Unlocking Epigenetic Therapeutics to Revolutionize Medicine

May 2023

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Company Highlights

- Harnessing the power of epigenetic regulation
- Larsucosterol: Potential first-in-class treatment for AH
- Potential pivotal trial ongoing; data expected in 2H 2023
- Compelling Phase 2a data in AH
- Significant unmet need in AH – no approved therapy
- POSIMIR® launched in September 2022

AH = Alcohol-associated hepatitis

Late Stage Pipeline Addressing Potentially Large 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 Launched in September 2022

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

Larsucosterol Overview

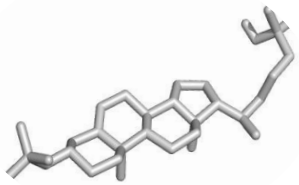
Lead Compound in DURECT's Epigenetic Modulator Program

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 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

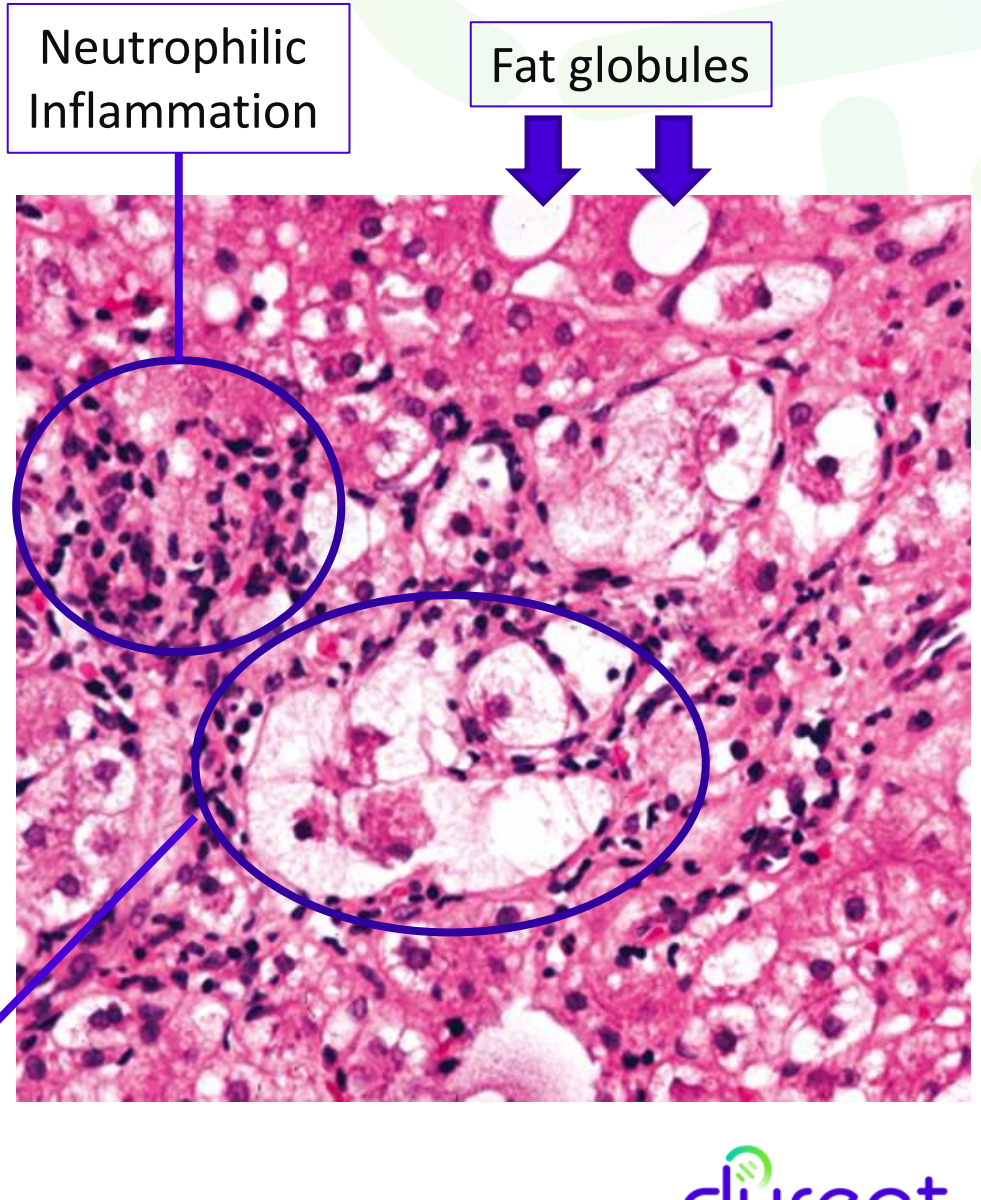
- MOA[1] supports investigating larsucosterol for the treatment of multiple acute organ injury and chronic diseases
- Phase 1b NASH data suggest broad activity

[1]MOA = Mechanism of Action

Larsucosterol
Potential in Alcohol-associated Hepatitis

What is Alcohol-associated Hepatitis?

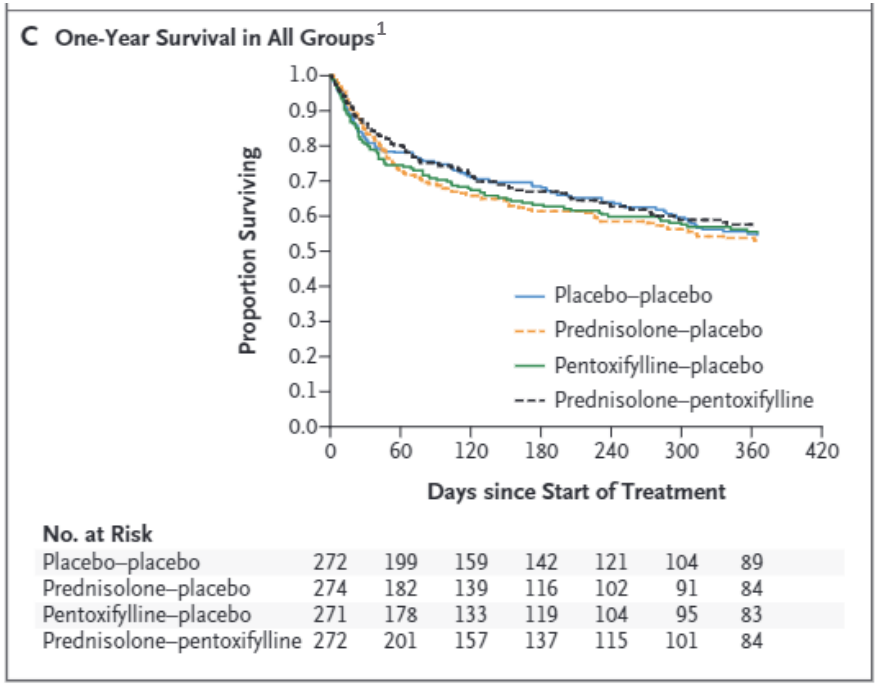
- A subset of alcohol-associated liver disease (ALD)
- May occur suddenly after binge drinking episode
- Characterized by jaundice and severe inflammation – indicative of SIRS (Systemic Inflammatory Response Syndrome)
- SIRS causes a sepsis-like state that may progress to multi-organ failure and ultimately 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 requires lifelong immunosuppression
  - 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; [4]Bitterman T et al. 2021, JAMA Network, 4(7):e2118713; [5]Bentley TS and Ortner NJ 2020, U.S. organ and tissue transplant: cost estimates, discussion, and emerging issues (Milliman Research Report, 2020)

AH Imposes High Economic Burden on Healthcare System

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

References:
[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.

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 (30mg, 90mg or 150mg) on Day 1 and Day 4 (if still hospitalized)
- 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
- Oral late-breaking presentation delivered by Dr. Tarek Hassanein[1]
  - Selected for 'Best of The Liver Meeting' summary slide presentation in the alcohol-related liver disease category
- Results published in peer-reviewed journal

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AJG The American Journal of GASTROENTEROLOGY

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

durect

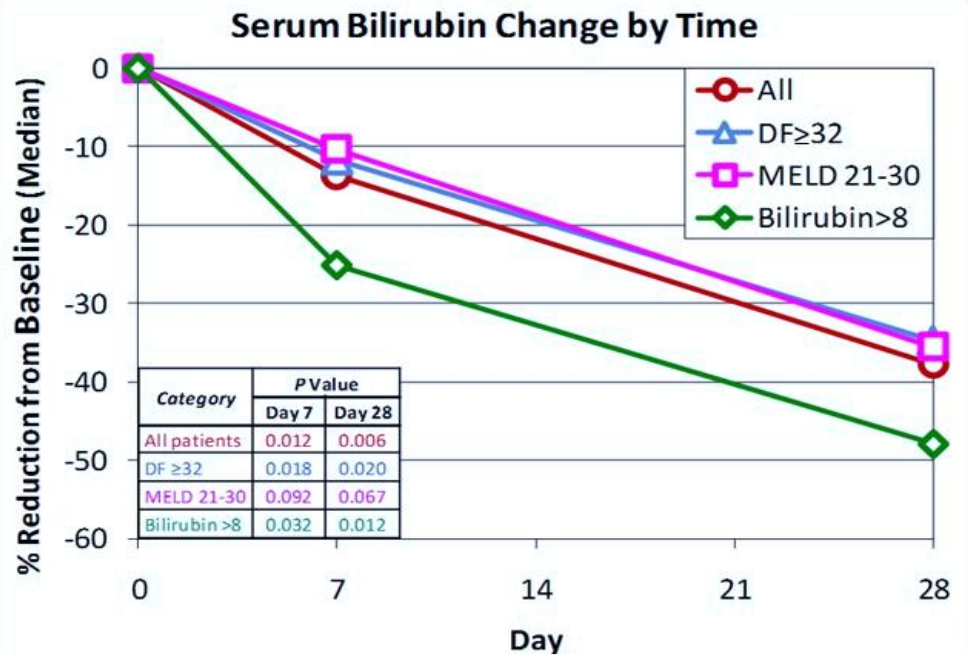
Phase 2a: Majority of Patients Discharged After One Dose

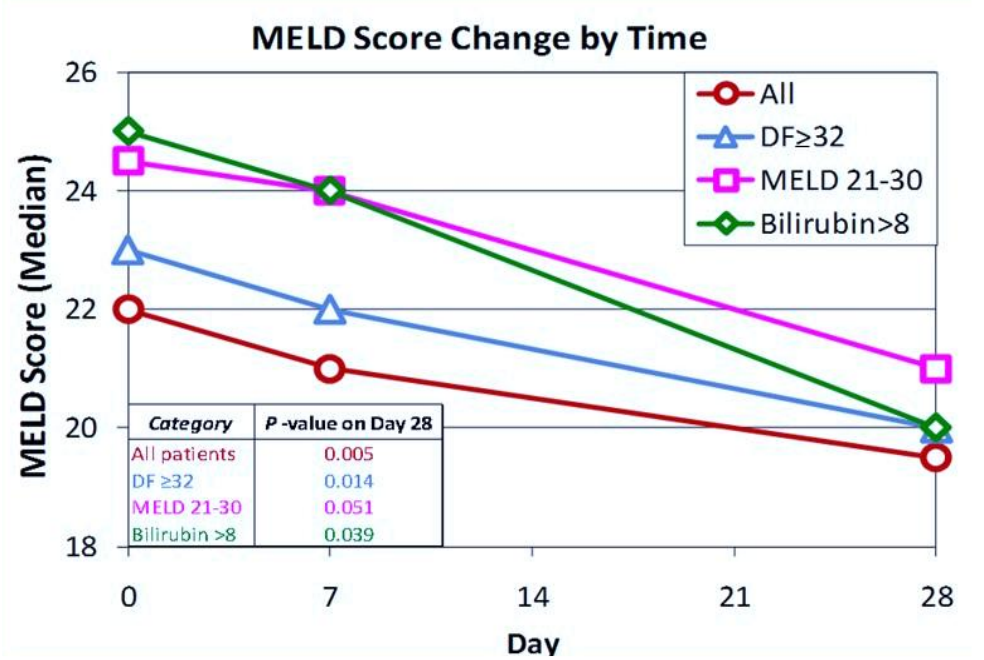
Potential Pharmacoeconomic Benefit as Measured by Time to Discharge

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





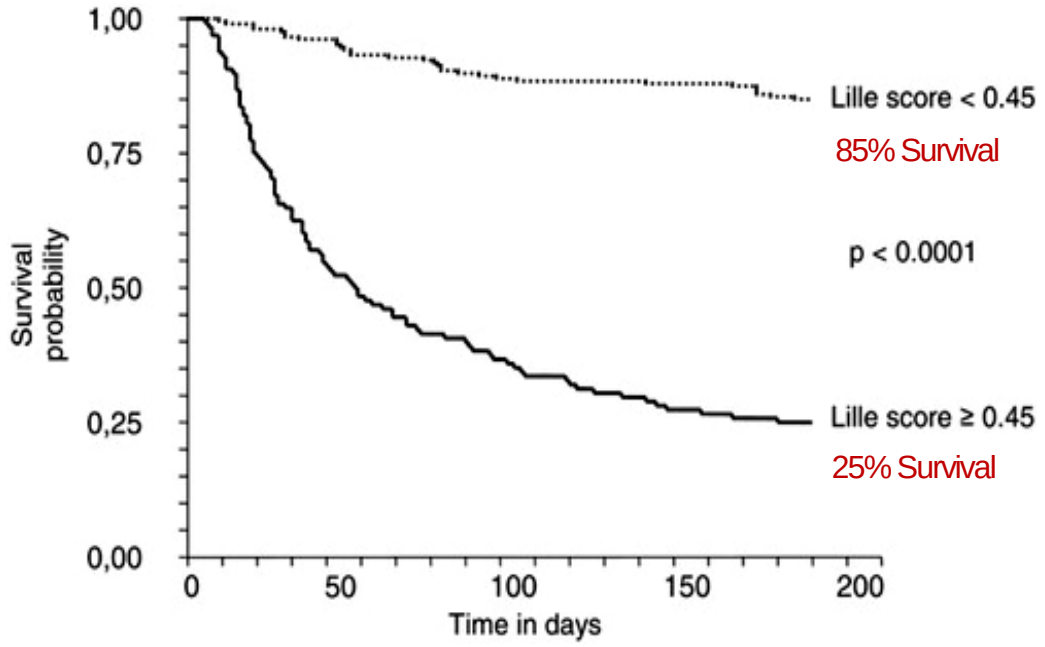
One of 19 patients did not return for the follow-up visits on Day 7 and Day 28; all data were analyzed based on those who completed visits.

Phase 2a: Lille Score Provides Strong Signal for Survival

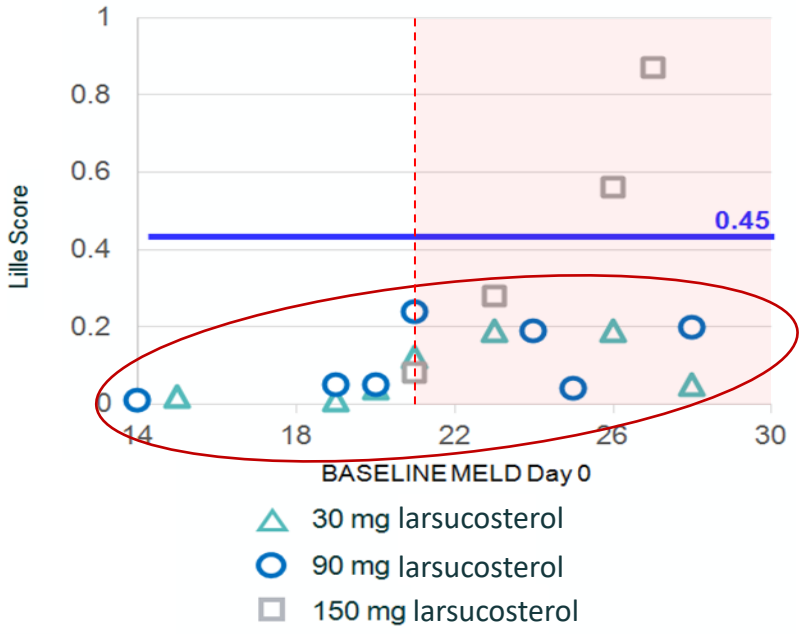
Composite score that determines response to treatment and risk of death

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

Survival Probability by Lille Score[1]



Larsucosterol[2]

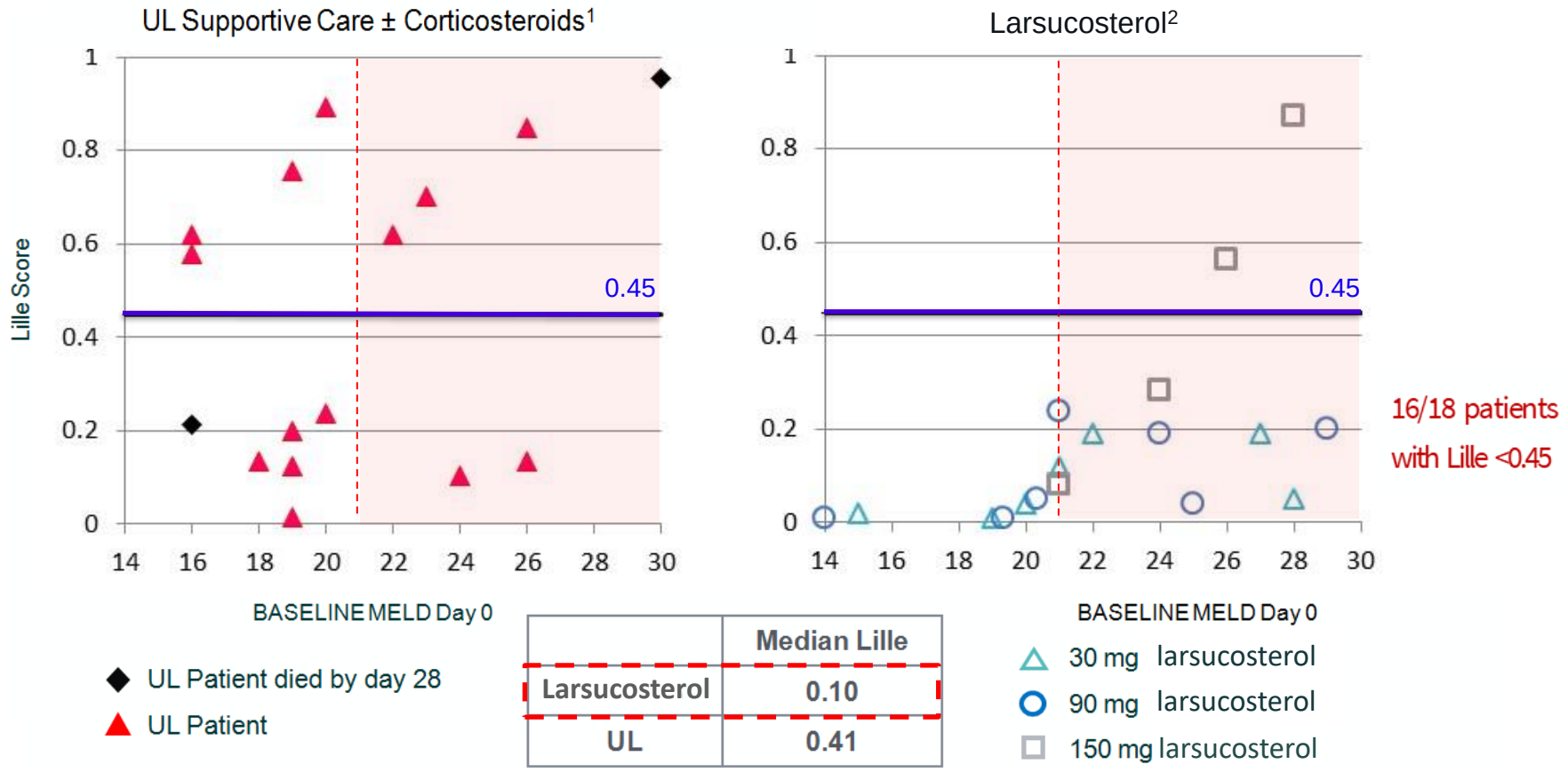


[1]Louvet, A et al. Hepatology 2007; 45:1348-1354.

[2]n=18 ; one patient did not return for the day 7 visit.

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

[1]Anonymized data provided by Dr. Craig McClain from the University of Louisville (UL) from his separate Trial, in which 16 AH patients with initial MELD scores ranging from 15-30 received either supportive care alone (n=9) 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. Non-head-to-head comparison. Results of a head-to-head comparison may differ significantly from those set forth herein.

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

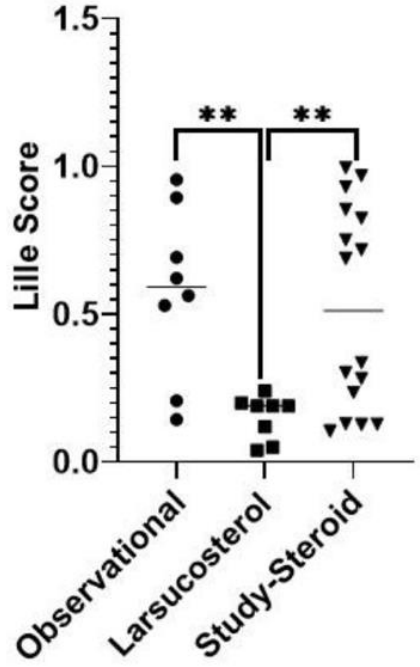
Statistically-significant Reduction in Lille Score in Severe AH Patients

Article published in peer-reviewed journal

- Severe AH patients who received 30 or 90 mg of larsucosterol in Phase 2a (n=8) had lower Lille scores than patients from contemporaneous NIH-funded DASH study
  - Observational (n=8) and Study-Steroid arm (n=16) received standard-of-care, including corticosteroids
  - Comparative arm patients well-matched by MELD score to larsucosterol-treated patients

Arm	Median Baseline MELD
Observational	24.5
Larsucosterol	24.5
Study-Steroid	24.0

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



** Represents p<0.01 by T-test

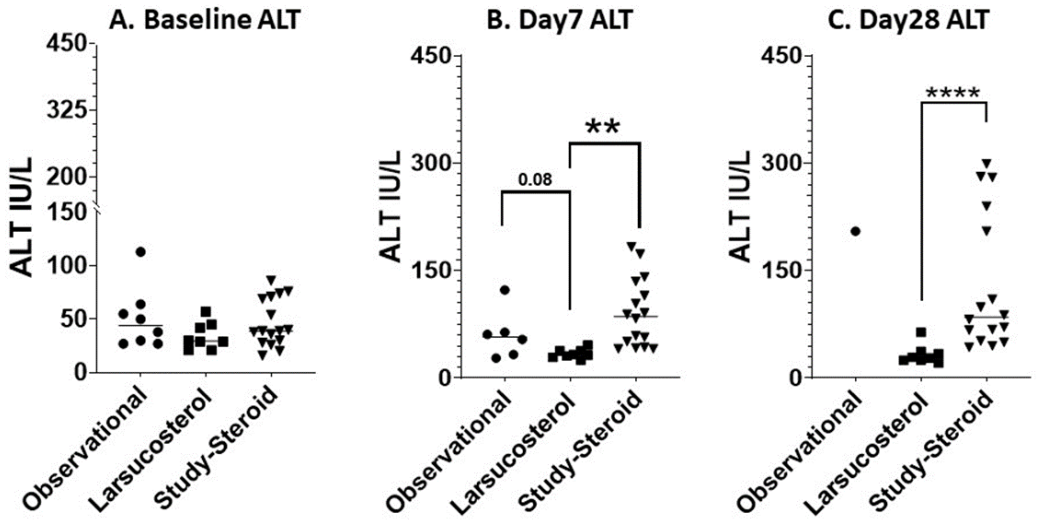
References:
Hassanein, et. al., (2023) Safety, Pharmacokinetics, & Efficacy Signals of Larsucosterol (DUR-928) in Alcohol-associated Hepatitis. *The American Journal of Gastroenterology*. Non-head-to-head comparison. Results of a head-to-head comparison may differ significantly from those set forth herein.

Larsucosterol Improved Liver Enzymes in Severe AH Patients

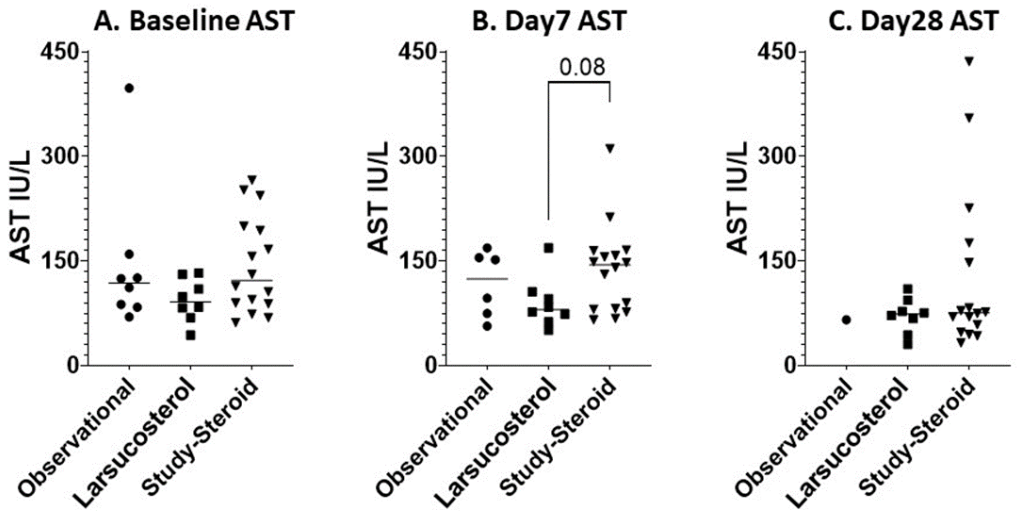
Statistically-significant reductions in ALT vs. comparison groups

- Both ALT and AST enzymes decreased rapidly in severe AH patients in the 30 and 90 mg larsucosterol cohorts

Change in ALT from Baseline



Change in AST from Baseline



** Represents p<0.01 by T-test
**** Represents p<0.0001 by T-test

References:
Hassanein, et. al., (2023) Safety, Pharmacokinetics, & Efficacy Signals of Larsucosterol (DUR-928) in Alcohol-associated Hepatitis. *The American Journal of Gastroenterology*. Non-head-to-head comparison. Results of a head-to-head comparison may differ significantly from those set forth herein.

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 in Q2 2023 with topline data in 2H 2023
  - Primary endpoint is reduction in mortality or liver transplant at 90 days
- Potential NDA filing subject to achievement of primary endpoint
  - 42% of new drugs launched in the U.S. in 2018 were approved based on single trial[1]
  - Previously granted Fast Track Designation

References:
[1] IQVIA Institute, Mar 2019

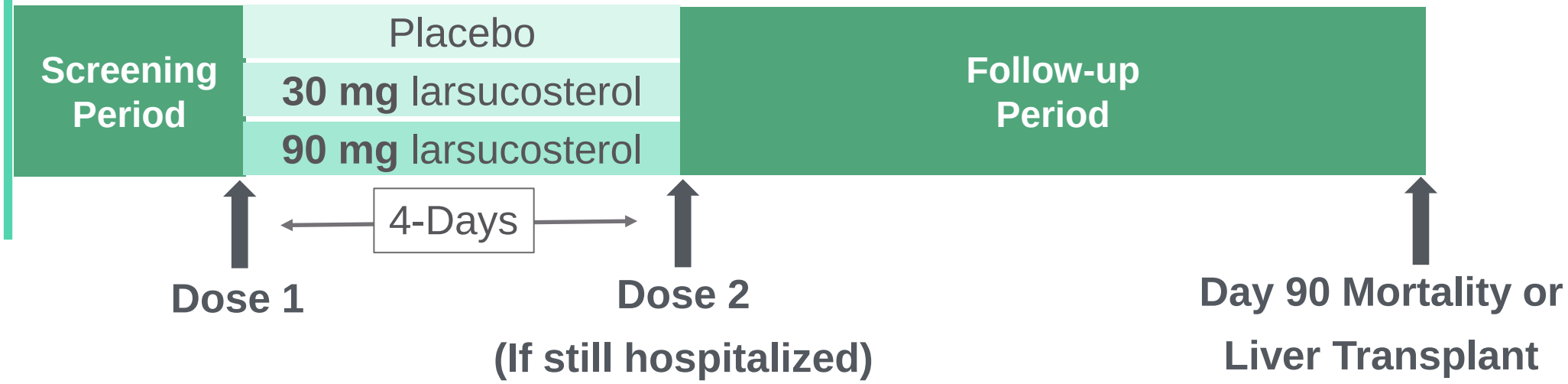
AHFIRM Trial Design Leverages Lessons from Phase 2a Trial

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.

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 – launched in September 2022
3. Earned $10 million in milestones during Q3 2022 based on recent patent issuance and first commercial sale
4. Additional future milestones of up to $122 million, plus low double-digit to mid-teen royalties

For full prescribing information including Boxed Warning, see www.posimir.com. POSIMIR is a trademark of Innocoll Pharmaceuticals in the US and DURECT Corp. ex-US; SABER is a trademark of DURECT Corp.

Financial Overview and Summary

Financial Overview

Nasdaq	DRRX
Market Cap	$102.8 MM[1]
Shares O/S	24.5 MM[2]
Cash & Cash Equivalents	$52.4 MM[2]
Debt	$21.2 MM[3]
Federal NOLs	$352 MM[4]

Cupertino, CA headquarters

[1] As of May 1, 2023
[2] As of December 31, 2022; pro forma for equity offering completed in February 2023
[3] As of December 31, 2022
[4] As of December 31, 2021

Larsucosterol – Positioned for Success in AH

Robust Phase 2b Trial w/ Registration Potential

- Global, randomized, double-blind, placebo-controlled efficacy trial
- 300 patient, 3 arm trial
- Clearly-defined patient population
- Straightforward endpoint
- Well positioned to show potential clinical benefit
- Fast Track Designation

Clinical Efficacy Demonstrated in Phase 2a Trial

- 100% 28-day survival
  - 20-26% historical mortality rate at 28 days[1]
- 74% of patients discharged in ≤ 4 days after 1 dose
- 67% of severe patients discharged in ≤ 4 days after 1 dose

Clinical Safety

- Well tolerated
- No drug-related SAEs
- No discontinuations
- More than 350 patients dosed in multiple Phase 1 & 2 trials
- Multiple dose levels studied (30mg, 90mg, 150mg)

Clinically Relevant Mechanism of Action

- Upregulation of DNMTs differentiates AH from other liver diseases
- Larsucosterol inhibits DNMT activity
- Protective against multi-organ failure in multiple nonclinical models

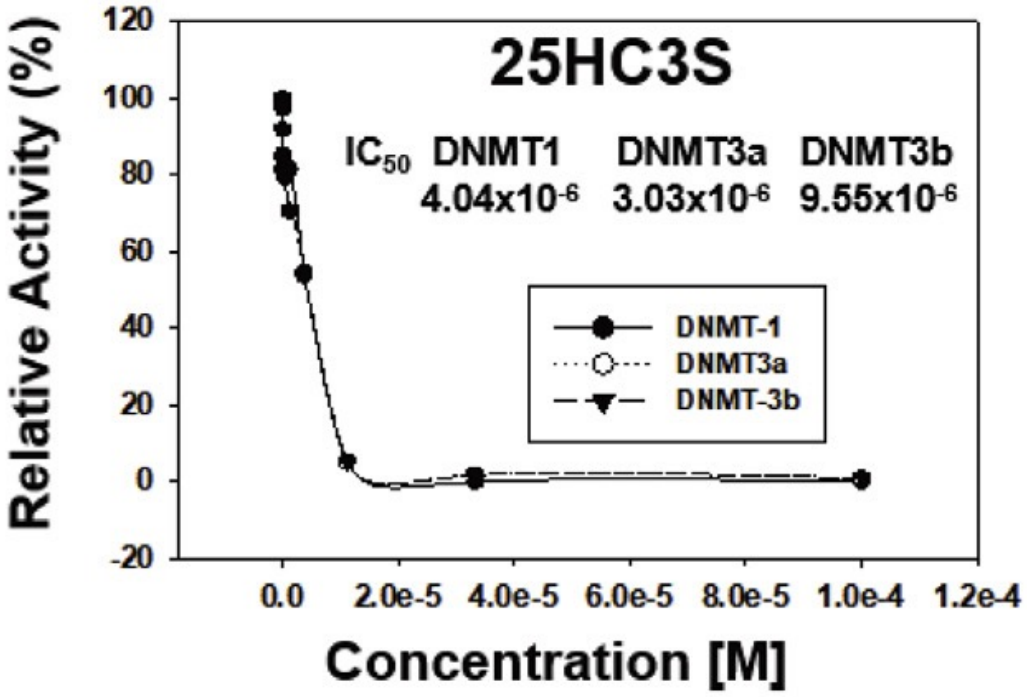
Enrollment completion anticipated in 2Q23 with topline data expected in 2H23

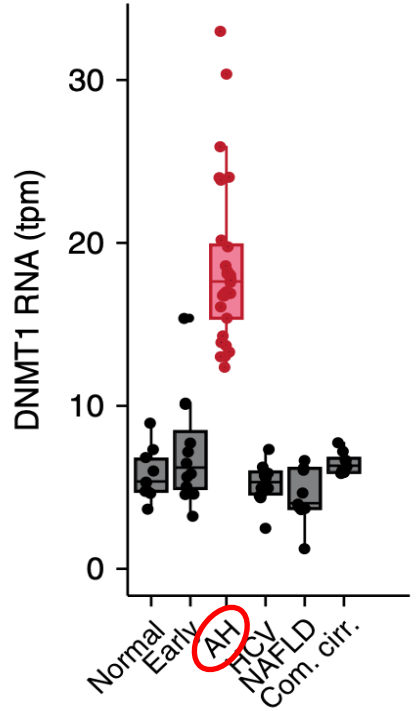
References:
[1] Hughes, et al., 2018, PLOS ONE

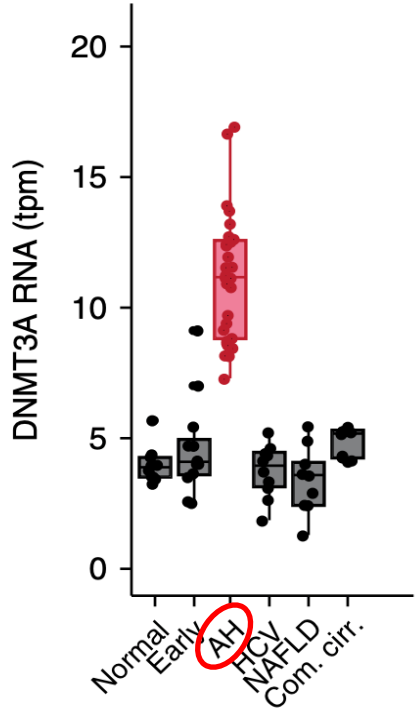
Appendix

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