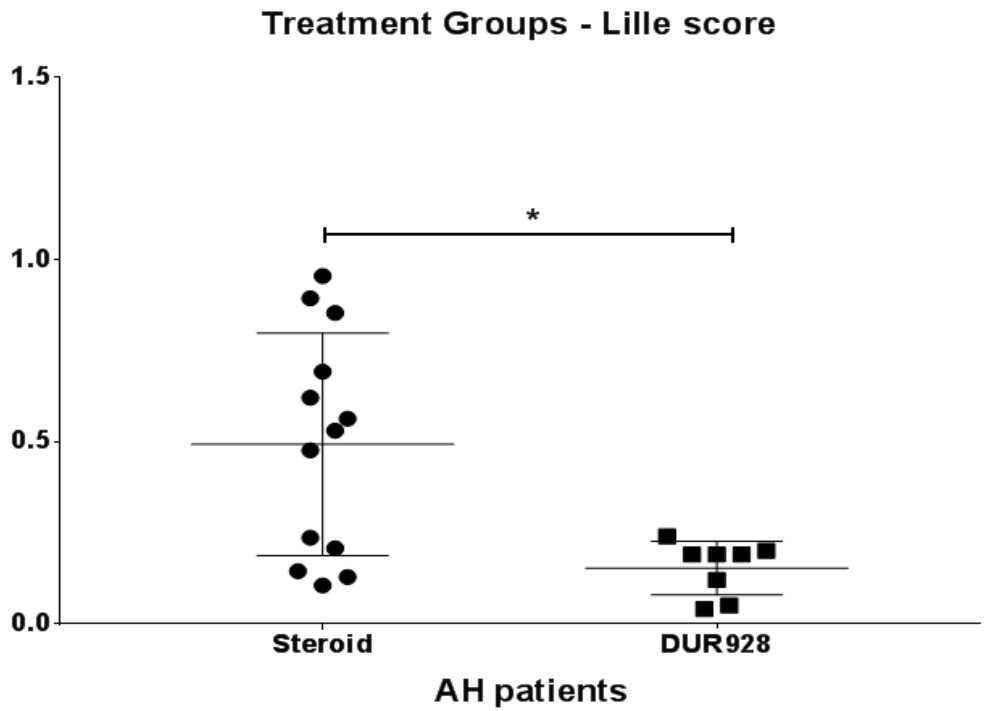
Lille Score Comparison vs. Historical Control in Severe AH

Larsucosterol AHFIRM doses (30mg & 90mg) produced lower Lille scores in Phase 2a vs. historical control (corticosteroids)

- U. of Louisville AH patients in a contemporaneous trial who received corticosteroids for 28 days
- Larsucosterol (30 mg or 90 mg dose) treated severe AH patients from Phase 2a trial

Baseline AH Severity	Steroid (n=13)	Larsucosterol (n=8)
Mean Baseline MELD (Severe AH ≥ 21)	24.5	24.5
Mean Baseline MDF (Severe AH ≥ 32)	63.0	61.3

Well-matched **severe** AH patients in the two treatment arms



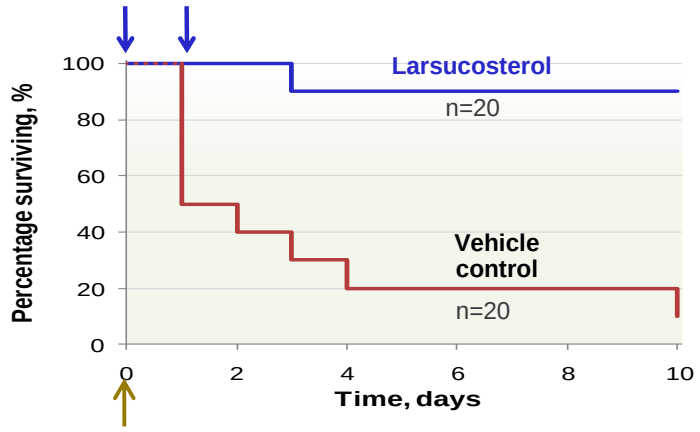
References:
McClain, et. al., "DUR-928 Therapy for Acute Alcoholic Hepatitis: A Pilot Trial" AASLD The Liver Meeting poster presentation, 11/10/2019. The steroid group in the above graph includes the 7 severe AH patients treated with steroids from the UL group shown in the MELD vs Lille graph plus an additional 6 severe AH patients subsequently treated in the UL study.

Larsucosterol
Potential Beyond AH

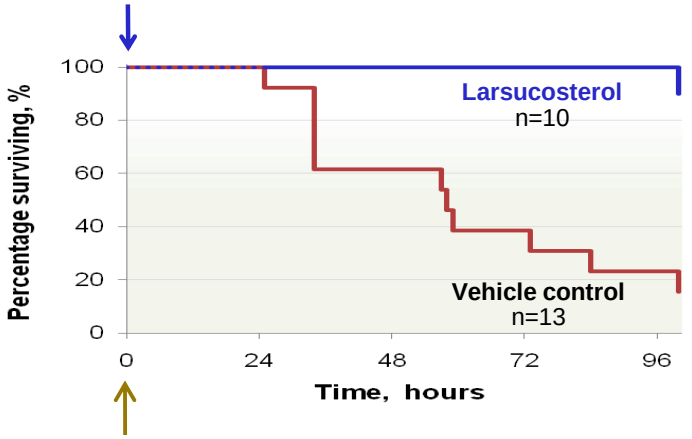
Larsucosterol in Acute Multi-Organ Injury Models

- Larsucosterol reduced the absolute mortality rate by 80% in two pre-clinical multi-organ injury models
  - Protected multiple organs, including kidneys, liver, and lungs
  - Additional supportive data in AKI, sepsis, pancreatitis, cholestatic liver injury models, and other preclinical acute models

Larsucosterol or vehicle control dosed 2 times after APAP/EtOH [1]



Larsucosterol or vehicle control before LPS [2]



References:
[1] Ren et. al., AASLD 2017, Poster #2777667; [2] Ning, Ren, et. al. Metabolism Clinical and Experimental 71 (2017) 83-93.

Larsucosterol: Potential indications beyond AH

NASH: Phase 1a & 1b trials completed in more than 70 patients

- Reduced liver enzymes, fibrosis markers and by imaging liver fat, stiffness and elasticity
- Reduced circulating fats including triglycerides
- Reduced cell death markers
- Improved insulin resistance
- Encouraging safety profile

Potential additional indications supported by pre-clinical data

- Acute kidney injury, pancreatitis, metabolic syndrome, and others

POSIMIR® (bupivacaine solution)

POSIMIR® (bupivacaine solution) for infiltration use

Up to 72 hrs of Non-Narcotic Post-Operative Pain Reduction Utilizing SABER® Technology

1. FDA approved in arthroscopic subacromial decompression
2. Exclusive U.S. license to Innocoll Pharmaceuticals
3. Received $8 million milestone based on recent patent issuance with additional $2 million earned on first commercial sale
4. Additional future milestones of up to $122 million, plus low to mid double-digit royalties

Financial Overview and Summary

DURECT Corporation

Financial Overview

Nasdaq	DRRX
Market Cap	$156 MM[1]
Shares O/S	227.8 MM[2]
Cash & Investments	$62.3 MM[3]
Debt	$20.9 MM[3]
Federal NOLs	$352 MM[4]

Cupertino, CA headquarters

[1] As of September 8, 2022
[2] As of August 3, 2022
[3] As of June 30, 2022 pro forma for $8MM milestone payment due from Innocoll
[4] As of December 31, 2021

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