Unlocking Epigenetic Therapeutics to Revolutionize Medicine

January 2024

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Company Highlights

- Larsucosterol: Potential first-in-class treatment for AH
- Phase 2b showed compelling trend in mortality reduction
- Strong rationale for advancing to registrational Phase 3
- Well tolerated with numerical reduction in TEAEs
- Significant unmet need in AH – no approved therapy

AH = Alcohol-associated Hepatitis
TEAE = Treatment-Emergent Adverse Events

Pipeline

Program	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Marketed	Status
Epigenetic Modulator Program							
Larsucosterol	Alcohol-Associated Hepatitis (AH) (intravenous administration)						Completed Phase 2b AHFIRM trial; FDA meeting planned for Q1 2024
NCEs[1]	Hematology/Oncology (small molecules)						Preclinical studies ongoing
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

Key Takeaways from Phase 2b AHFIRM Trial

- Pronounced reduction in mortality at 90 days in U.S. population
  - 57% reduction with 30 mg dose (p= 0.014)
  - 58% reduction with 90 mg dose (p= 0.008)
- Compelling trend in the key secondary endpoint of mortality reduction at 90 days
  - 41% reduction with 30 mg dose (p= 0.070)
  - 35% reduction with 90 mg dose (p= 0.126)
- Numerical improvement in primary endpoint of mortality or transplant at 90 days did not achieve statistical significance
- Both doses of larsucosterol were well-tolerated

Strong rationale for advancing larsucosterol to a registrational Phase 3 trial with 90-day mortality as the primary endpoint

Larsucosterol
Potential in Alcohol-associated Hepatitis

Larsucosterol Overview

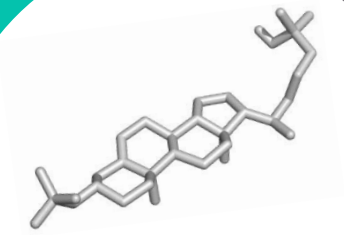
Lead Compound in DURECT's Epigenetic Modulator Program

Modulator of DNA methylation

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

Clinical Profile

- Phase 2b trial showed trend in mortality reduction
- 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] and clinical data support investigating larsucosterol for the treatment of multiple acute organ injuries and chronic liver diseases

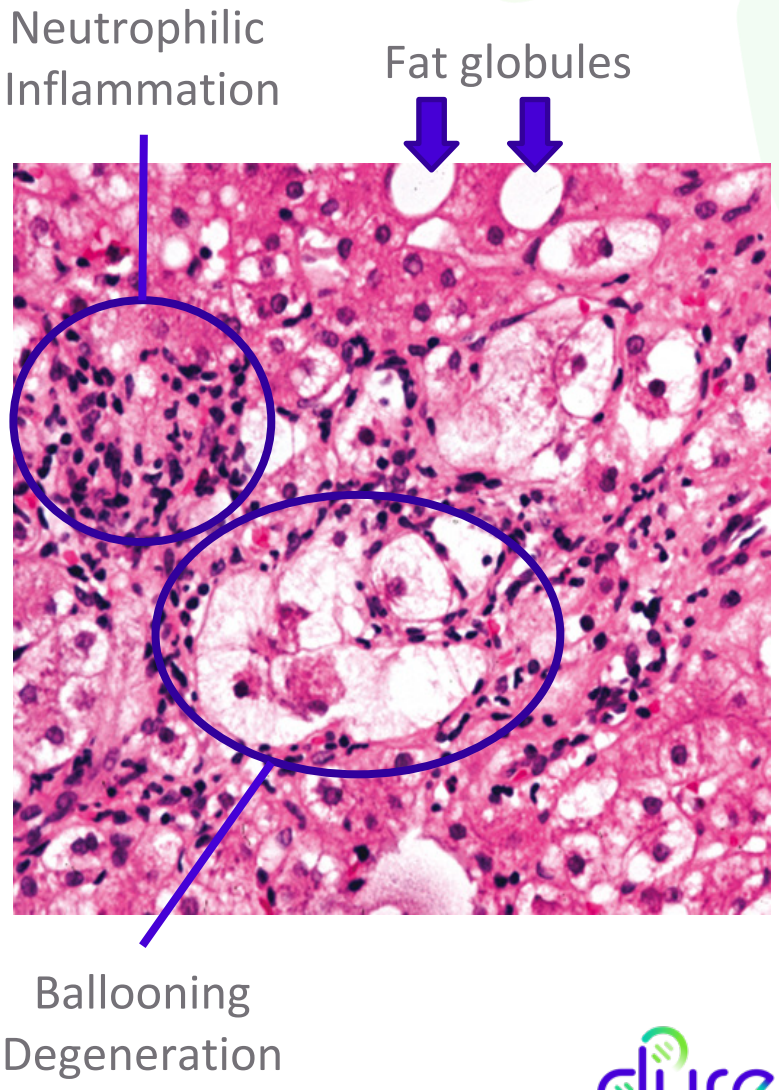
[1]MOA = Mechanism of Action

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

Current Treatments for AH are Inadequate with No Approved Therapies

Corticosteroids

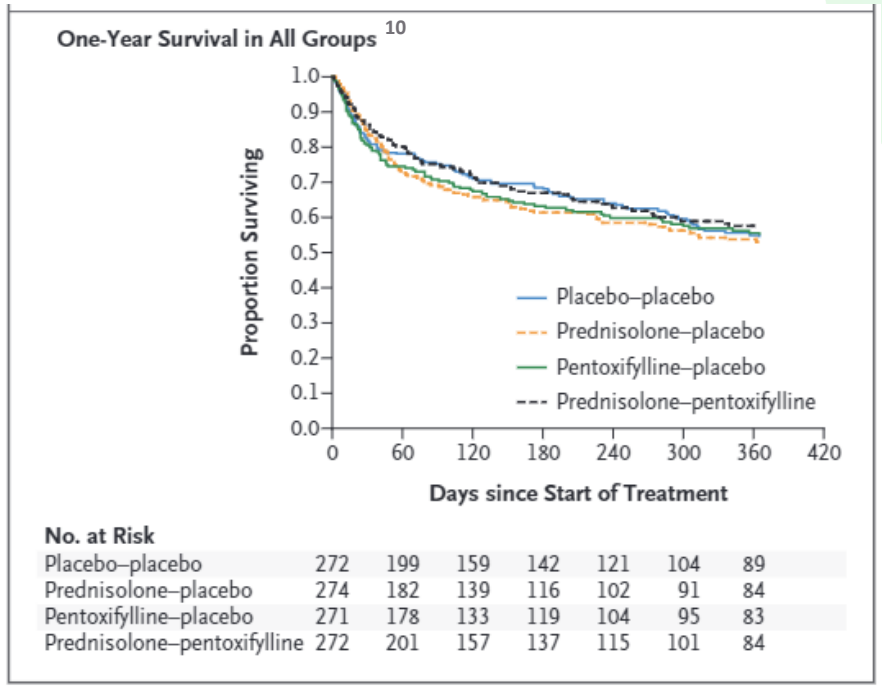
- Used as first-line treatment despite limited and inconsistent survival benefits and widely acknowledged contraindications[1,2,3]
- Only 25% to 45% of patients are eligible for corticosteroids[4,5,6]

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

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.

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

Phase 2b AHFIRM Trial Design

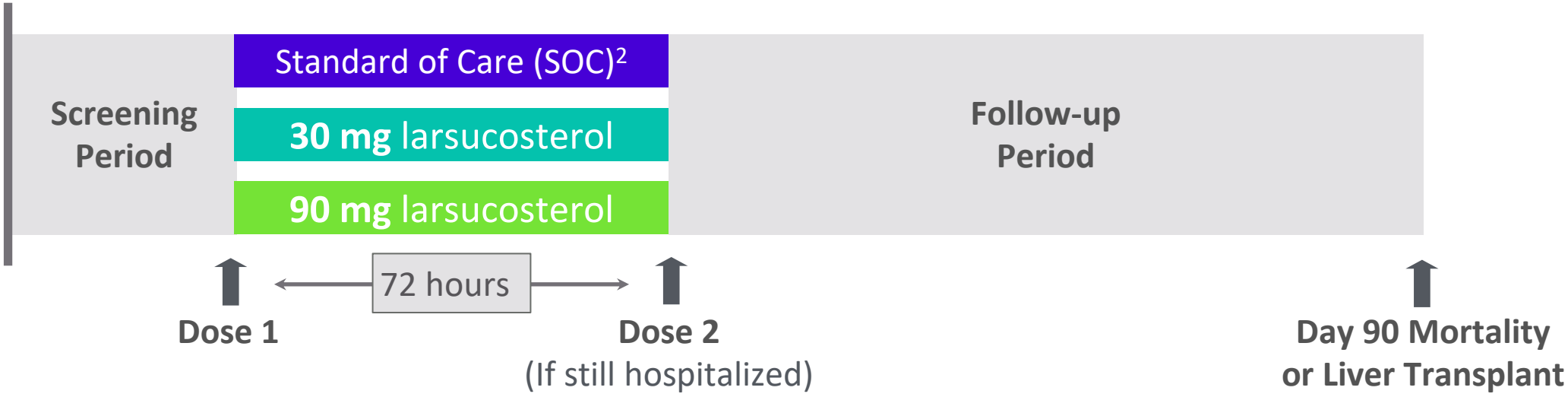
Trial Overview

Severe AH patients with MDF[1] score ≥ 32 and MELD[1] score 21-30

307 subjects randomized to three groups in a 1:1:1 ratio

Global trial conducted in U.S., E.U., Australia and U.K.

Study Design



[1] Maddrey's Discriminant Function (MDF); Model for End-Stage Liver Disease (MELD)

[2] All patients received supportive care, which for standard of care (SOC) patients included methylprednisolone capsules at the investigators' discretion. In order to maintain blinding, patients in the two larsucosterol arms received matching placebo capsules if the investigator prescribed steroids.

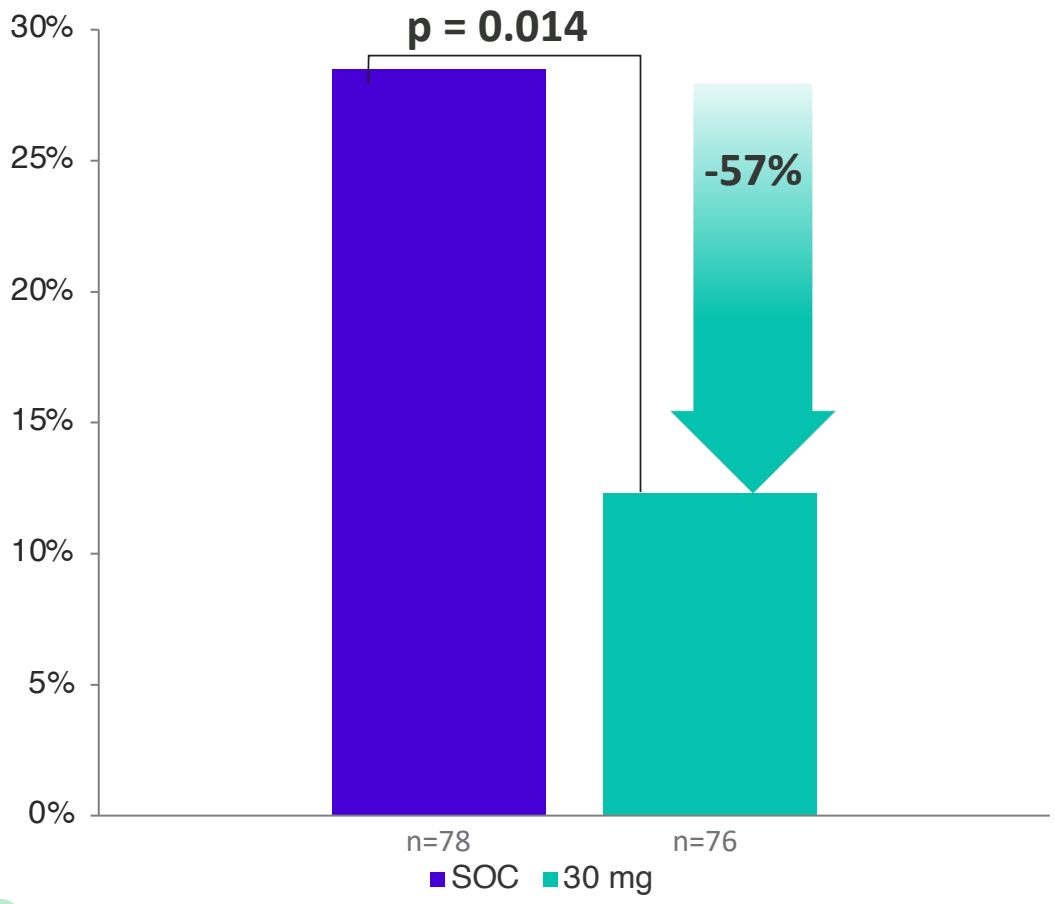
Median Baseline Characteristics and Trial Outcome by Arm

	SOC	Larsucosterol 30 mg	Larsucosterol 90 mg
Number of patients randomized	103	102	102
Number of patients with 90-day outcome data	102	99	101
MELD[1]	25.0	24.0	25.0
MDF	61.50	57.20	63.00
Age	47.0	44.0	43.0
Deaths (%)	**25 (24.5%)**	**15 (15.2%)**	**17 (16.8%)**
Transplants (%)	**4 (3.9%)**	**6 (6.1%)**	**9 (8.9%)**
Alive & Transplant-free (%)	**73 (71.6%)**	**78 (78.8%)**	**75 (74.3%)**
All Alive (%)	**77 (75.5%)**	**84 (84.8%)**	**84 (83.2%)**

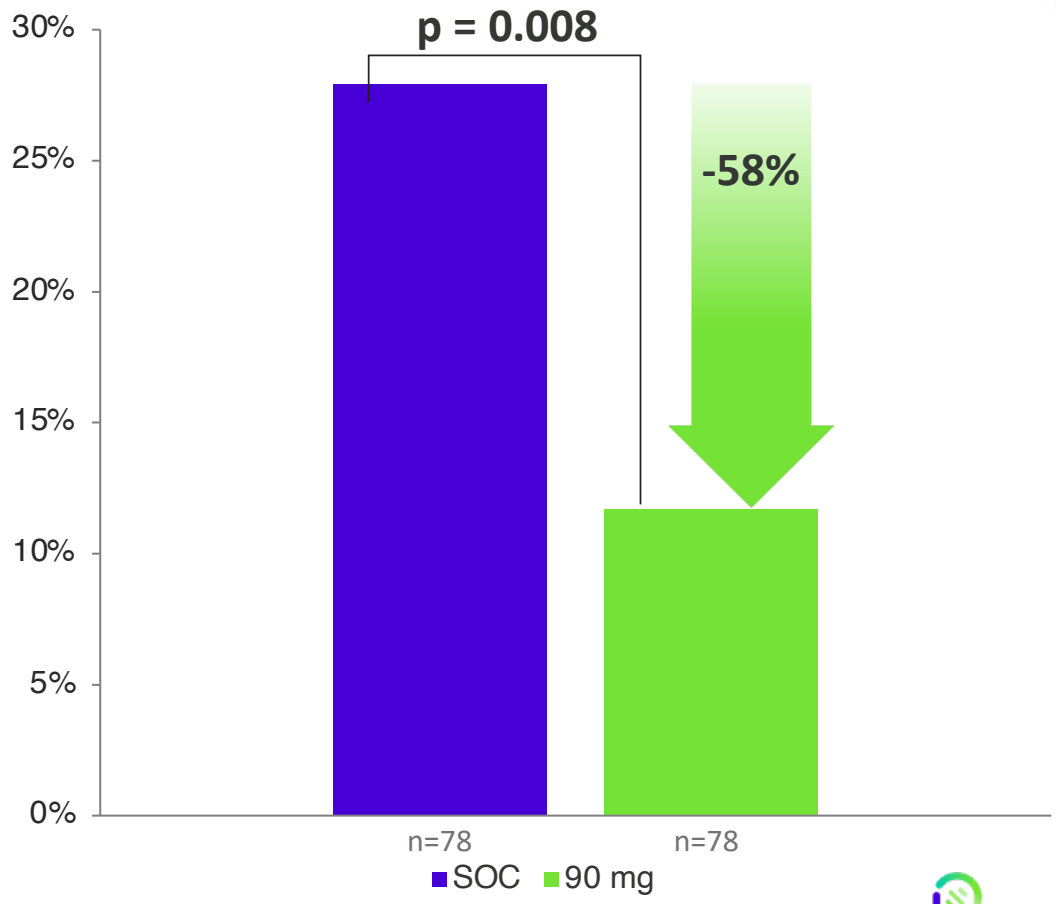
[1] Based on central lab MELD score

Pronounced Reduction in Mortality Observed in U.S.

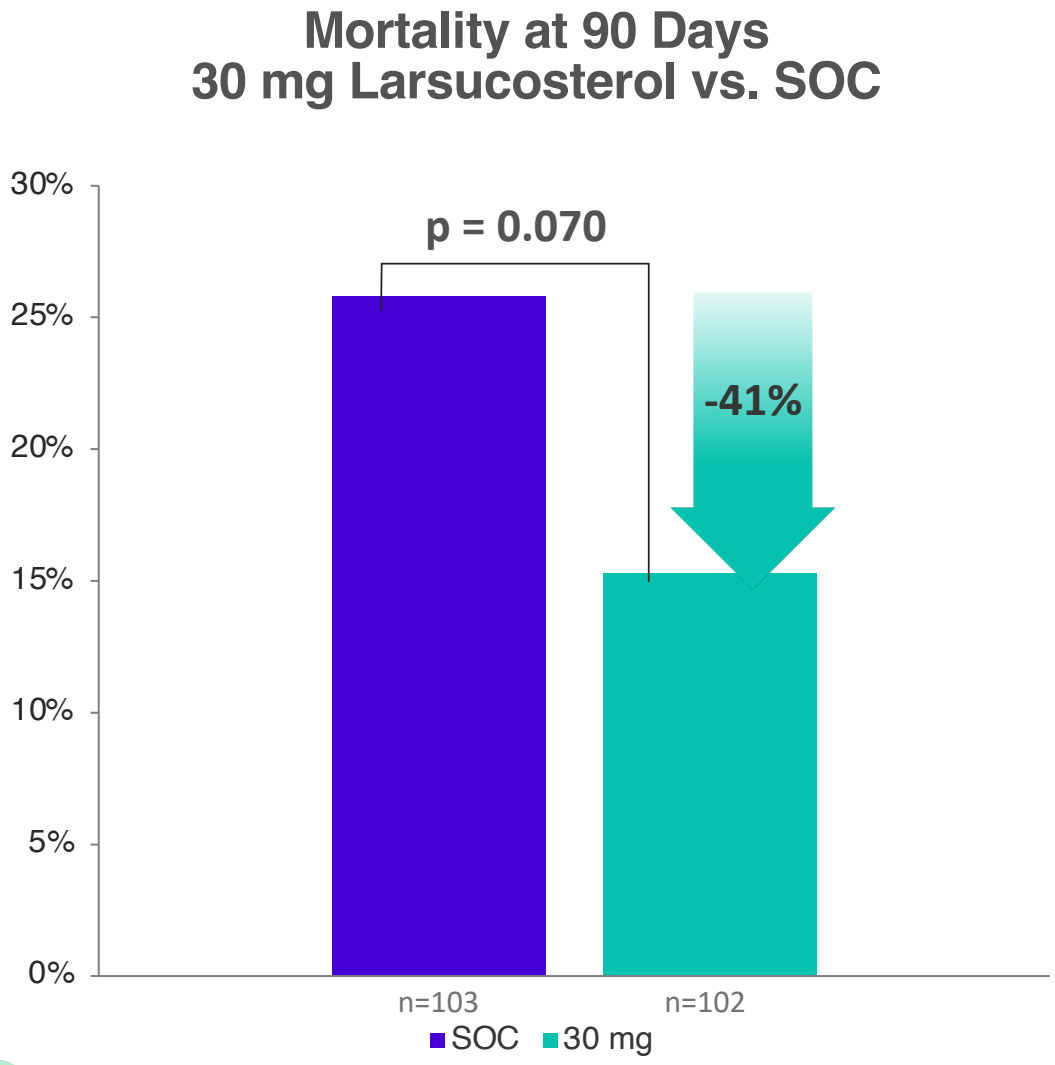
Mortality at 90 Days – U.S. Patients 30 mg Larsucosterol vs. SOC

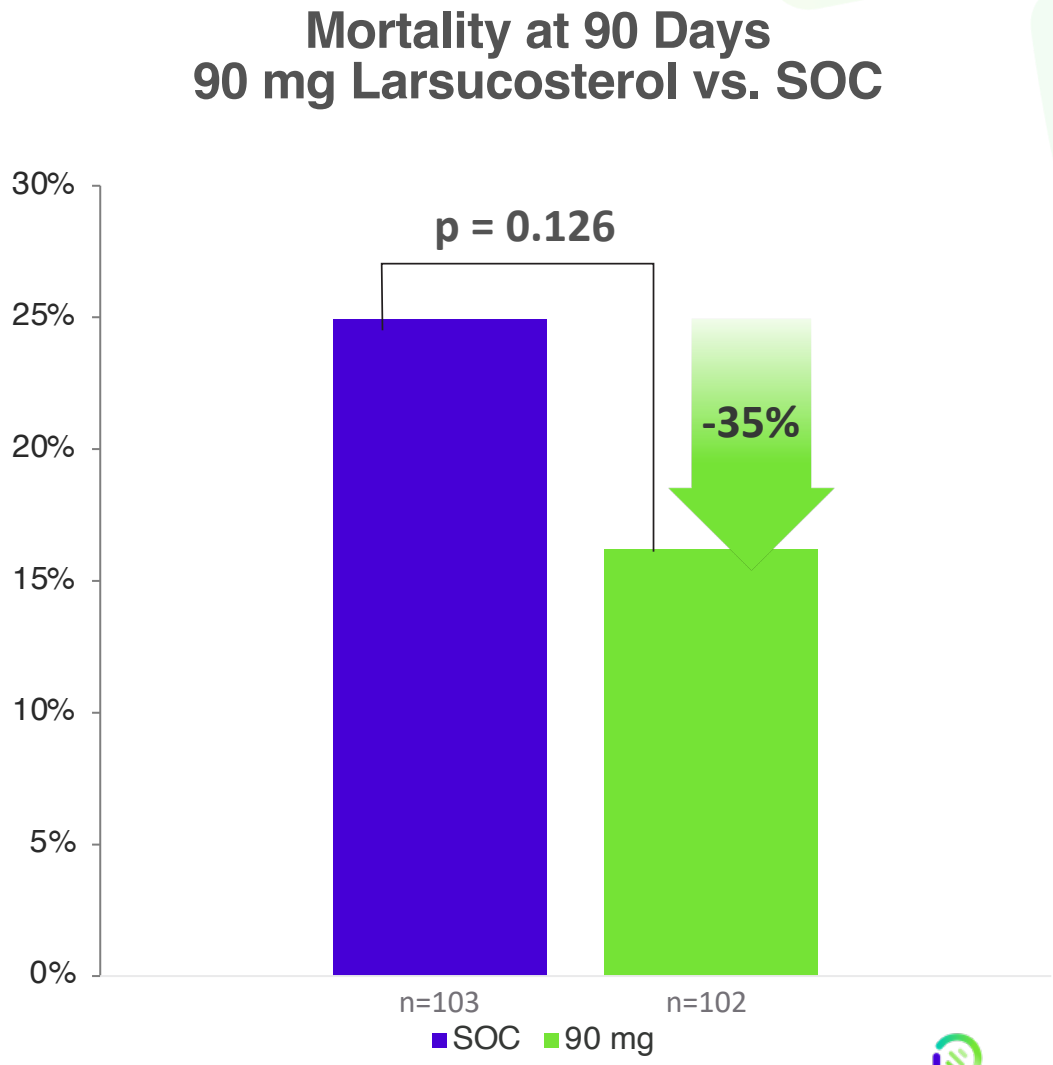


Mortality at 90 Days – U.S. Patients 90 mg Larsucosterol vs. SOC



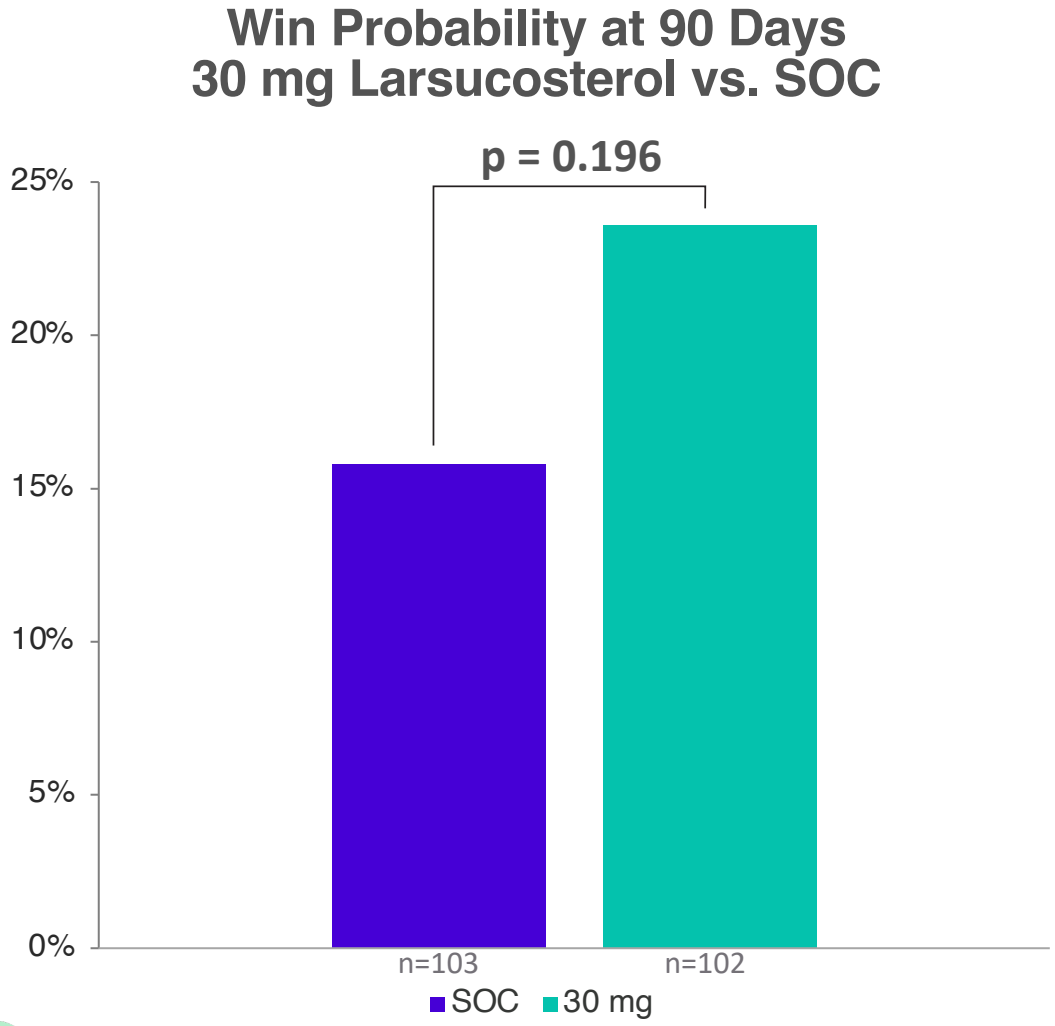
Clinically Meaningful Trend Toward Reduced Mortality (Global Data)

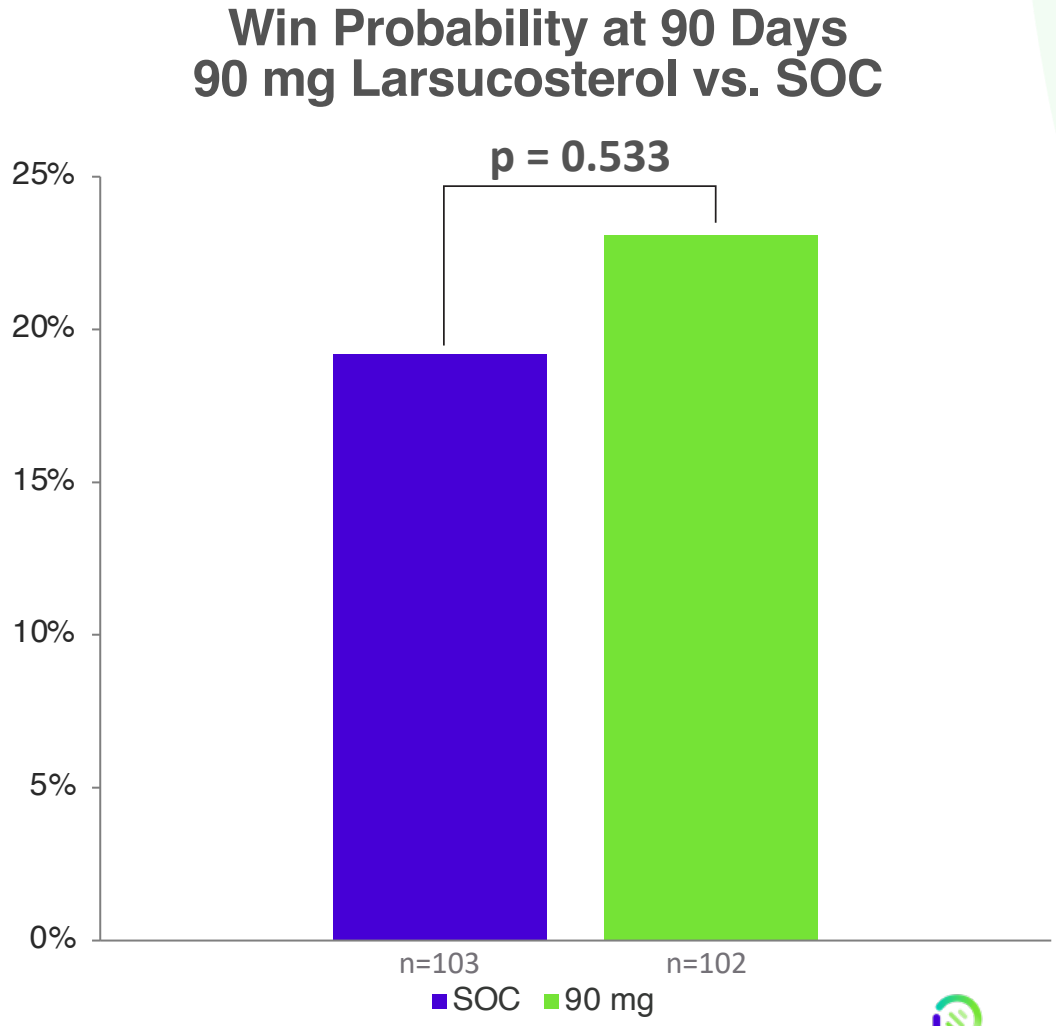




Numerical Improvement in Primary Endpoint

Did not achieve statistical significance

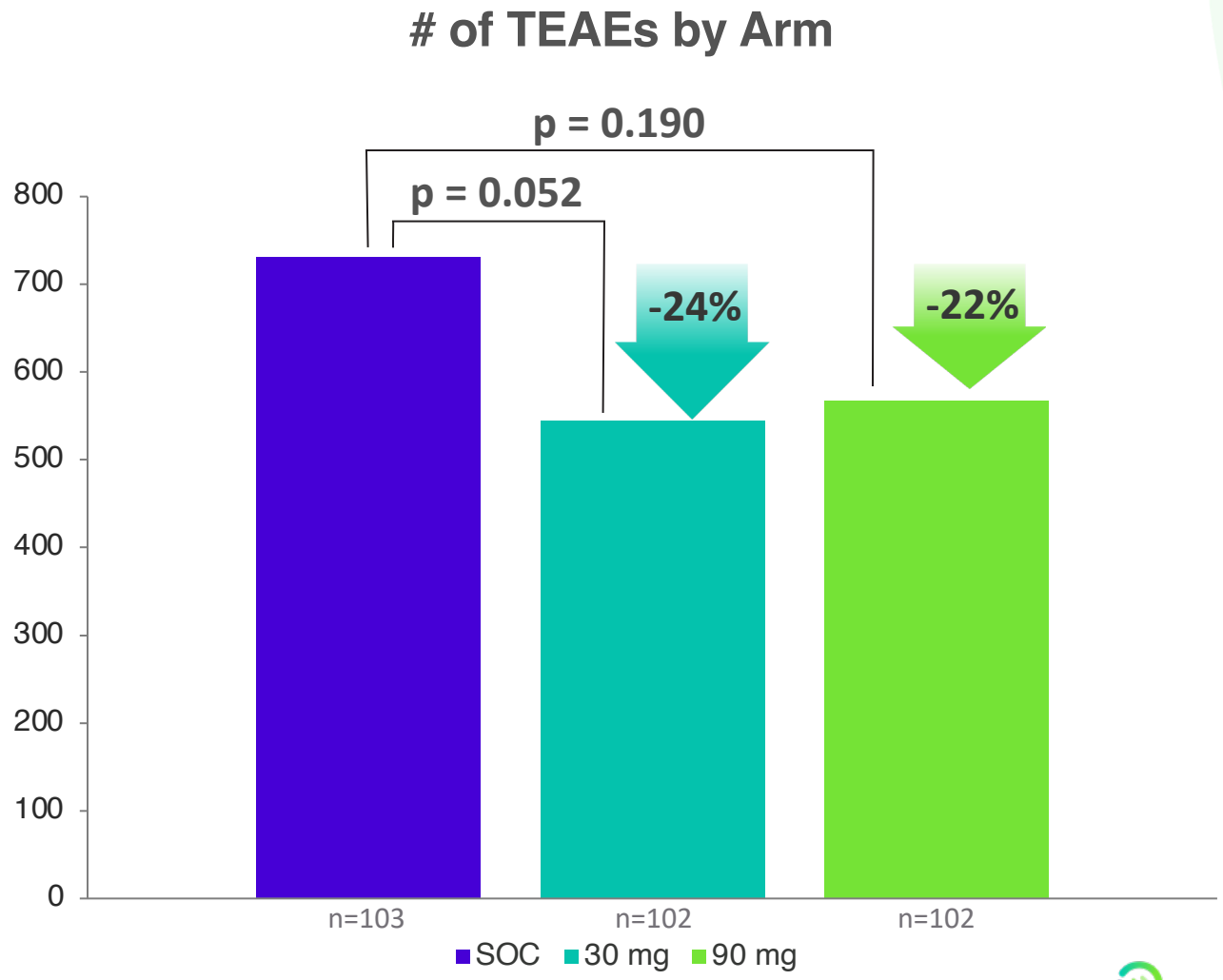




Primary endpoint was analyzed using a hierarchical assessment of patient outcomes to calculate a win probability for each of the 30 mg and 90 mg doses of larsucosterol compared with standard of care. Win probability was calculated on the hierarchy of alive and transplant-free being superior to transplant and death, and transplant being superior to death. Comparisons of the same outcome were included in the denominator as ties.

Larsucosterol Was Well-Tolerated

- Numerically fewer TEAEs in both 30 mg and 90 mg arms compared with SOC
- No meaningful difference in serious AEs and none attributed to larsucosterol



TEAEs = Treatment Emergent Adverse Events

Conclusions and Next Steps for Larsucosterol in AH

- Compelling efficacy outcome in favor of larsucosterol in key secondary endpoint of reduced mortality at 90 days; 41% for the 30 mg dose (p=0.070) and 35% for the 90 mg dose (p=0.126) compared with SOC
- In U.S. patients, larsucosterol treatment reduced mortality at 90 days by 57% for the 30 mg dose (p=0.014) and by 58% for the 90 mg dose (p=0.008) compared with SOC
- Larsucosterol was well-tolerated; both dose groups had numerically fewer adverse events than standard of care

NEXT STEPS

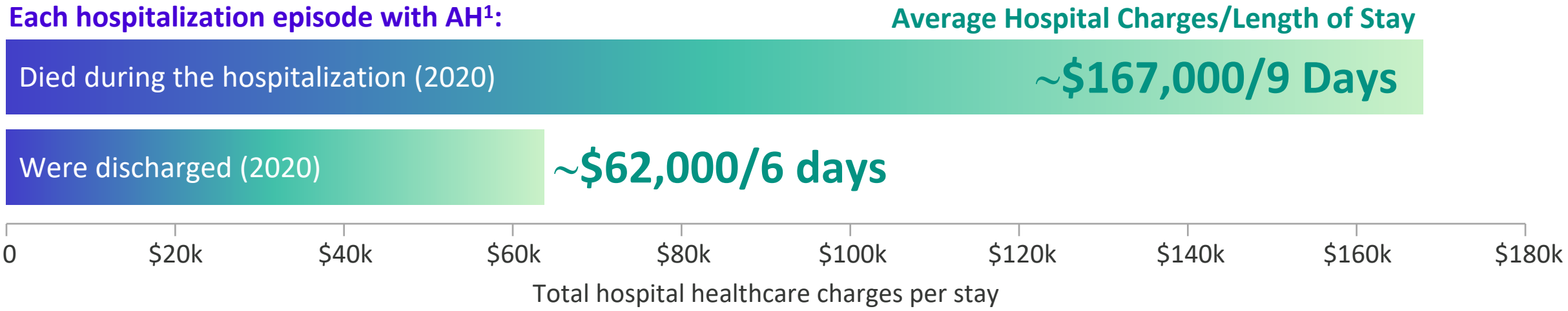
- Discuss AHFIRM data with FDA in first quarter of 2024
- Strong rationale for advancing larsucosterol to a registrational Phase 3 trial with 90-day mortality as the primary endpoint
- AHFIRM data to be presented at upcoming scientific meeting

Larsucosterol

Commercial Opportunity in AH

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 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
- 86% of hospitalized AH patients are insured[3]



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.

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, if approved

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.

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 an advancement, 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

Financial Overview and Summary

Financial Overview

Nasdaq	DRRX
Market Cap	$16.6 MM[1]
Shares O/S	29.8 MM[2]
Cash & Cash Equivalents	$39.1 MM[3]
Debt	$18.7 MM[3]
Federal NOLs	$317.7 MM[4]

Cupertino, CA headquarters

[1] As of January 5, 2024
[2] As of November 13, 2023
[3] As of September 30, 2023
[4] As of December 31, 2022

Larsucosterol – Positioned for Success in AH

AHFIRM Mortality Results Support Advancement to Phase 3

- Global, randomized, double-blind, placebo-controlled efficacy trial
- Compelling outcome on key secondary endpoint of mortality reduction at 90 days
- Pronounced reduction in mortality at 90 days in U.S. population
- Fast Track Designation

Clinical Safety

- Well tolerated
- No discontinuations
- More than 500 patients dosed in multiple Phase 1 and 2 trials
- AHFIRM results showed numerically fewer TEAEs in both 30 mg and 90 mg arms compared with SOC
- No serious AEs in AHFIRM attributed to larsucosterol

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

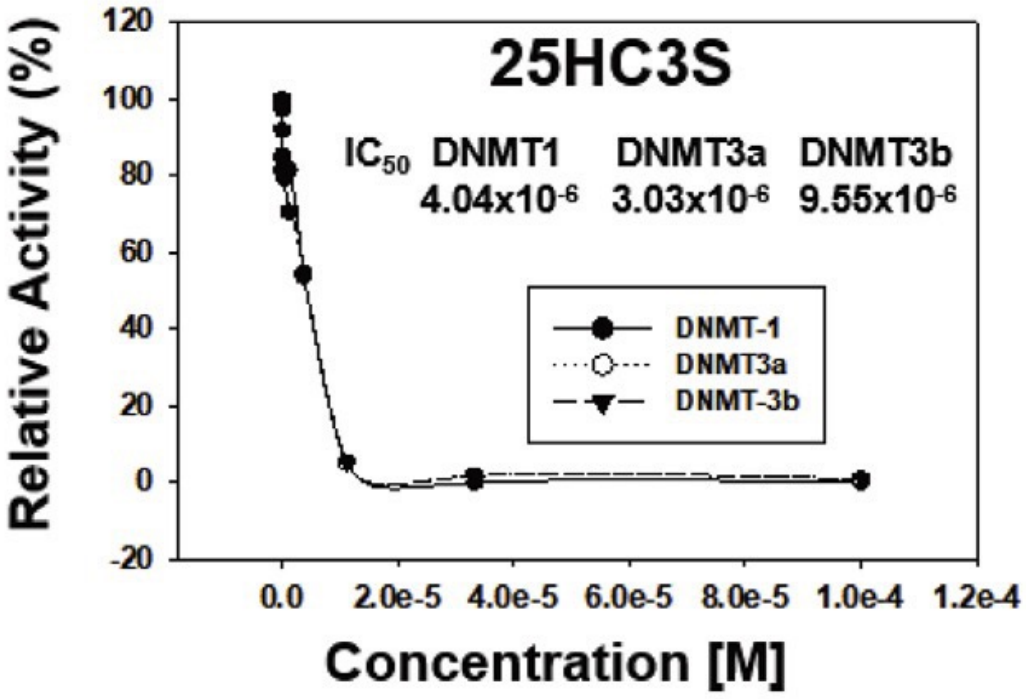
FDA meeting to discuss Phase 3 trial and next steps planned for Q1 2024

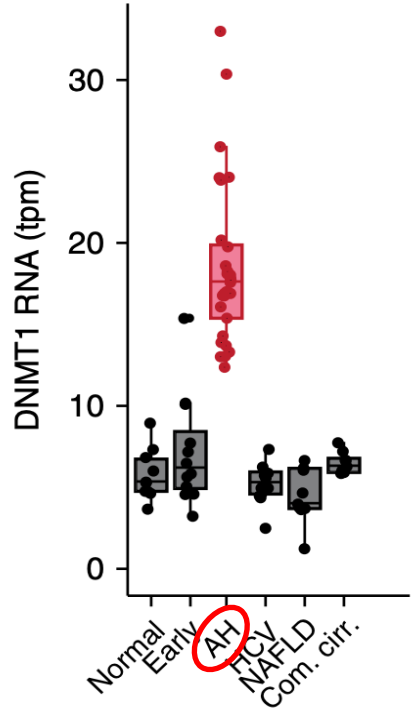
References:
[1] Hughes E, Hopkins LJ, Parker R. 2018. *PLOS ONE,* 13(2): e0192393

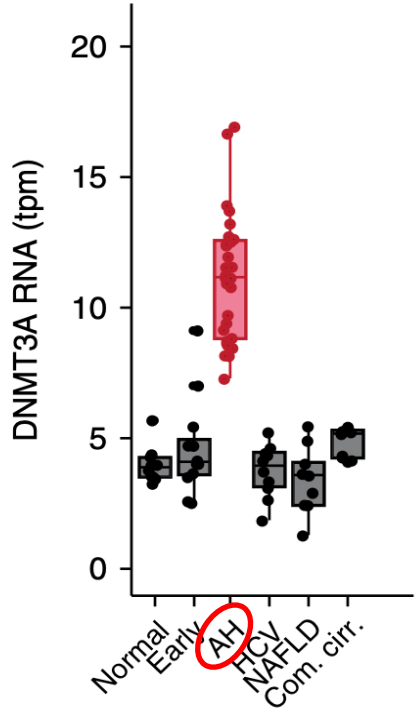
Appendix

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