Unlocking Epigenetic Therapeutics to Revolutionize Medicine

September 2023

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Company Highlights

- Harnessing the power of epigenetic modulation
- Larsucosterol: Potential first-in-class treatment for AH
- Potential pivotal trial ongoing; data expected in Q4 2023
- Compelling Phase 2a data in AH
- Significant unmet need in AH – no approved therapy

AH = Alcohol-associated hepatitis

PIPELINE

Program	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Marketed	Status
Epigenetic Modulator Program							
Larsucosterol	Alcohol-Associated Hepatitis (AH) (intravenous administration)						Enrollment completed in Phase 2b AHFIRM trial; topline data expected Q4 2023
	Non-Alcoholic Steatohepatitis (NASH) (oral administration)						Positive Phase 1b topline data
NCEs[1]	Hematology/Oncology (small molecules)						Molecule selection targeted for Q4 2023
Partnered Program							
POSIMIR® (bupivacaine solution)	Post-surgical pain[2]						Sold by Innocoll in the U.S.; DURECT maintains ex-U.S. rights

[1] New chemical entities; [2]Indicated for post-surgical analgesia for up to 72 hours following arthroscopic subacromial decompression

Larsucosterol Overview

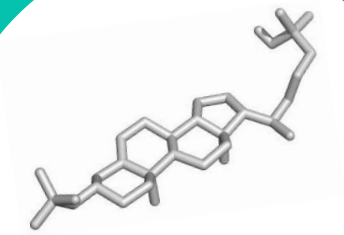
Lead Compound in DURECT's Epigenetic Modulator Program

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 500 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
- Regulates inflammatory or stress response
- Promotes cell survival

Broad therapeutic potential

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

[1]MOA = Mechanism of Action

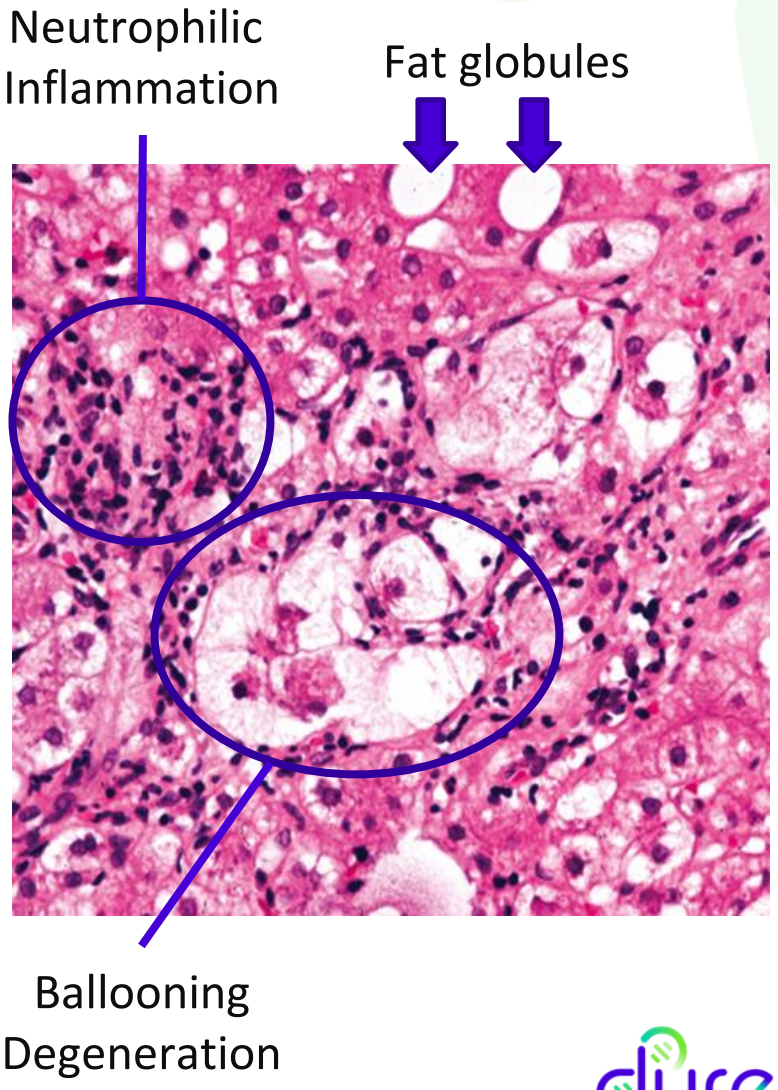
Larsucosterol
Potential in Alcohol-associated Hepatitis

What is Alcohol-associated Hepatitis?

- Life-threatening form of alcohol-associated liver disease (ALD)
- Can occur in individuals who chronically misuse alcohol—frequently after increased consumption
- 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

~26%
28-day mortality rate[1]

~30%
90-day mortality rate[1]



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

AH Imposes High Economic Burden on US Healthcare System

- ~158,000 U.S. hospitalizations in 2020[1]
- Incidence may yield ~300K hospitalizations by 2034[2] based on historical rapid yearly growth rate of 5.5% between 2015-2019[3]
- Increased physician and hospital awareness of AH could result in more robust ICD-10 coding and increased recorded hospitalizations
- 87% of hospitalized AH patients are insured[3]

Each hospitalization episode with AH[4]:

Total hospital healthcare charges per stay

References:
[1] Marlowe N, Lam D, Liangpunsakul S. 2023. *Alcohol Clin Exp Res,* 00:1-7; [2]Market Research – ClearView Analysis 2023; [3]Marlowe N et al. 2022. *Alcohol Clin Exp Res,* 46(8):1472-1481; [4]DURECT Corporation. Data on file.

Current Treatments for AH are Inadequate with No Approved Therapies

Corticosteroids

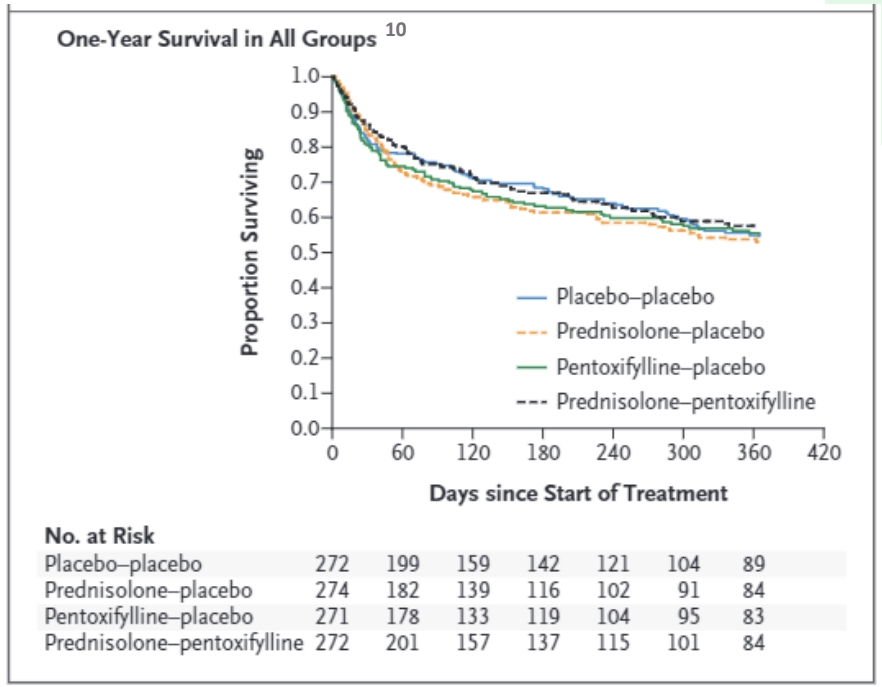
- Used as first-line treatment despite limited and inconsistent survival benefits and widely acknowledged contraindications[1,2,3]
- Only 25% to 45% of patients are eligible for corticosteroids[4,5,6]

Stopping Alcohol Consumption

- Not sufficient in many patients[7]

Liver Transplant

- Becoming more common for AH[8] but unavailable to most patients due to:[3,9]
  - High liver transplant costs >$875,000
  - Requirement of lifelong immunosuppression
  - Limited availability of donated organs



Larsucosterol could be the first drug approved for AH by the FDA and EMA

References:
[1]Crabb DW et al. 2016. *Gastroenterology,* 150:785-790; [2]Shipley LC and Singal AK. 2020. *Transl Gastroenterol Hepatol,* 5:26; [3]Singal AK et al. 2018. *Am J Gastroenterol,* 113:175-194; [4]Singal AK et al. 2018. *J Hepatol,* 69:534-543; [5]Singal AK and Mathurin P. 2021. *JAMA*, 326:165-176; [6]Bataller et al. 2022. *N Engl J Med*, 387:2436-2448; [7]Singal AK et al. 2014. *Clin Gastroenterol Hepatol*, 12:555-564; [8]Cotter TG et al. 2021. *Am J Transplant*, 21:1039-1055; [9]Tornai D and Szabo G. 2020. *Clin Mol Hepatol,* 26:686-696; [10]Thursz M et al. 2015. *NEJM*, 372: 1619-1628.

Physicians and Hospital Stakeholders need therapy that:

CAN REDUCE MORTALITY

Steroids have no significant effect on 90-day mortality

NOT SUBJECT TO PATIENT COMPLIANCE

Given low compliance and follow-up, issues with 28-day steroid courses are common;
An acute inpatient drug with short treatment course would be beneficial

ADDRESSES MILD/MODERATE AH

There would be a clinical benefit in catching these patients early in their disease trajectory, who currently have no options

PREVENTS ALCOHOL USE POST-DISCHARGE

30-40% of AH patients drink alcohol following discharge with low compliance with support programs

Larsucosterol Near-Term Opportunity

Larsucosterol Long-Term Opportunity

Source: Physician Interviews; ClearView Analysis 2023.

Larsucosterol

Phase 2a Trial in AH

Larsucosterol: Summary of Phase 2a Trial in AH[1,2]

100% survival (19/19) at 28 days 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) - statistically better than those of well-matched patients from an Observational Arm and Study-Steroid Arm of the DASH Consortium trial in a cross-study comparison
- Well tolerated across all dose levels with no drug-related SAEs
- Oral late-breaking presentation delivered by Dr. Tarek Hassanein[2]
  - Selected for 'Best of The Liver Meeting' summary slide presentation in the alcohol-related liver disease category

AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AJG The American Journal of GASTROENTEROLOGY

References:
[1]Hassanein T et al. 2023. *Am J Gastroenterol*, DOI: 10.14309/ajg.0000000000002275; [2]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.

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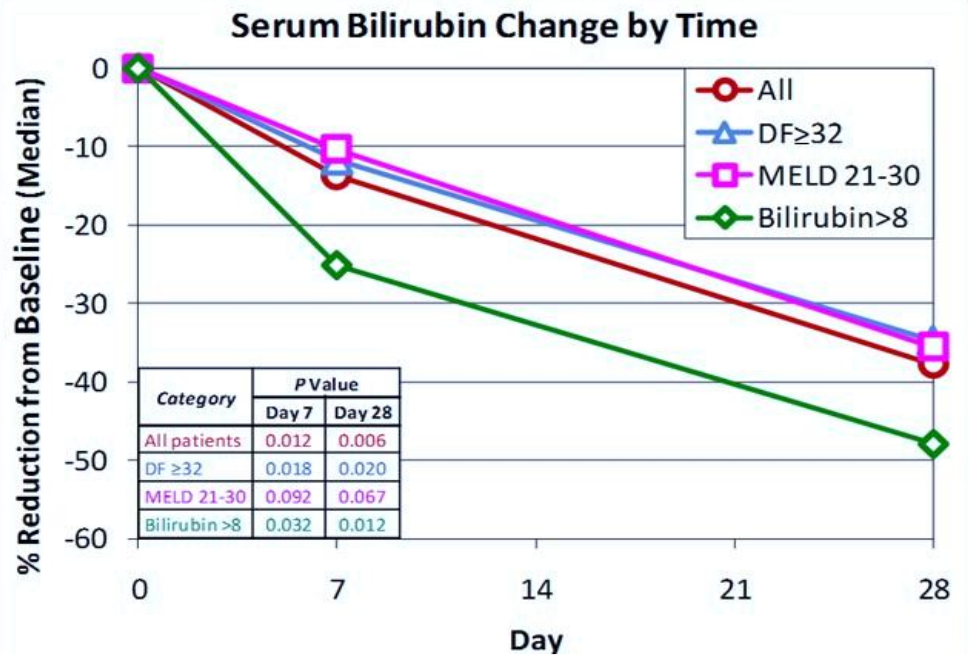
Phase 2a: Majority of Patients Discharged After One Dose

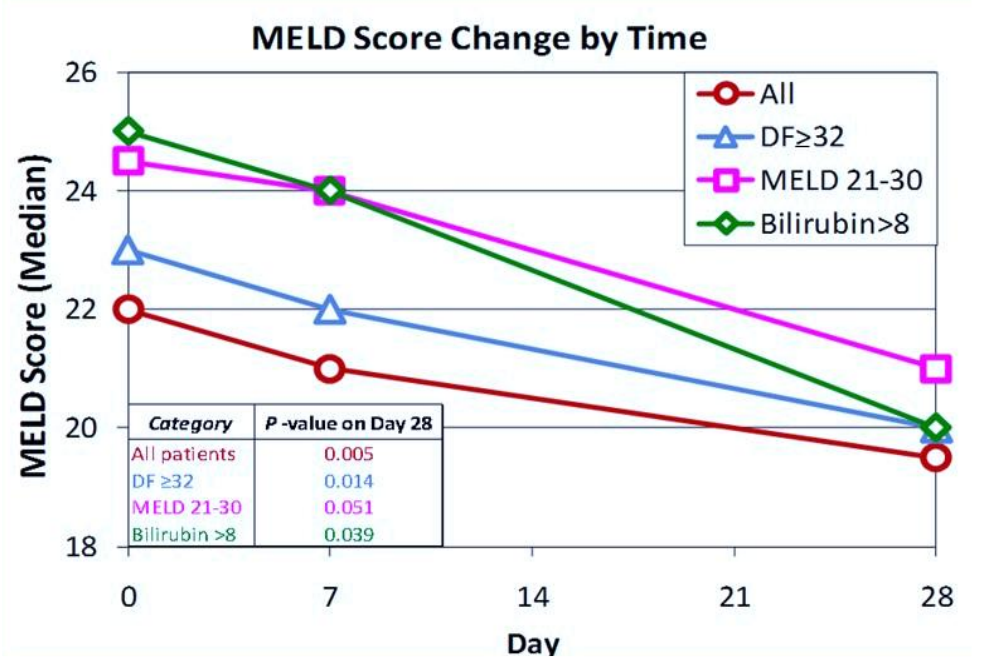
Potential Pharmacoeconomic Benefit as Measured by Time to Discharge

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

More Pronounced Effect in Patients with Higher Bilirubin





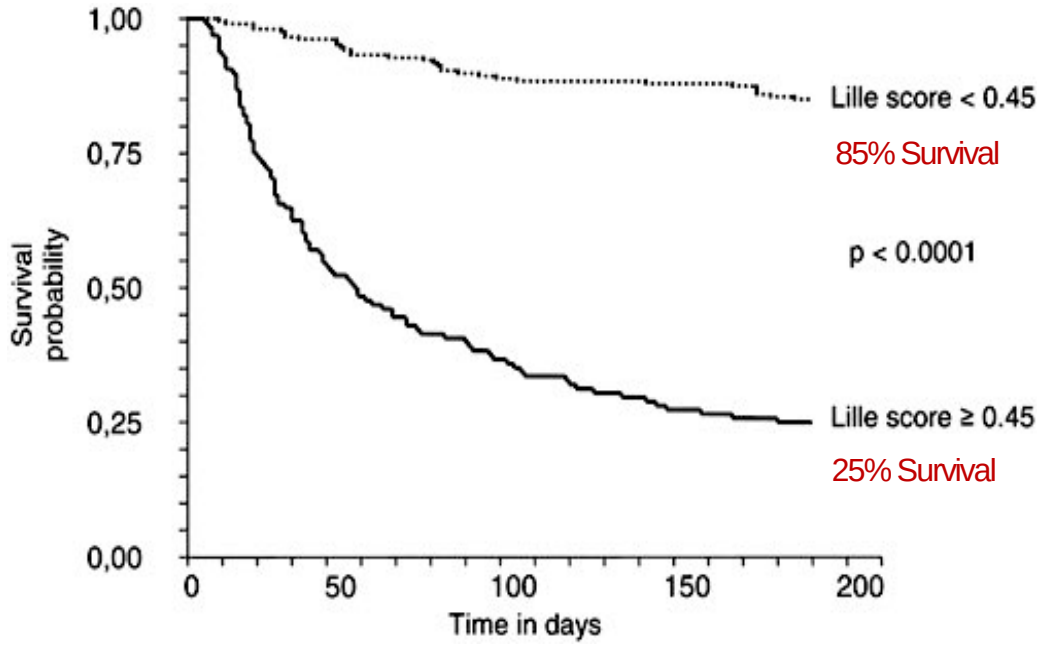
One of 19 patients did not return for the follow-up visits on Day 7 and Day 28; all data were analyzed based on those who completed visits.

Phase 2a: Lille Score Provides Strong Signal for Survival

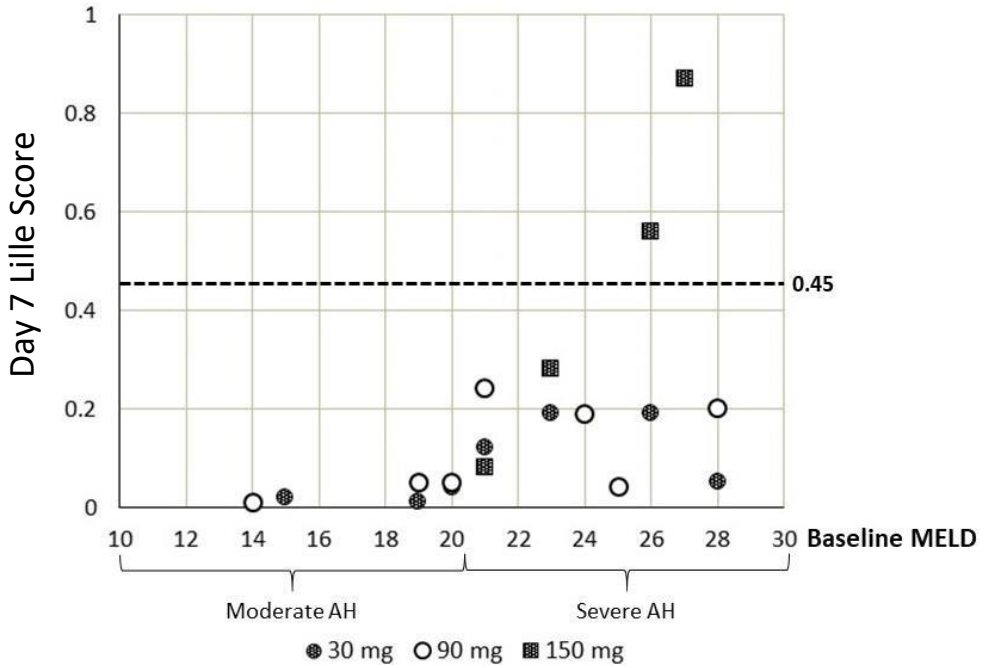
Composite score that determines response to treatment and risk of death

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. 2007. *Hepatology,* 45:1348-1354.

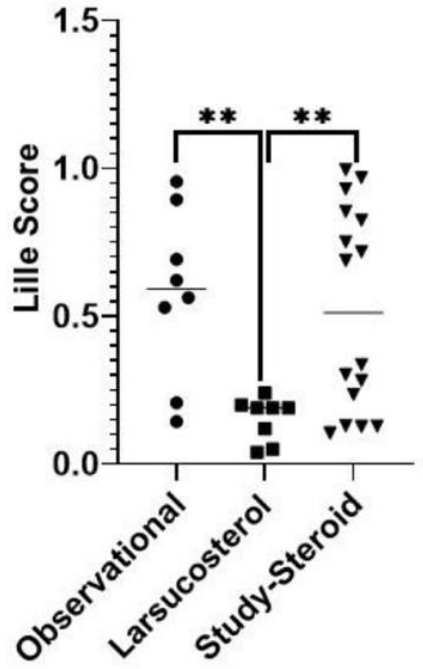
[2]n=18 ; one patient did not return for the day 7 visit.

Statistically-significant Reduction in Lille Score in Severe AH Patients

- 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
  - Comparator 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 comparator arms



** Represents p<0.01 by T-test

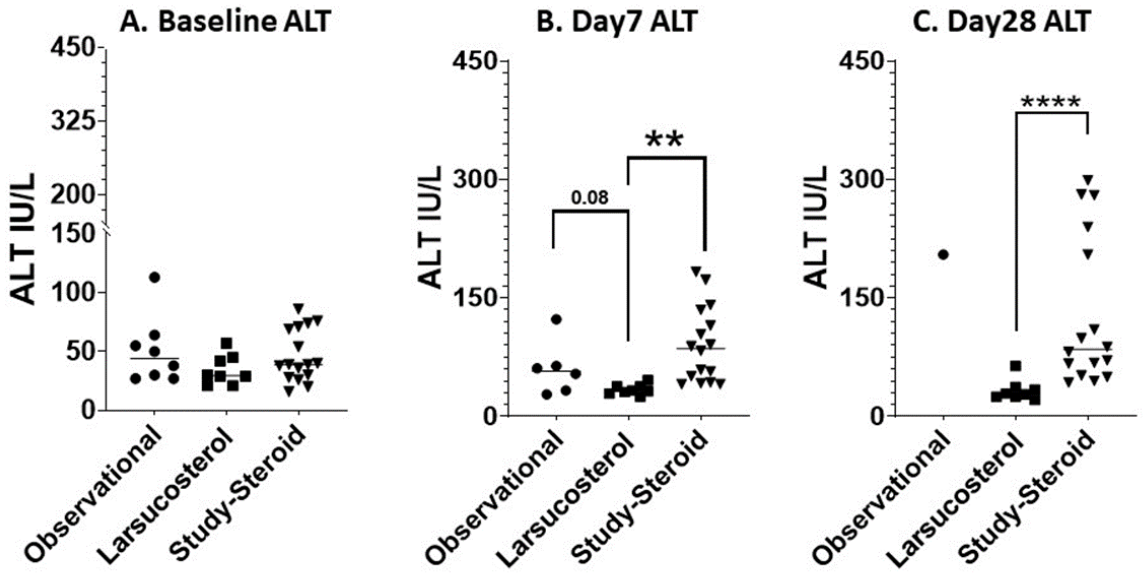
References:
Hassanein T et al. 2023. *Am J Gastroenterol*, DOI: 10.14309/ajg.0000000000002275; Non-head-to-head comparison. Results of a head-to-head comparison may differ significantly from those set forth herein.

Larsucosterol Improved Liver Enzymes in Severe AH Patients

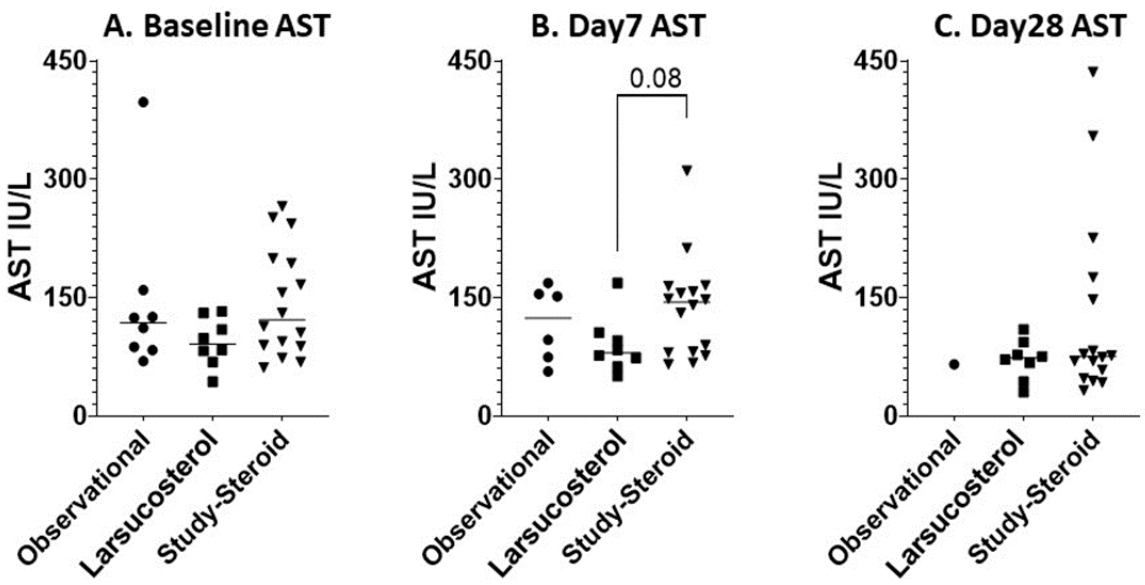
Statistically-significant reductions in ALT vs. comparison groups

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
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References:
Hassanein T et al. 2023. *Am J Gastroenterol*, DOI: 10.14309/ajg.0000000000002275; 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 larsucosterol-related adverse events
- 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 Phase 2b AHFIRM Trial

- AHFIRM: Phase 2b double-blind, placebo-controlled, multi-center, international efficacy trial in severe AH patients (n=301)
  - Completed enrollment in Q2 2023; topline data expected in Q4 2023
  - Primary endpoint is reduction in mortality or liver transplant at 90 days
- Potential NDA filing subject to achievement of primary endpoint
  - 65% of new drugs approved in the U.S. in 2020 were approved based on single pivotal trial[1]
  - Previously granted Fast Track Designation

References:
[1] Kaplan RM. Koong Aj, Irvin V. 2023. *JAMA Netw Open,* 6(8):e2327650.

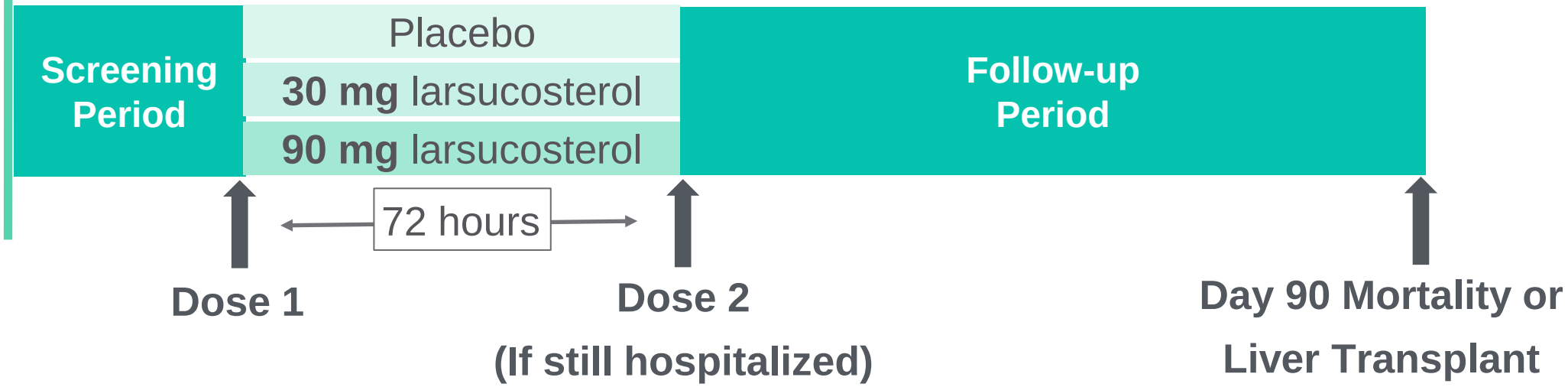
AHFIRM Trial Design Leverages Lessons from Phase 2a Trial

Aim: Demonstrate Safety and Efficacy in Severe AH

Key Inclusion Criteria

- **Severe AH patients** with MDF[1] score ≥ 32 and MELD score 21-30
- **301 subjects** randomized to 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.

Physicians are enthusiastic about larsucosterol, given:

MECHANISM OF ACTION (MOA)

High enthusiasm for novel, specific MOA which targets the underlying liver inflammation and degradation

CLINICAL EFFICACY

Reduction in 90-day mortality viewed as advance, as steroids do not show an effect on mortality past 28 days

SAFETY AND TOLERABILITY

Larsucosterol safety profile was well-received, with hundreds of patients dosed viewed as compelling for use

DOSING AND ADMINISTRATION

Physicians saw no issues with inpatient IV doses

Level of enthusiasm

Source: Physician reactions to larsucosterol blinded product profile (n=25) - ClearView Analysis 2023

Distinct value drivers across stakeholders highlight importance of tailored framing of larsucosterol value proposition

Larsucosterol has the potential to become a >$1B/yr drug in the U.S. for the AH indication alone

Reduction in Mortality

Physicians prioritize **mortality** as the **most important endpoint**, and nearly all found a potentially 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

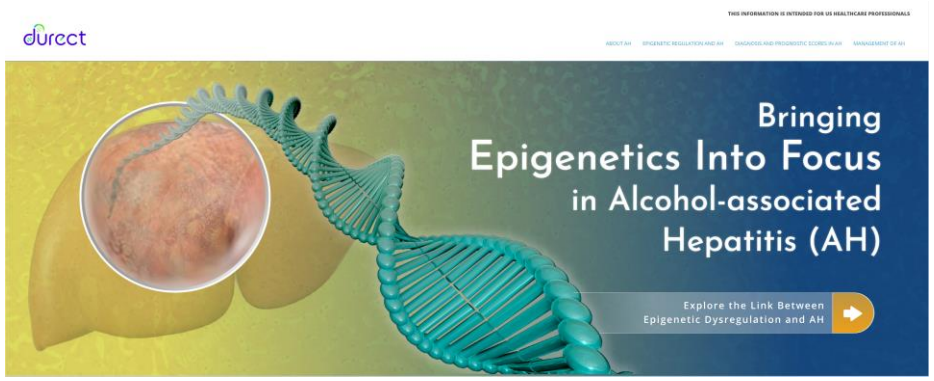
Hospital economics and payer stakeholders may use **reduction in 30-day readmissions** to assess impact on per-patient cost burden, while **reduction in AH liver transplants** supports cost-benefit to the overall healthcare system

Source: Stakeholder Interviews; ClearView Analysis 2023.

Shaping the AH Market

Educate on the impact of epigenetic dysregulation and larsucosterol's potential value

AH AND EPIGENETICS WEBSITE LAUNCH



- **GOAL**: Raise awareness of AH unmet needs and increase understanding of epigenetic regulation as a potential link to AH
- **TARGET AUDIENCE**: US HCPs (primarily: hepatologists, GIs; secondarily: ER physicians, hospitalists, and advance practice providers**.**
- **Domain name:** https://www.exploreAHepigenetics.com/

KOL ENGAGEMENT

Growing medical team engaging with KOLs at key conferences and through long-term physician personal relationships

Financial Overview and Summary

Financial Overview

Nasdaq	DRRX
Market Cap	$84.5 MM[1]
Shares O/S	27.6 MM[2]
Cash & Cash Equivalents	$48.7 MM[3]
Debt	$20.7 MM[4]
Federal NOLs	$317.7 MM[5]

Cupertino, CA headquarters

[1] As of August 31, 2023
[2] As of August 7, 2023
[3] As of June 30, 2023. Pro forma for receipt of $13.8M of net proceeds from July 2023 registered direct offering.
[4] As of June 30, 2023
[5] As of December 31, 2022

Larsucosterol – Positioned for Success in AH

Robust Phase 2b Trial w/ Registration Potential

- Global, randomized, double-blind, placebo-controlled efficacy trial
- 301 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
  - 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 discontinuations
- More than 500 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

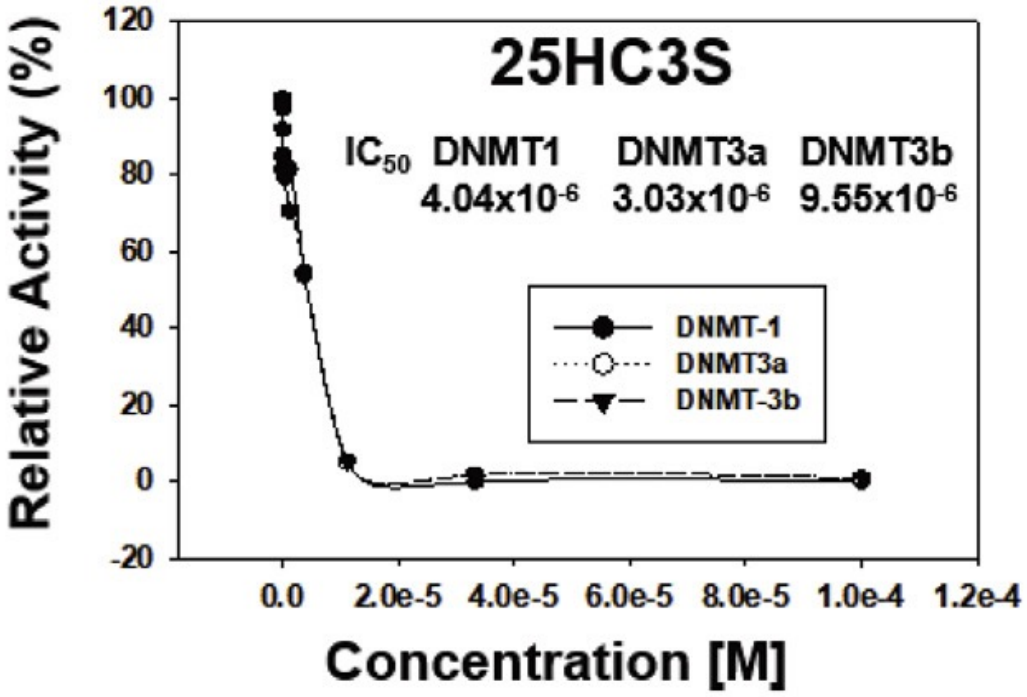
Topline data from AHFIRM Phase 2b trial expected in Q4 2023

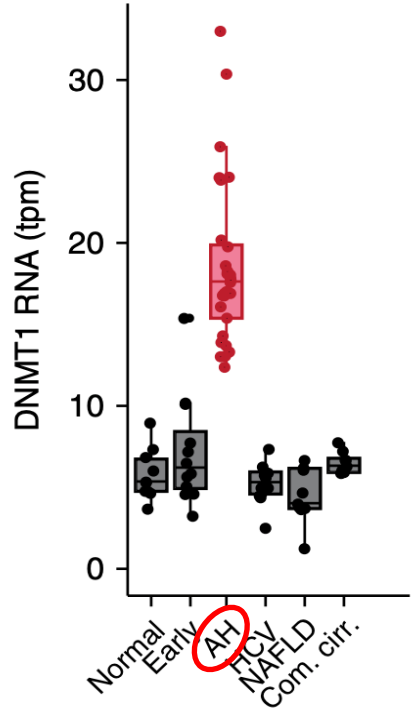
References:
[1] Hughes E, Hopkins LJ, Parker R. 2018. *PLOS ONE,* 13(2): e0192393

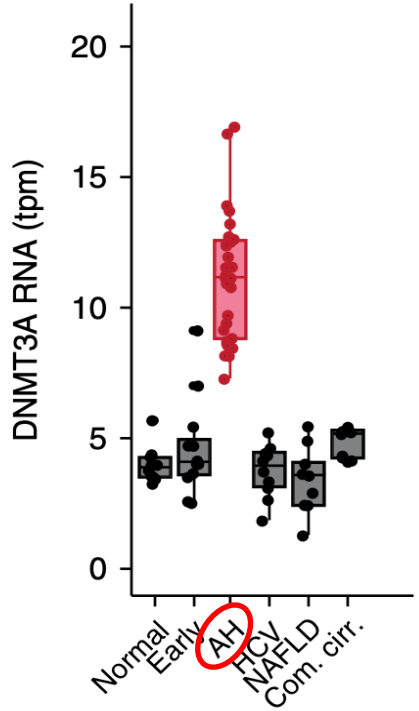
Appendix

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

Larsucosterol AH Launch; Strategic Imperatives (SI)

SI1	SI2	SI3	SI4	SI5
Shape the AH Market	Build the Brand	Define Patient Access	Drive Rapid Adoption	Maximize Long-Term Value

Large Alcohol Use Outside of the U.S. Calls for New Treatments

GERMANY

"Harmful alcohol consumption in Germany is a serious public health problem: About 7.7 million adults in Germany can be classified as risky alcohol consumers, about 74,000 deaths per year are related to alcohol consumption, and about 1.8 million adults in Germany (18–64 years) are classified as alcohol dependent." – Hoffmann et al. 2019. *BMC Fam Pract,* 20, 115.

FRANCE

"Almost 10% of French adults drink daily, 5% report binge drinking at least once a week, and 3.8% (approximately 2 million people) report regular alcohol intoxication" - Costa et al. 2022. *BMC Public Health*, 20: 358.

ENGLAND

Almost 980,000 admissions to hospital in 2019/2020 were linked to alcohol-liver disease; this represents 5.7% of all hospital admissions in England - NHS Digital 'Statistics on Alcohol, England 2021' Publication date: 27.01.22

We estimate that the NHS in England spends a total of around £45 million per year on caring for patients with AH." – Turner et al. EASL 2023

SPAIN

"Admissions due to AH have increased recently, potentially related to COVID. Access to liver transplant is very limited (<2%), mainly due to contraindications, social, addiction-related, or medical comorbidities."

- Garcia et al. EASL 2023

ASIA

"The overall prevalence of ALD is 4.8%; ALD prevalence in Asia increased over the past two decades, calling for the implementation of specific actions to invert this trend." – Sun et al. 2022. *Liver International,* 42: 1926-1929.

AUSTRALIA

"Alcohol use contributed to 4.5% of the total burden of disease in Australia in 2018." – Australian Institute of Health and Welfare: https://www.aihw.gov.au/reports/alcohol/alcohol-tobacco-other-drugs-australia/contents/impacts/health-impacts - Accessed June 2023.