Unlocking epigenetic therapeutics to revolutionize medicine

JUNE 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."

DURECT Company Highlights

1	**Unmet Need: Alcohol-associated Hepatitis**	• ~137,000 hospitalizations per year for AH • ~30% mortality rate within 90 days • No approved therapy labeled for AH
2	**Larsucosterol (DUR-928) Phase 2a AH Data**	• 100% survival at 28 days in Phase 2a AH trial vs 26% historical mortality rate • No drug-related serious adverse events • MOA aligns with AH epigenomic dysregulation
3	**Larsucosterol AHFIRM Trial**	• Phase 2b ~300 AH patient placebo-controlled trial; over 100 patients dosed • Robust survival benefit may support NDA filing • potential to be first approved treatment for AH • Fast Track Designation

4	**Beyond AH**	• Potential indications: Positive clinical NASH data for larsucosterol
		  • Strong pre-clinical support for multiple high unmet need indications
		• POSIMIR: Innocoll Pharmaceuticals expected to launch in Q3 2022
		  • DURECT to receive up to $132 million in milestones & double-digit royalties

AH Pharmacoeconomics

- ~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]	Total healthcare cost per hospitalization episode[2]
Died during the hospitalization	9 days	$151,500
Were discharged	6 days	$56,000

- 86% of hospitalized AH patients are insured[1]
- Larsucosterol could be the first drug approved for AH

References:
[1] US Department of Health and Human Services' Healthcare Cost and Utilization Project reports https://hcupnet.ahrq.gov (accessed January 2022); [2] Marlowe, et. al., AASLD 2021 Poster No. 381

Larsucosterol (DUR-928)
Potential in Alcohol-associated Hepatitis (AH)

Alcohol-associated Hepatitis (AH)

AH patients typically have a history of daily alcohol use of:

>40g alcohol/day (female), which is about 3 standard drinks, for 6 months or longer[1,2]

OR

>60g alcohol/day (male), which is about 4 standard drinks, for 6 months or longer[1,2]

What is a Standard Drink?

12 fl oz of regular beer
about 5% alcohol

8-9 fl oz of malt liquor
about 7% alcohol

5 fl oz of table wine about 12% alcohol

1.5 fl oz of shot of distilled spirits
about 40% alcohol

Individuals with a sudden increase in alcohol intake or intermittent heavy drinking may also be affected[1,2]

AH can also develop in patients with a much shorter history of heavy alcohol use[1,2]

Common symptoms include

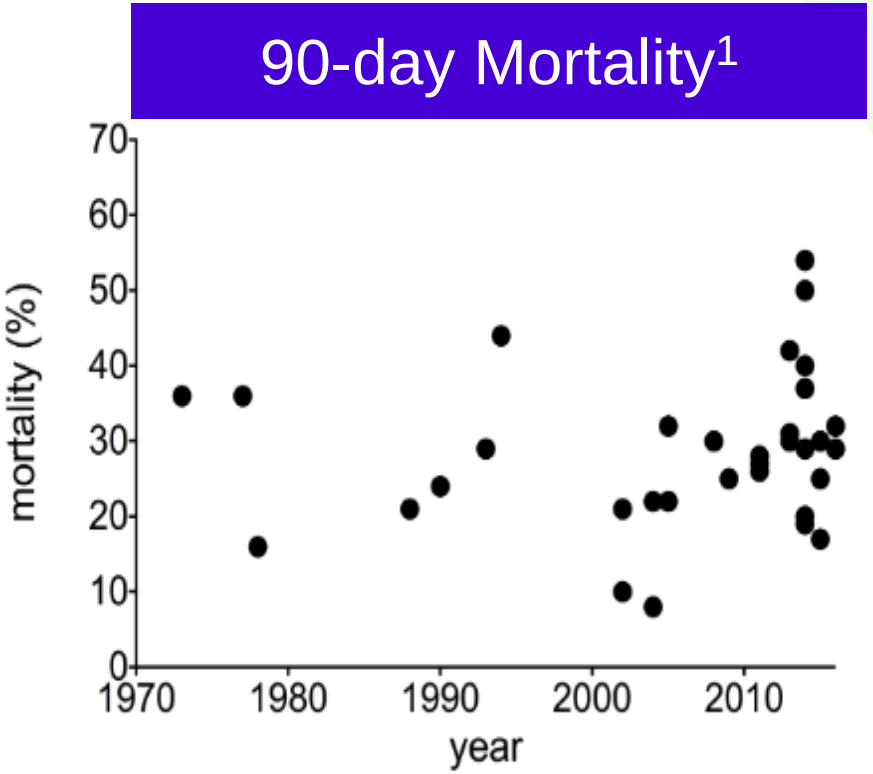
- Nausea
- Vomiting blood
- Loss of appetite
- Fever
- Fatigue and weakness
- Negative changes in mental state
- Rapid onset of jaundice (yellowing of skin or eyes)

Acute severe cases may lead to life-threatening complications, including acute renal injury, liver failure and multi-organ failure associated with systemic inflammatory responses

References:
[1] Friedman, et al., 2018, UptoDate; [2] Crabb, et al. 2016. Gastroenterology, 150: 785-790

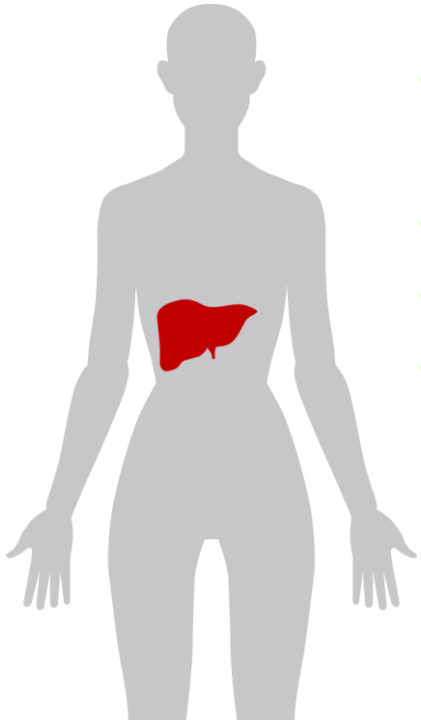
What is Alcohol-associated Hepatitis (AH)?

- A subset of alcohol-associated liver disease (ALD)
- Seen with heavy alcohol use
- Presents as acute hepatitis
- Characterized by severe inflammation
    - May progress to multi-organ failure
- 26% mortality rate at 28 days and 29% at 90 days[1]
- Recovery is slow (3-12 months)
- No satisfactory therapy



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

Unmet Need: No Approved Therapy Labeled for AH

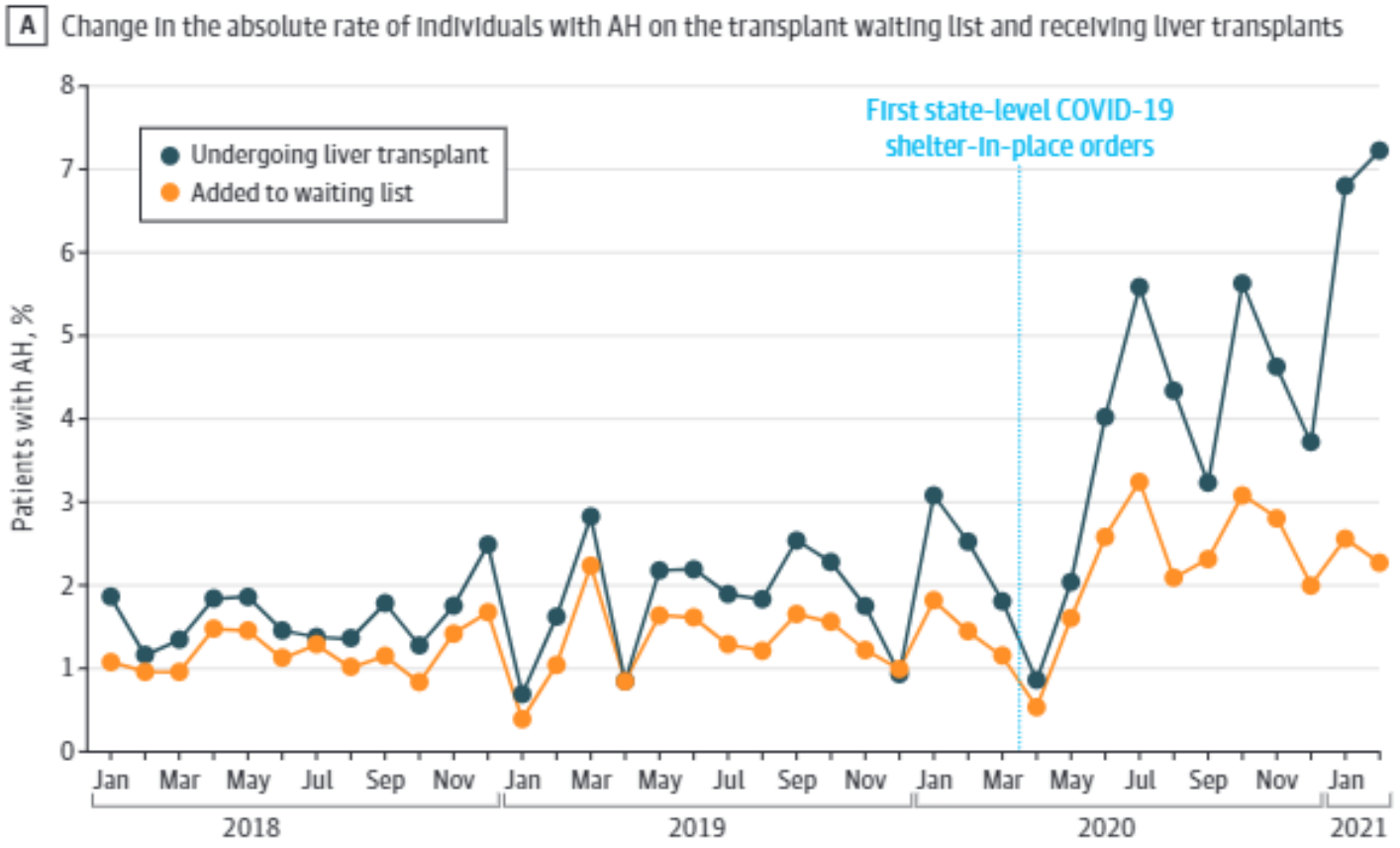


- Corticosteroids have no survival benefit at 90 days or 1 year and increased risk of infection[1]
  - Less than 50% of AH patients are eligible for corticosteroids[2]
- Stopping alcohol consumption is not sufficient in many patients[3]
- Alcohol consumption increased by over 30%[4] and hospitalizations have increased during the pandemic
- Liver transplants becoming more common for AH[5]
  - Rate of AH patients undergoing liver transplants has more than doubled since the first COVID-19 shelter in-place orders in early 2020[5]
  - Liver transplant costs >$875,000[6]
  - Long waiting period, burdensome selection process and a life-altering procedure

"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

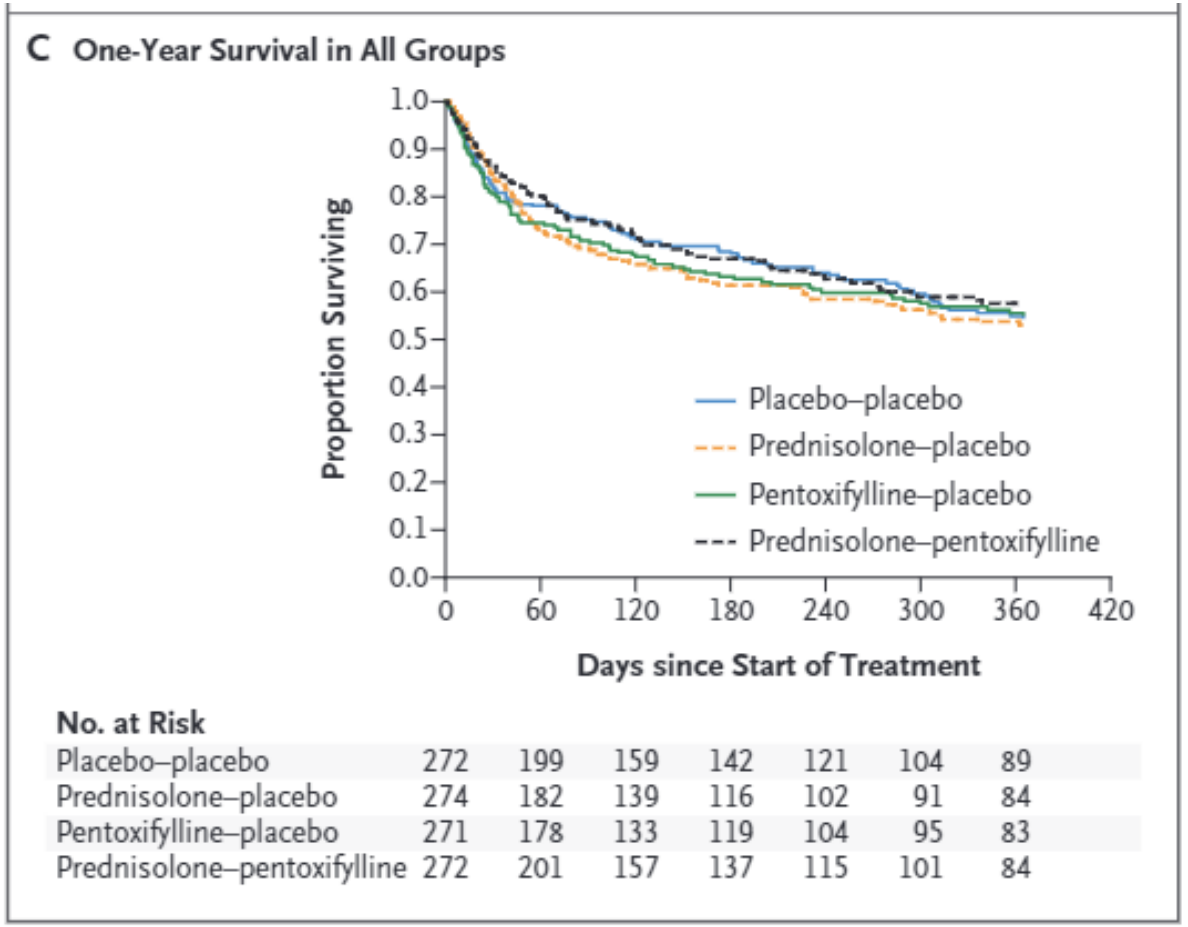
References:
[1] Thursz M, et al. 2015, *NEJM*, 372: 1619-1628; [2]Singal AK et al. 2018, Journal of Hepatology, 69: 534-543; [3] Singal AK, et al. 2014, Clin Gastroenterol Hepatol., 12:555-564; [4]Lee BP et al. 2021, Ann Intern Med, 147 (7): 1027-1029; [5]Bitterman T et al. 2021, JAMA Network, 4(7):e2118713; [6]Bentley, TS and Ortner NJ 2020, U.S. organ and tissue transplant: cost estimates, discussion, and emerging issues (Milliman Research Report, 2020)

Change in the Rates of Additions to the Liver Transplant Waiting List and Receipt of Liver Transplants Among Patients With Acute Alcohol-associated Hepatitis (AH) Nationally From March 2018 through February 2021



References:
Bitterman, T, Mahmud, N, Abt, P. JAMA Network Open. 2021;4(7):e2118713. doi:10.1001; July 21, 2021

STOPAH Trial – No Long-term Benefit from Steroids or Pentoxifylline in AH



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

Larsucosterol
Alcohol-associated Hepatitis (AH)

Phase 2a

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

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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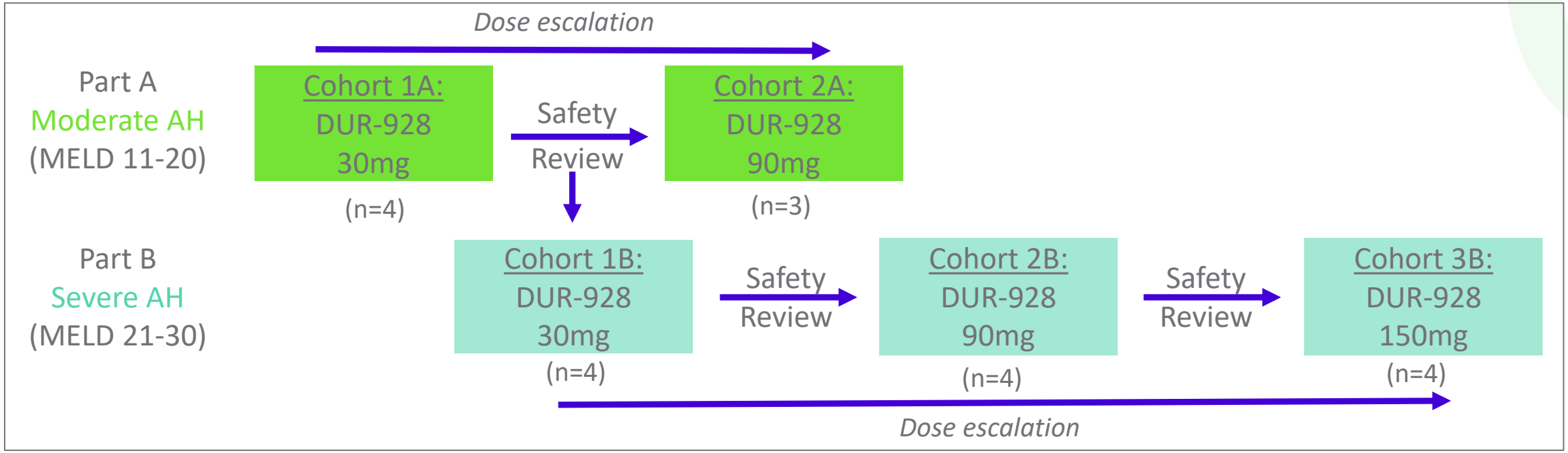
Larsucosterol (DUR-928) Alcohol-associated Hepatitis (AH) Phase 2a

Open label, dose and severity escalation, multi-center U.S. trial (n=19)



- Trial subjects received up to 2 doses of DUR-928 (1st dose on Day 1; 2nd dose on Day 4, if still hospitalized)
- 28-day follow up

- Key endpoints: safety, PK, PD, liver biochemistry, biomarkers prognostic score (e.g., Lille, MELD)

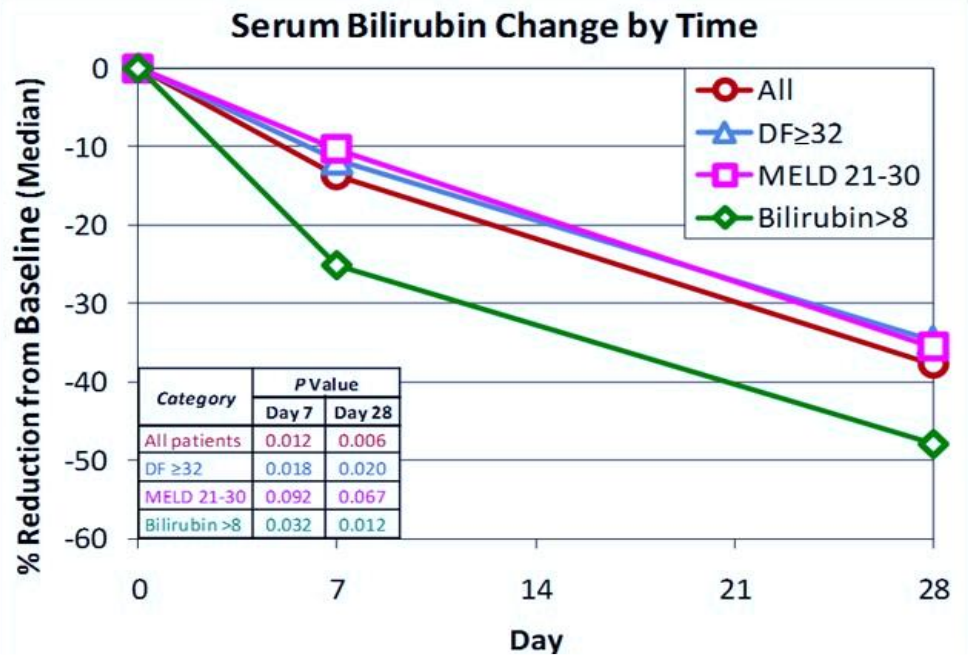
Larsucosterol (DUR-928) Alcohol-associated Hepatitis (AH) Phase 2a: Dosing and hospitalization

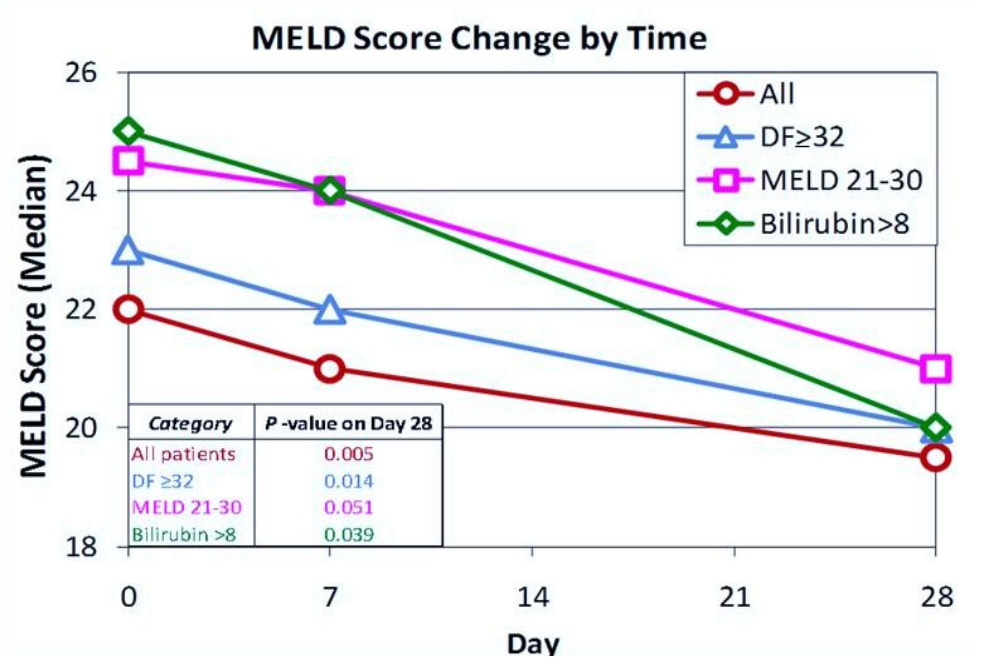
Larsucosterol Resulted in Potential Pharmacoeconomic Benefit as Measured by Time to Discharge

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%)

Larsucosterol (DUR-928) Alcohol-associated Hepatitis (AH) Phase 2a: Bilirubin and MELD

DUR-928 Reduces Bilirubin & MELD Across Patient Categories, Especially Those with Higher Bilirubin



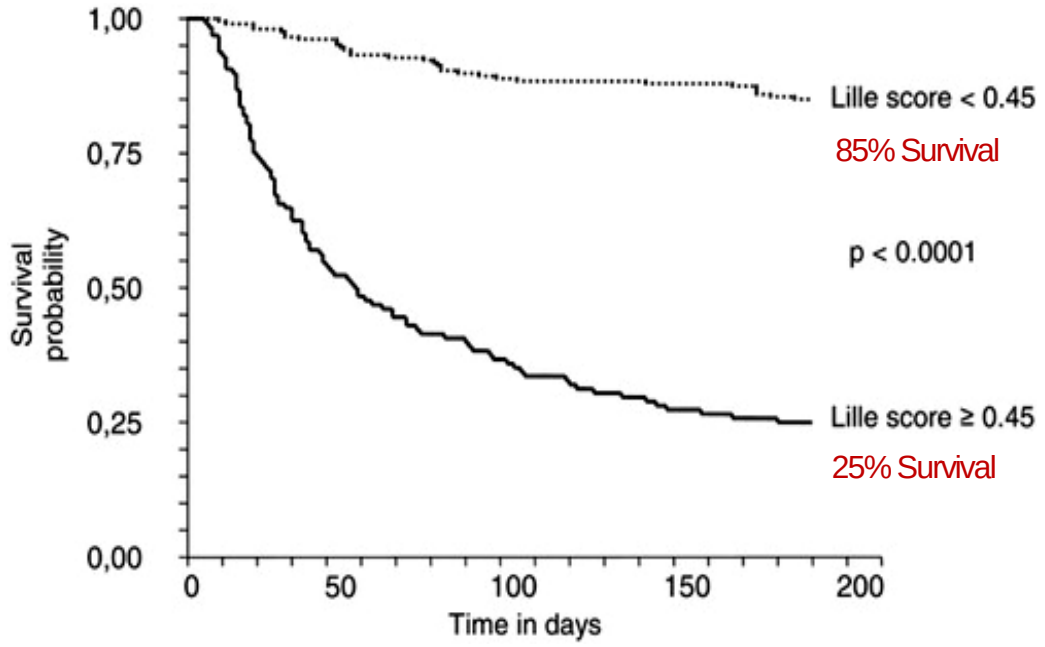


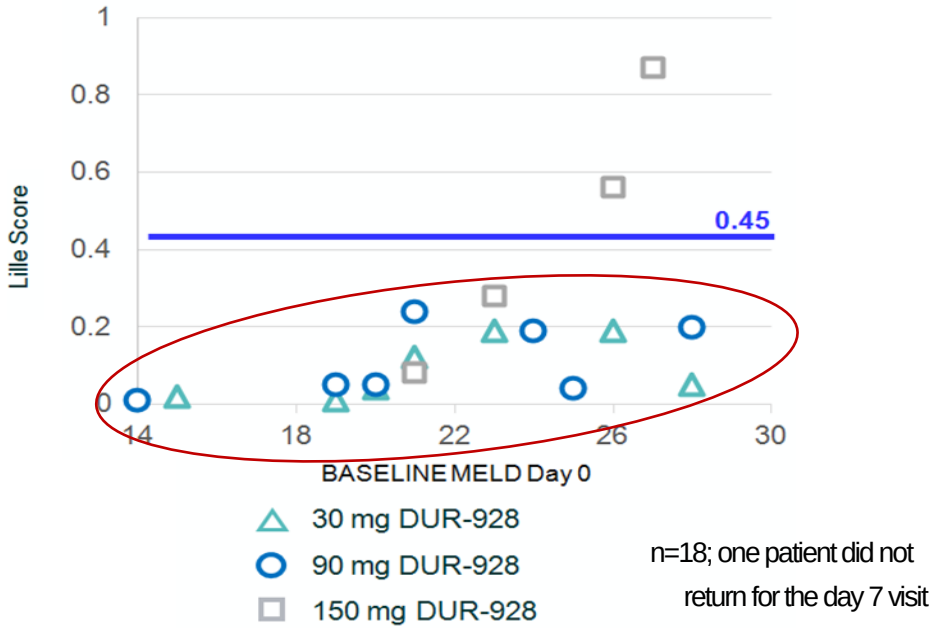
One of 19 patients did not return for the follow-up visits on Day 7 and Day 28; all data were analyzed based on those who completed visits.

Larsucosterol (DUR-928) AH Phase 2a: Lille Score

Larsucosterol treatment resulted in 89% (16/18) Response Rate (Lille < 0.45) across all patients

Composite score used to determine how a therapy is working after 7 days; prognostic indicator of mortality



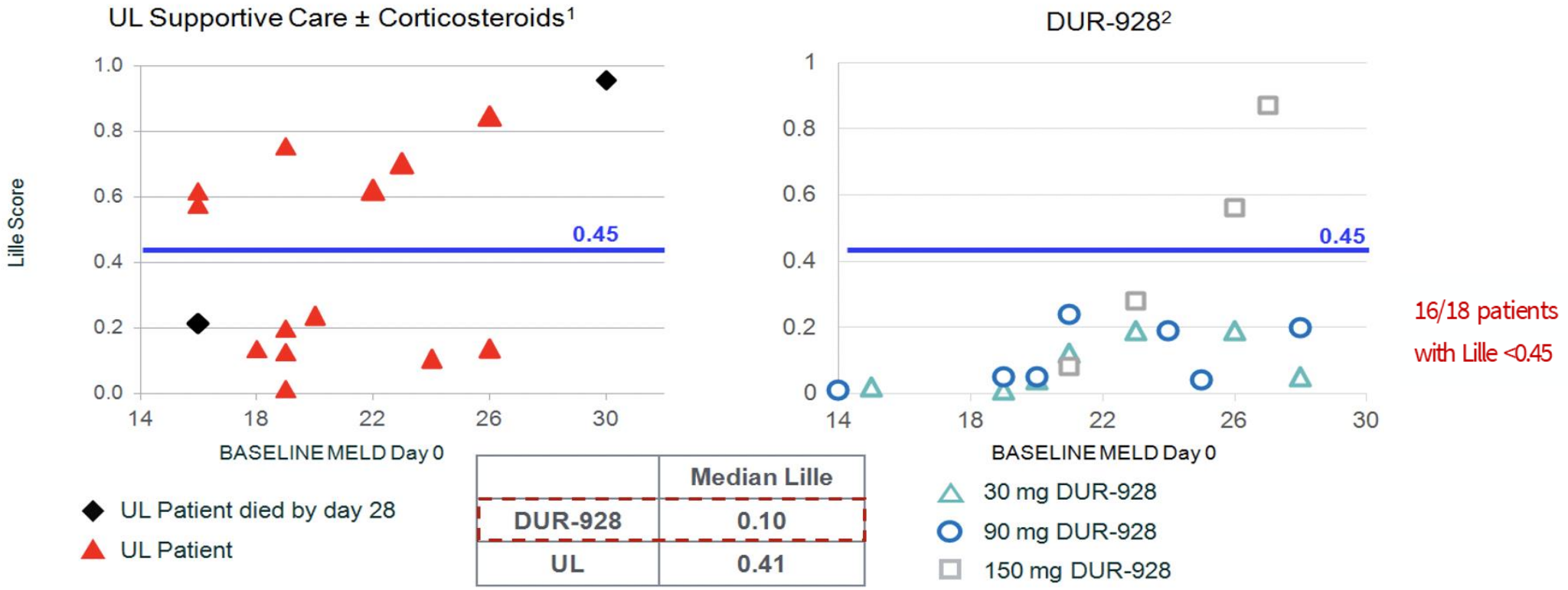


n=18; one patient did not return for the day 7 visit

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

Larsucosterol - AH Phase 2a: Lille Score Comparison to UL Historical Control

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



	Median Lille
DUR-928	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.

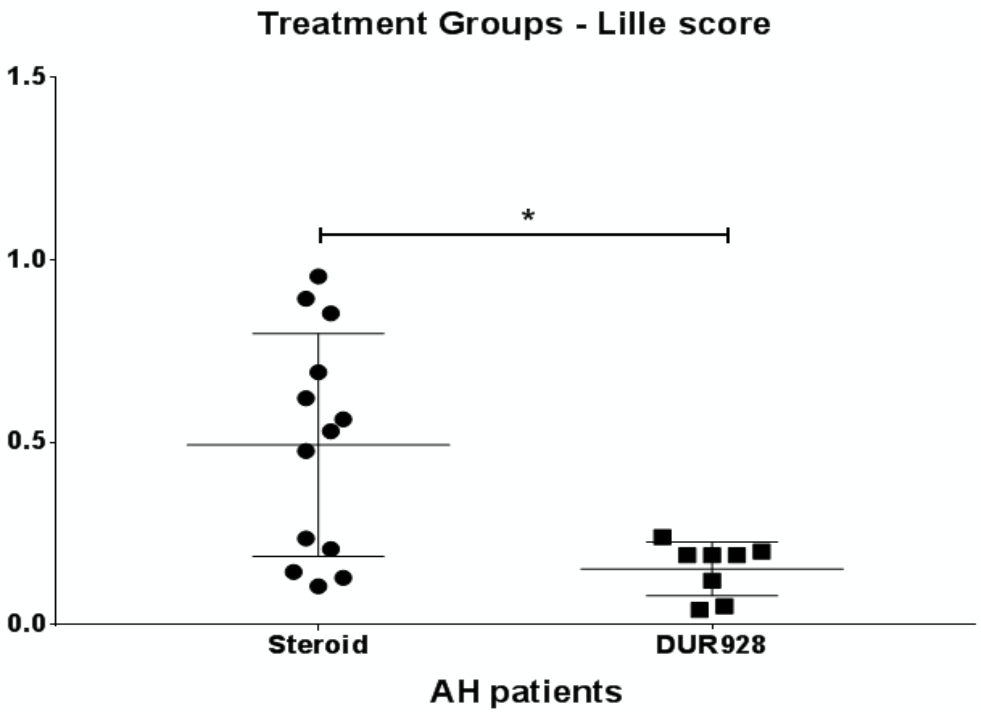
Larsucosterol - AH Phase 2a: Subgroup Analysis vs. Historical Control

Larsucosterol AHFIRM doses (30mg & 90mg) vs. Corticosteroid treatment in Severe AH Patients

- U. of Louisville AH patients in a contemporaneous trial who received corticosteroids for 28 days (n=13)
- DUR-928 treated severe AH patients (either 30mg or 90mg of DUR-928) (n=8)

Baseline AH Severity	DUR-928	Steroid (UL)
Mean Baseline MELD (Severe AH ≥ 21)	24.5	24.5
Mean Baseline Maddrey's Discriminant Function (Severe AH ≥ 32)	61.3	63.0

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 - Alcohol-associated Hepatitis (AH) Phase 2a: Safety

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

100% of patients (n=19) survived through 28-day follow up period
- Historical mortality rate of 26% at 28 days[1]

References:
[1] PLOS ONE | https://doi.org/10.1371/journal.pone.0192393, Feb. 14, 2018.

Larsucosterol (DUR-928)
Alcohol-associated Hepatitis (AH)

Mechanism of Action (MOA)

Larsucosterol (DUR-928)

Lead Compound in DURECT's Epigenetic Regulator Program

Regulator of DNA Methylation

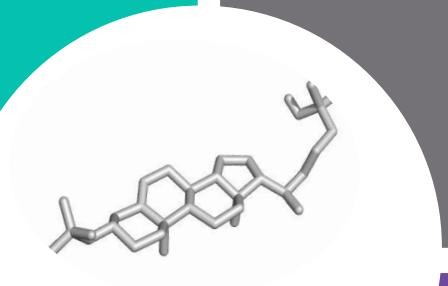
New class of therapeutics

Endogenous sulfated oxysterol

Highly conserved across all 7 species studied to date

Clinical safety

Well tolerated at all doses more than 350 subjects (healthy volunteers and patients) 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

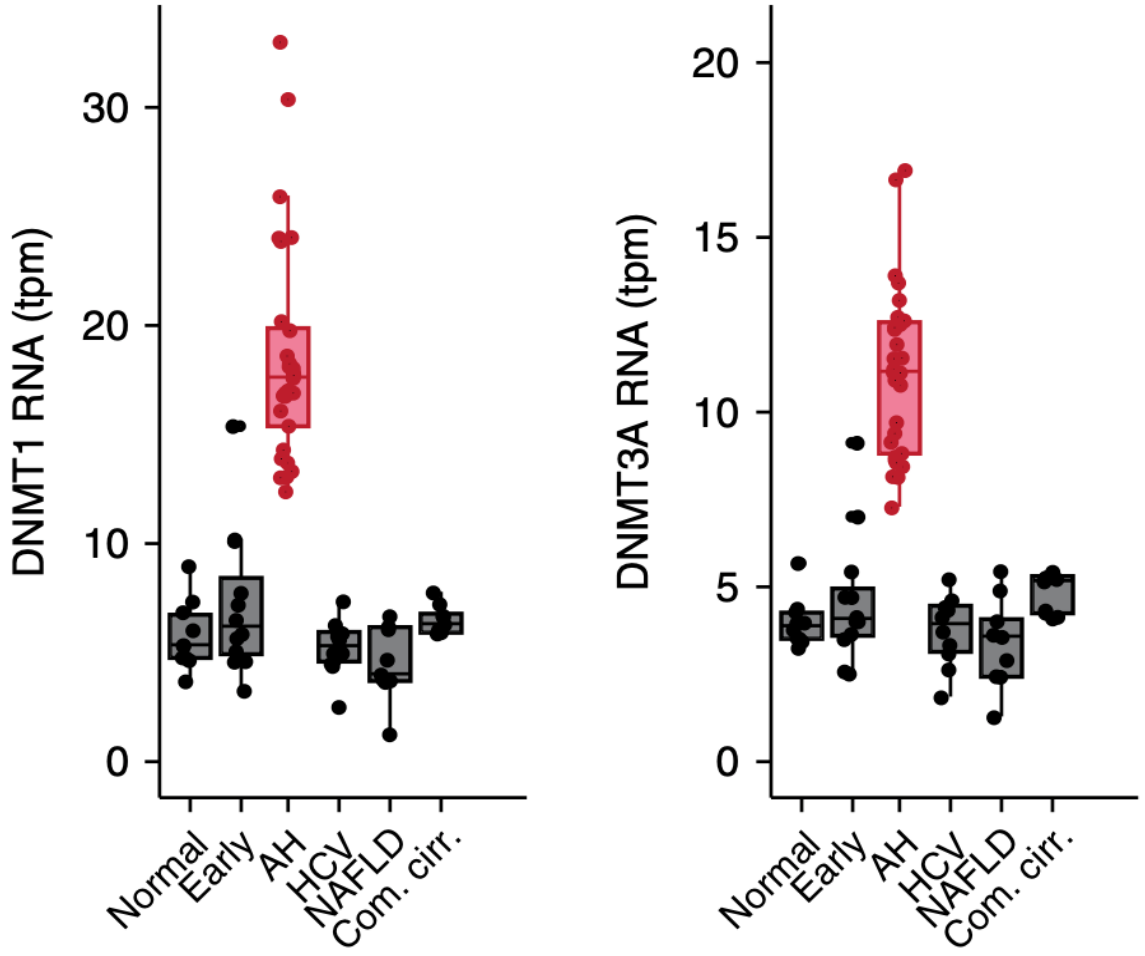
Improves cell survival and tissue regeneration

Therapeutic potential

Mechanism of action (MOA) as regulator of DNA Methylation supports investigating larsucosterol for the treatment of multiple acute organ injury and chronic diseases

Epigenetic Dysregulation in AH Patients

- Aberrant DNA methylation is associated with many diseases, including AH
- Liver samples from patients with AH have increased expression of DNA Methyltransferases (DNMT 1&3a)
- Increased DNMT levels are associated with DNA hypermethylation, transcriptomic reprogramming, and loss of mature cell function
- Hypermethylated genes are involved in stress response, energy / lipid metabolism, and cell death / survival

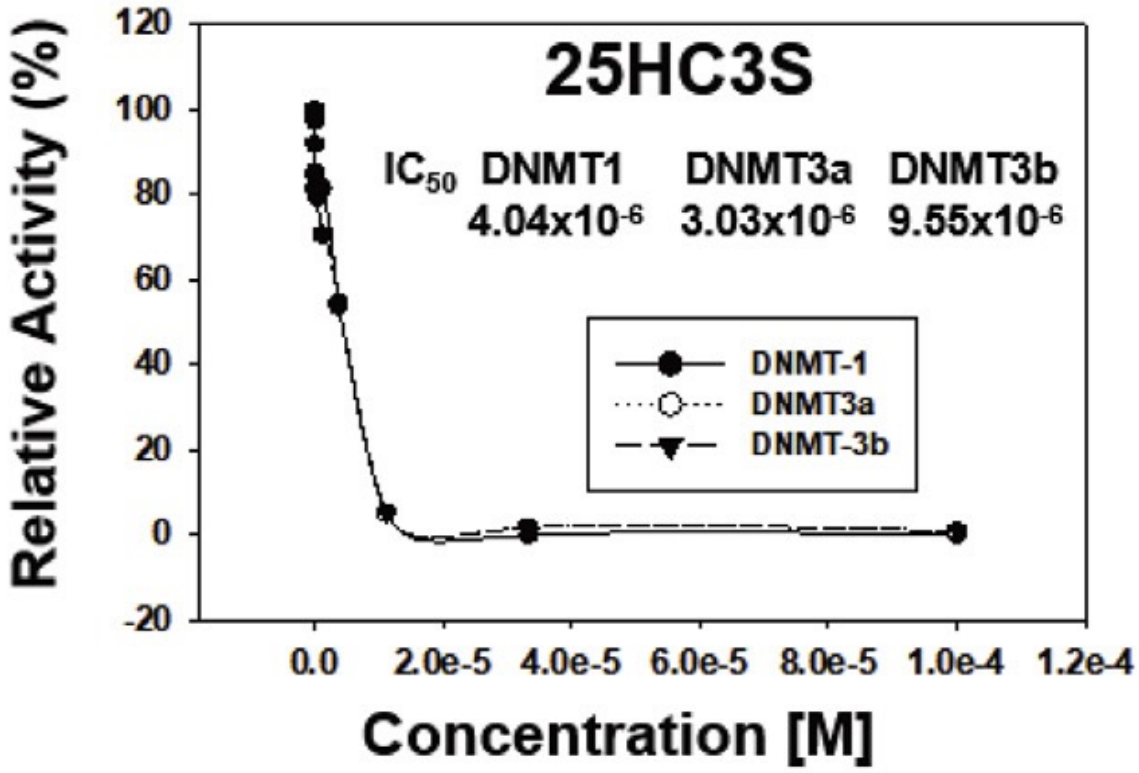


References:
Argemi et al. 2019. Nature Communications, 10: 3126; https://doi.org/10.1038/s41467-019-11004-3 Creative Commons Attribution 4.0 International License

Larsucosterol (DUR-928) Epigenetic Mechanism of Action (MOA)

- Larsucosterol binds to and inhibits the activity of DNMTs and DNA hypermethylation, thereby regulating the expression of genes involved In stress response, energy / lipid metabolism, and cell death / survival

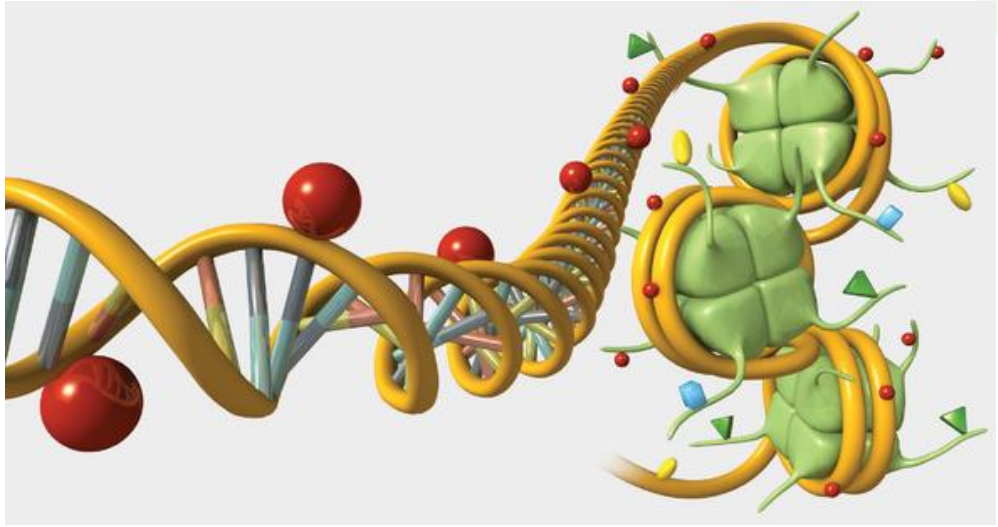
- The modulation of DNA methylation by larsucosterol may lead to increased cell survival, improved cellular function, and reduced inflammation, as observed in various *in vivo* animal models and in the results from our completed AH and NASH clinical trials



References:
Wang Y et al. 2021, Journal of Lipid Research, 62:1-14 *Note: in this paper, larsucosterol is referred to as 25HC3S*

Larsucosterol (DUR-928) Mechanism of Action (MOA)

- Larsucosterol inhibits activity of DNA methyltransferases DNMT 1, 3a, and 3b
- Reduces DNA hypermethylation
- Demethylates CpG promoter regions and modulates important cell signaling pathways
    - Such as: MAPK-ERK and Ca-AMPK pathways
    - Regulates crucial cellular functions/activities
    - Including cell survival/death, stress response, inflammation, and lipid biosynthesis

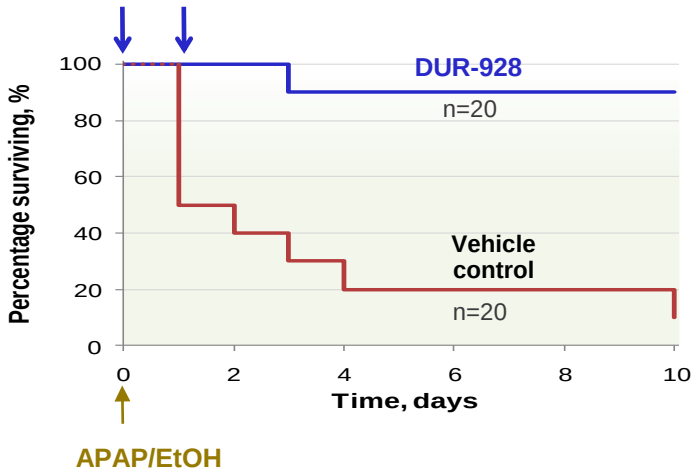


Larsucosterol in Acute Multi-Organ Injury Models

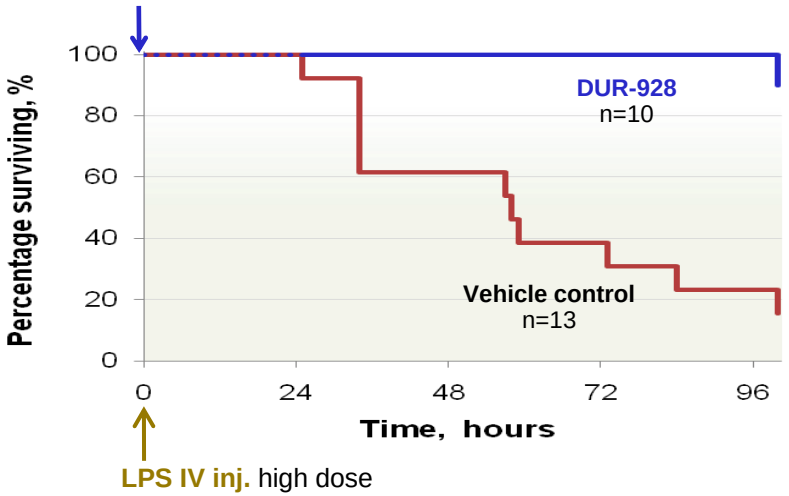
DUR-928 reduced the absolute mortality rate by 80% in two pre-clinical multi-organ injury models

- Protected multiple organs, including kidneys, liver, and lungs
- Additional supportive data in AKI, sepsis, pancreatitis, cholestatic liver injury models, and other preclinical acute models

DUR-928 or vehicle control dosed 2 times after APAP/EtOH [1]



DUR-928 or vehicle control before LPS [2]



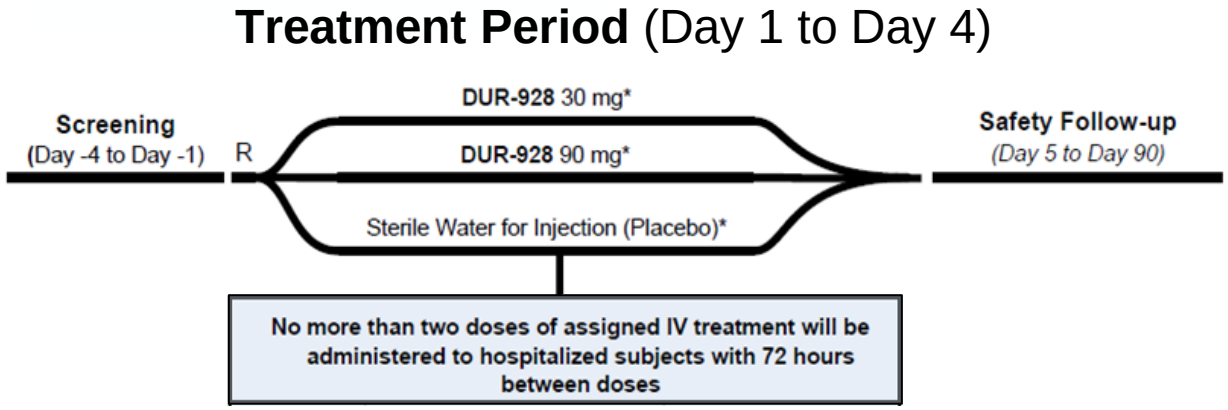
References:

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

Larsucosterol (DUR-928)
Alcohol-associated Hepatitis
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

Study Objectives, Design & Endpoints: AHFIRM



TRIAL ENDPOINTS

- Primary: Safety and efficacy (90-day mortality)
- Secondary: 28-day mortality, TESAEs, Lille score at Day 7, MELD scores at Day 28, and ICU days at Day 28

DESIGN

- Randomized, double-blind, placebo-controlled, multi-arm, multi-center, parallel design
- Severe AH patients with Maddrey's DF score ≥ 32 and MELD scores 21-30
- 300 subjects in three dosing groups at a 1:1:1 ratio (30mg, 90mg, Placebo + SOC)

Larsucosterol (DUR-928) in Alcohol-associated Hepatitis (AH)

Potential to be first approved therapy for AH

Positive Phase 2a Data Led to Ongoing AHFIRM Trial

- 100% survival at day 28 in Phase 2a trial; compared to 26% historical 28-day mortality rate[1]
- Larsucosterol was well tolerated across all doses
- MOA: Larsucosterol affects epigenetic dysregulation reported in AH patients
- Phase 2b double-blind placebo-controlled efficacy trial (AHFIRM) ongoing
    - Potential NDA filing, if robust survival benefit shown
        - 42% of new drugs launched in the US in 2018 were approved based on single trial[2]
- Fast Track Designation

References:
[1] Hughes, et al., 2018, PLOS ONE; [2] IQVIA Institute, Mar 2019

Larsucosterol (DUR-928) Potential Beyond AH

Larsucosterol: Potential indications beyond AH

NASH: Phase 1a & 1b trials 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
- Good safety profile

Potential Additional indications supported by pre-clinical data

- Acute kidney injury, pancreatitis, metabolic syndrome, stroke, sepsis, 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 – launch expected Q2 2022
3. Future milestones of up to $132 million, plus low to mid double-digit royalties

DURECT Corporation

Financial Overview

Nasdaq	DRRX
Market Cap	$112 MM[1]
Shares O/S	227.7 MM[2]
Cash & Investments	$64.4 MM[3]
Debt	$20.8 MM[3]
Federal NOL's	$352 MM[4]

Cupertino, CA headquarters

[1] As of May 4, 2022
[2] As of May 3, 2022
[3] As of March 31, 2021
[4] As of December 31, 2021

Summary

AHFIRM Phase 2b AH Trial Ongoing

- Placebo-controlled efficacy trial targeting 300 pts across 60+ global sites
- May support NDA filing if robust survival benefit is shown

Positive Phase 2a AH Trial and MOA

- 100% 28-day survival
- No drug-related SAEs
- DUR-928 affects epigenetic dysregulation reported in AH patients

DUR-928 Phase 1b NASH

- Positive Phase 1b data: improvements in liver enzymes, stiffness, biomarkers & serum lipids

POSIMIR®

- US commercial rights licensed to Innocoll Pharmaceuticals
- Launch expected Q2 2022
- Up to $132M milestones, plus low to mid double-digit royalties

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