Unlocking Epigenetic Therapeutics to Revolutionize Medicine

February 2024

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Company Highlights

Larsucosterol: Phase 3-ready, potential life-saving treatment for alcohol-associated hepatitis (AH)

- **Compelling Phase 2b AHFIRM trial results (November 2023)**
  - Reduction in mortality in 307-patient placebo-controlled trial
  - Well tolerated with no drug-related toxicities
- **Novel mechanism of action in hepatic disease**
  - Modulator of DNA methyltransferases (DNMTs)
- **Strong rationale for advancing to registrational Phase 3 trial**
  - FDA feedback expected in Q1 2024
  - Received Fast Track Designation
- **Significant unmet need: >$1 billion market opportunity in U.S.**
  - 90-day mortality rate of ~30%
  - No approved therapy for AH

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 feedback expected in 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

AH Represents a Large Market with Substantial Unmet Need

~158,000
Hospitalizations annually in U.S.[1]

~$10 billion
Annual direct hospital charges in U.S.[1]

0
Approved therapies for treatment of AH

>$1 billion annual peak sales potential in the U.S. for AH

References:
[1] Marlowe N, Lam D, Liangpunsakul S. 2023. *Alcohol Clin Exp Res,* 00:1-7

Key Takeaways from Phase 2b AHFIRM Trial

Pronounced reduction in mortality at 90 days with **both doses** of larsucosterol compared with SOC[1]

30 mg dose

U.S.: ↓57% (p=0.014)

Global: ↓41% (p=0.068)

90 mg dose

U.S.: ↓58% (p=0.008)

Global: ↓35% (p=0.124)

Both doses of larsucosterol were well-tolerated

Fewer TEAEs[2]

30 mg: ↓24%

90 mg: ↓22%

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

[1]Numerical improvement in primary endpoint of mortality or transplant at 90 days did not achieve statistical significance.
[2]Numerical reduction in total treatment-emergent adverse events (TEAEs) compared with standard of care (SOC).

Larsucosterol
Potential in Alcohol-associated Hepatitis

Larsucosterol: Our Lead Epigenetic Modulator Program

Phase 3-Ready in AH with Novel Mechanism of Action (MOA)

Demonstrated Clinical Efficacy and Safety

- Phase 2b AHFIRM trial showed signal in reducing mortality in AH patients
- Well tolerated at all doses
- >500 subjects dosed in multiple completed Phase 1 and 2 studies

Potent DNMT Modulator

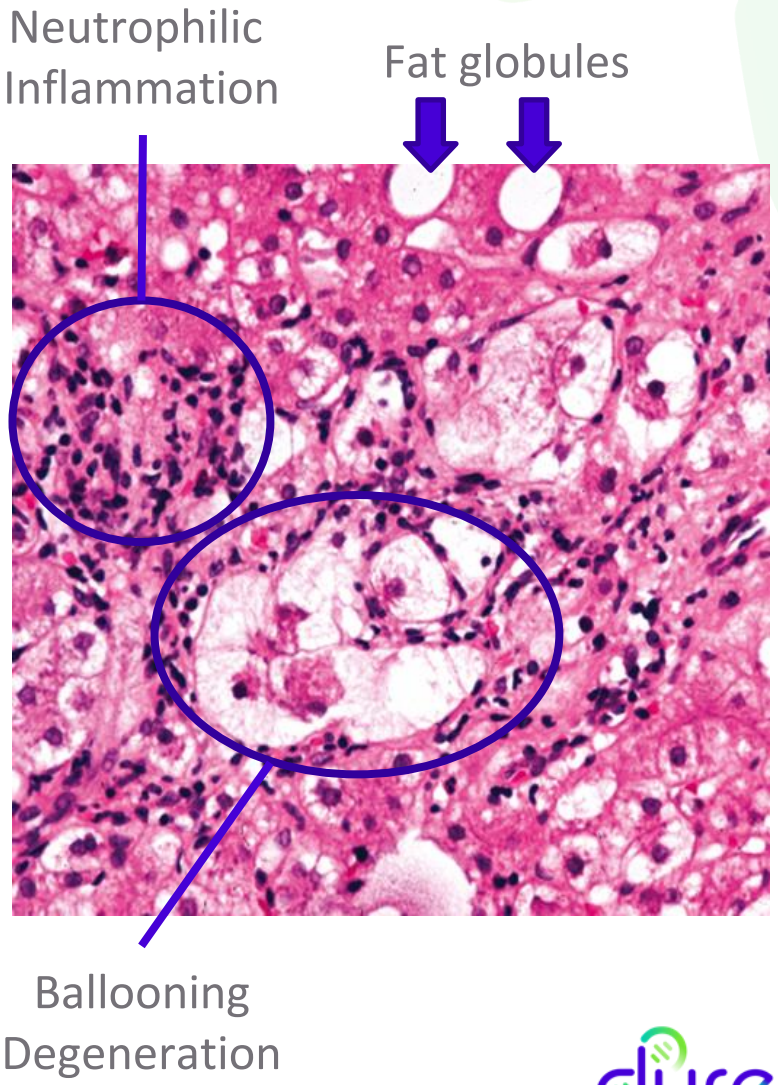
- Inhibition of DNMT-1, 3a & 3b aligns with AH biology
- Supports investigating larsucosterol for the treatment of multiple acute organ injuries and chronic liver diseases

Positive Effects on Key Cellular Functions

- Stabilizes mitochondria
- Reduces lipotoxicity
- Regulates inflammatory or stress response
- Promotes cell survival

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
- Excessive drinking can cause significant – but reversible – liver impairment leading to hepatocyte death
- Characterized by jaundice and severe multi-system inflammation – indicative of SIRS (Systemic Inflammatory Response Syndrome)[1]
- SIRS may progress to multi-organ failure and ultimately death



90-day mortality rate is ~30%[2]

Reference:
[1] Crabb DW, Im GY, Szabo G, Mellinger JL, Lucey MR. 2020. Hepatology 71: (1) 306-333
[2] Hughes E, Hopkins LJ, Parker R. 2018. *PLOS ONE,* 13(2): e0192393

Current Treatments for AH are Inadequate with No Approved Therapies

Corticosteroids

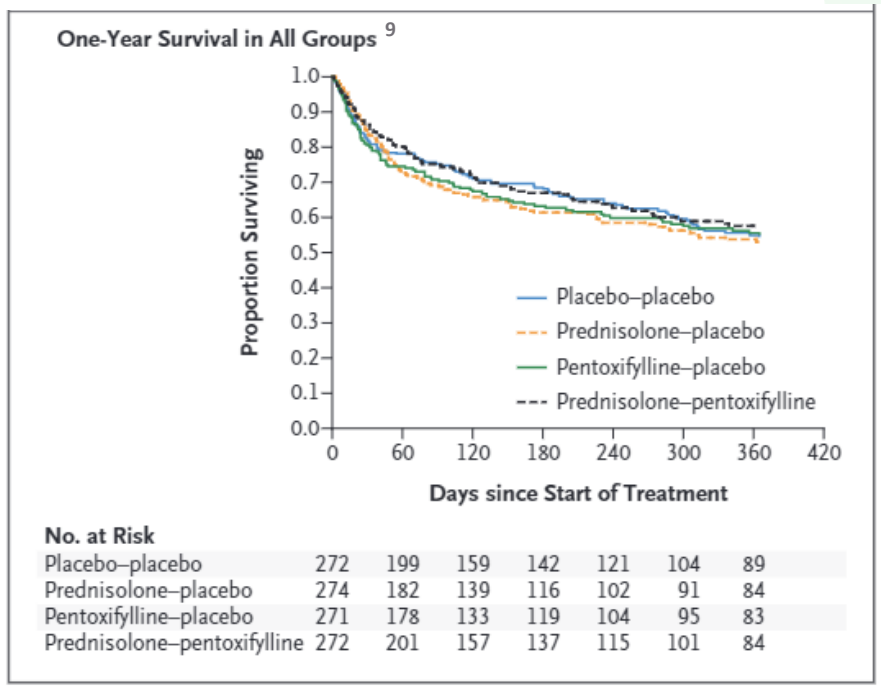
- Used as first-line treatment despite no proven survival benefit
- Only 25% to 45% of patients are eligible for corticosteroids due to well known complications and contraindications[1,2,3,4,5,6]

Liver Transplant

- Limited availability of donated organs restricts access[3,7,8]
  - High liver transplant costs >$875,000
  - Requires lifetime of immunosuppression

Few Programs in Clinical Development

- Most advanced competitive clinical program is in Phase 2a
- No other completed clinical trials have reduced 90-day mortality



Larsucosterol could be the first FDA-approved drug for AH

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]Cotter TG et al. 2021. *Am J Transplant*, 21:1039-1055; [8]Tornai D and Szabo G. 2020. *Clin Mol Hepatol,* 26:686-696; [9]Thursz M et al. 2015. *NEJM*, 372: 1619-1628.

Larsucosterol

AHFIRM Trial

Phase 2b Trial in Alcohol-associated Hepatitis to Evaluate Safety and Efficacy of Larsucosterol Treatment

Phase 2b AHFIRM Trial Design

Trial Overview

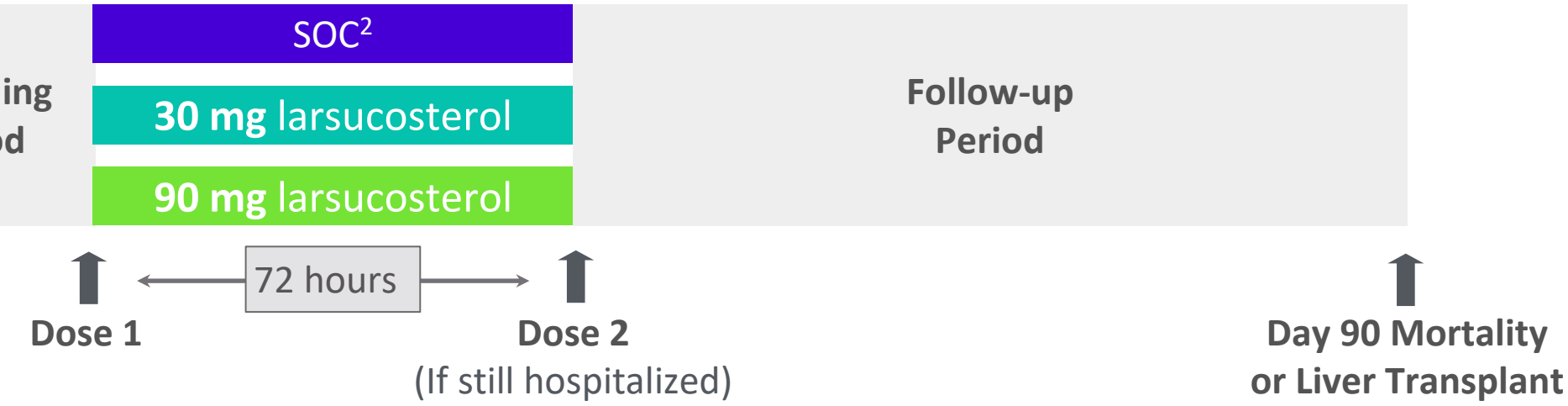
Severe AH patients with MDF[1] score ≥ 32 and MELD[1] score 21-30

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

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

Standard of Care (SOC) included active steroids at investigators' discretion[2]

Study Design



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

[2] All patients received supportive care, which for 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 by Arm – Global Population

	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

* One subject in SOC group was confirmed alive at Day 90 but transplant status unknown

[1] Based on central lab MELD score.

Trial Outcomes by Arm – Global Population

	SOC*	Larsucosterol 30 mg	Larsucosterol 90 mg
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%)

"The AHFIRM trial results represent the most promising data set I have seen on new therapy for severe AH with no important toxicity and a trend toward reducing mortality."[1]

Craig McClain, M.D., AGAF, FACG, FAASLD, FACN, Professor of Medicine and Pharmacology & Toxicology at University of Louisville School of Medicine

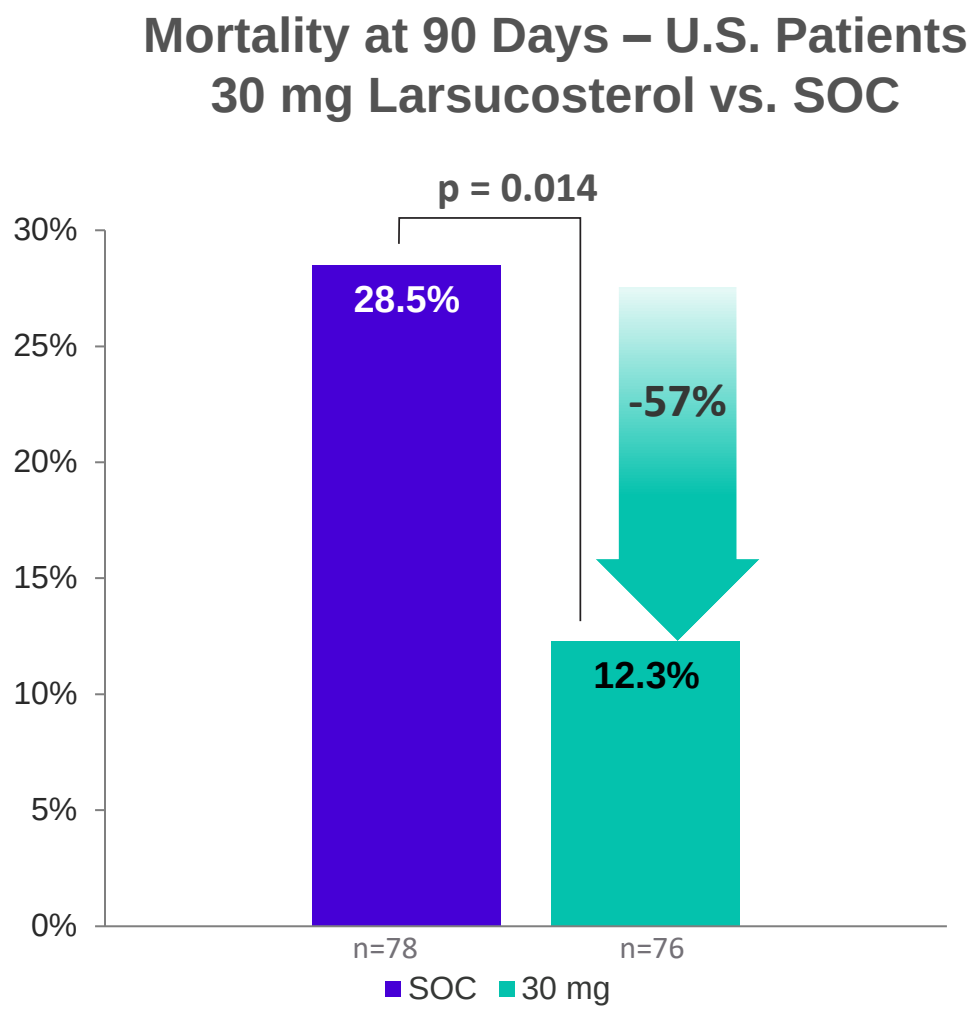
"[T]he results of the current study demonstrating survival benefit are exciting and provide hope for many patients with this condition."[2]

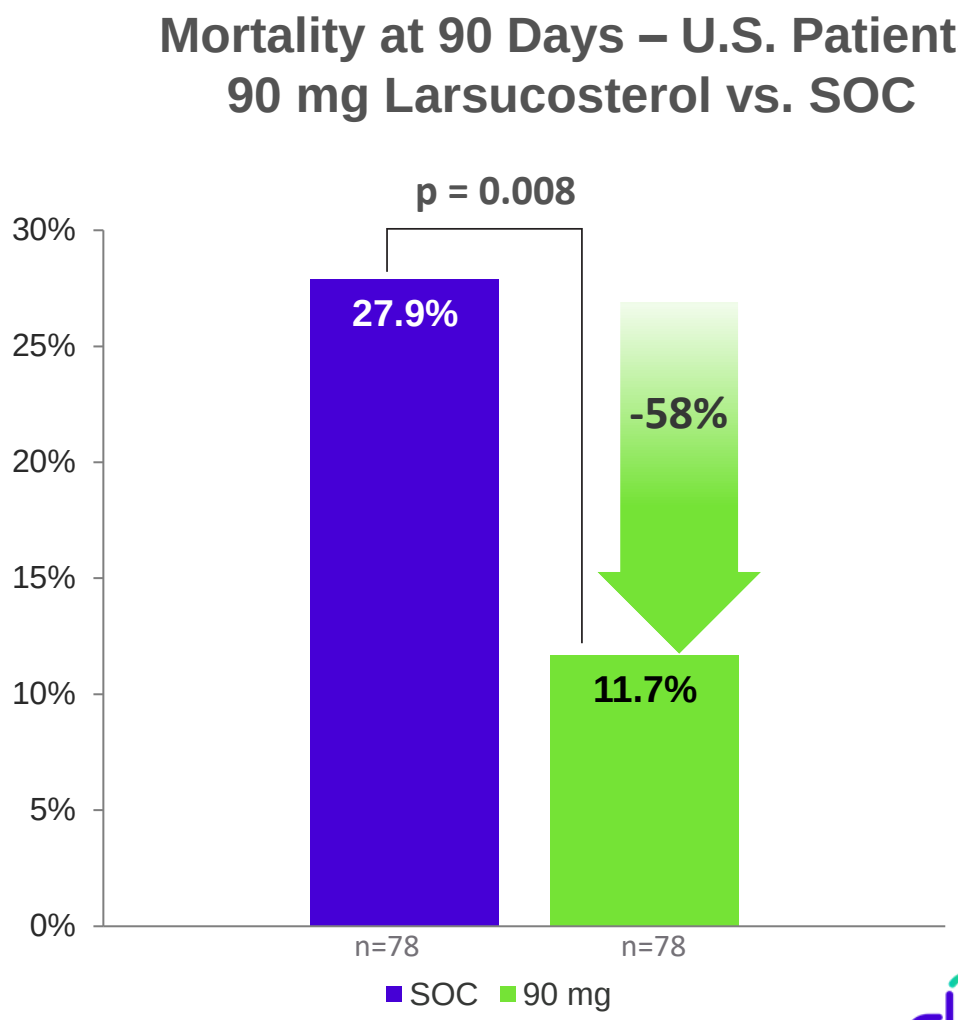
Arun Sanyal, MD, MBBS, Director of Stravitz-Sanyal Institute for Liver Disease & Metabolic Health at Virginia Commonwealth University

- One subject in SOC group was confirmed alive at Day 90 but transplant status unknown. One patient received a liver transplant and subsequently died.

[1] DURECT Corporation press release dated November 7, 2023. [2]DURECT Corporation press release dated November 13, 2023.

Pronounced Reduction in Mortality Observed in U.S. Patients (ITT)

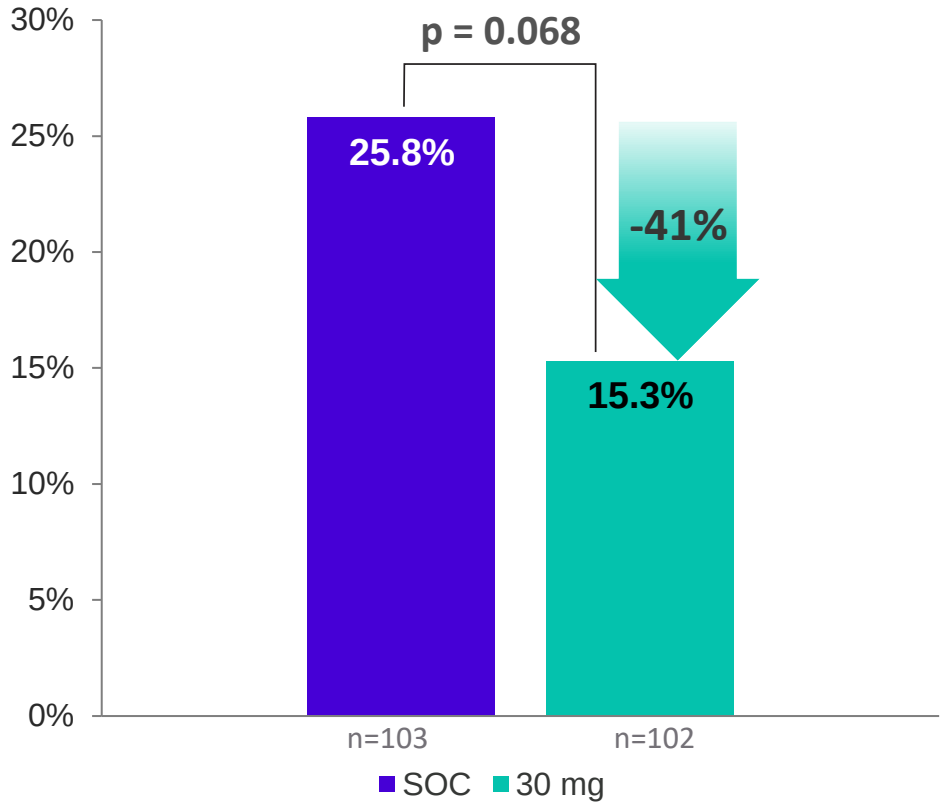




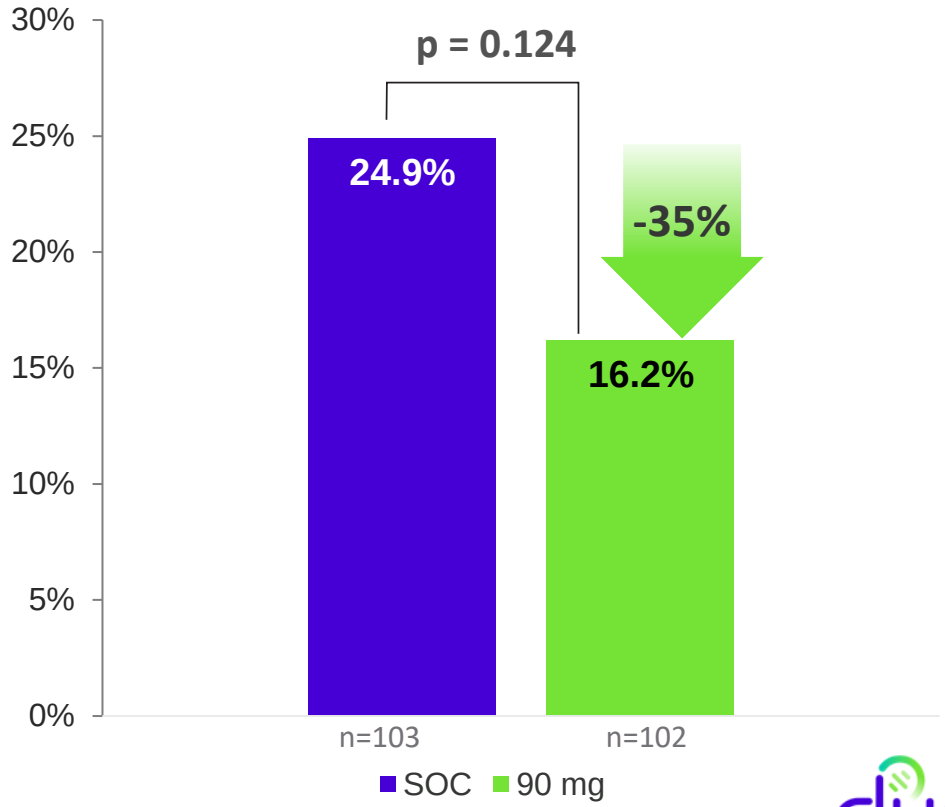
Intent-to-treat (ITT) includes patients with missing 90-day outcome data. The analyses were adjusted to account for subjects with missing outcome data by the method of multiple imputations.

Clinically Meaningful Trend Toward Reduced Mortality – All Patients (ITT)

Mortality at 90 Days
30 mg Larsucosterol vs. SOC



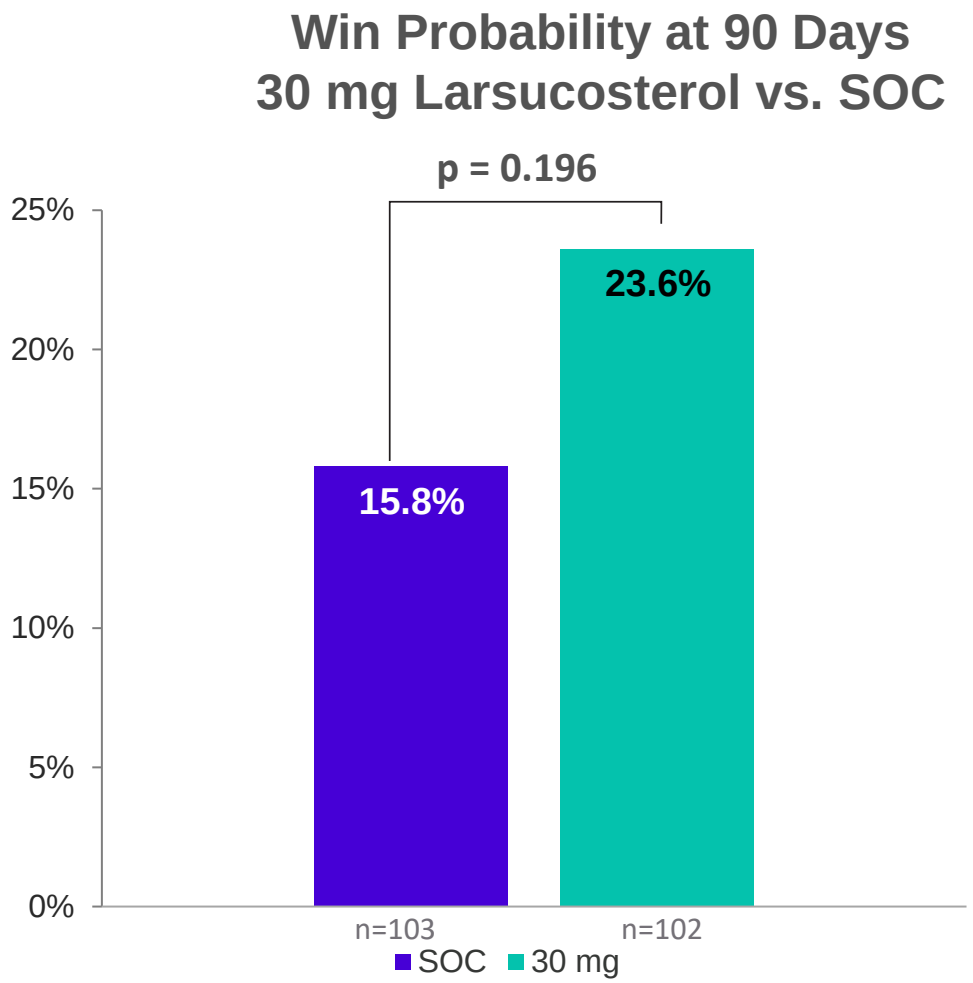
Mortality at 90 Days
90 mg Larsucosterol vs. SOC

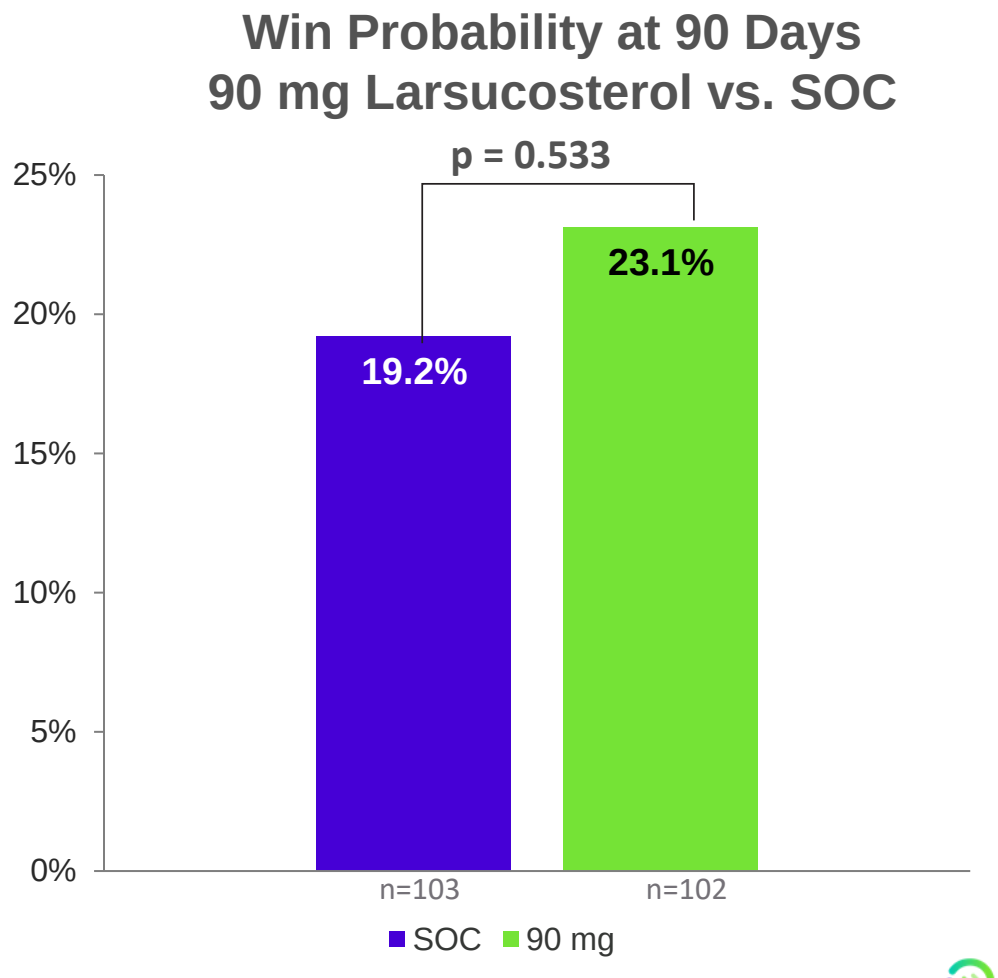


ITT includes patients with missing 90-day outcome data. The analyses were adjusted to account for subjects with missing outcome data by the method of multiple imputations.

Numerical Improvement in Win-Ratio Primary Endpoint – All Patients

Did not achieve statistical significance

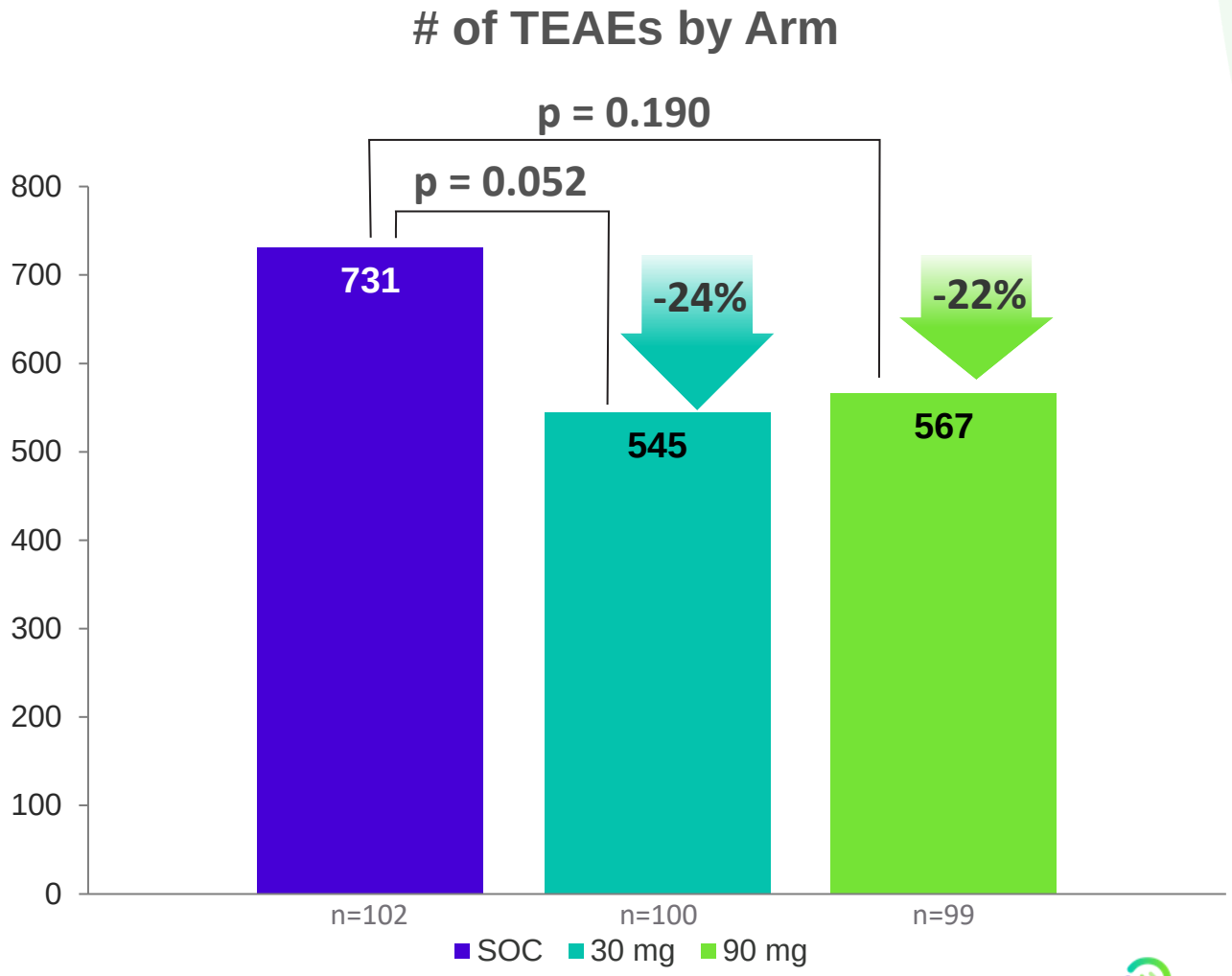




Primary endpoint was analyzed using a hierarchical assessment of patient outcomes to calculate a win probability for each of the 30 mg and 90 mg doses of larsucosterol compared with standard of care. Win probability was calculated on the hierarchy of alive and transplant-free being superior to transplant 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



AEs = 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% lower for the 30 mg dose (p=0.068) and 35% lower for the 90 mg dose (p=0.124) compared with SOC
- In U.S. patients, larsucosterol treatment reduced 90-Day mortality by 57% in the 30 mg dose (p=0.014) and by 58% in 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

- FDA feedback expected 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

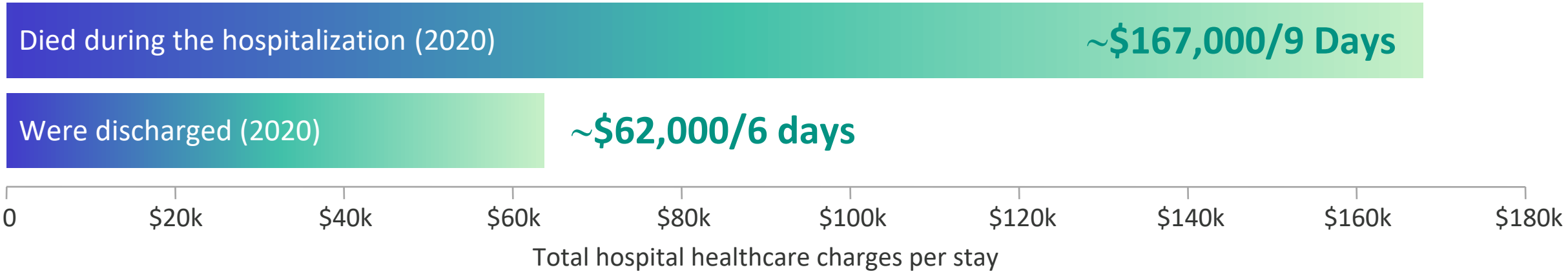
Larsucosterol

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]

Each hospitalization episode with AH[1]: **Average Hospital Charges/Length of 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.

Larsucosterol Value Proposition Supports Blockbuster Potential

Larsucosterol has the potential to become a >$1B/year 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 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

Source: Stakeholder Interviews; ClearView Analysis 2023.

Physicians Are Enthusiastic About Larsucosterol

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

AH Intellectual Property Highlights

8

PATENT FAMILIES

Includes pending patent applications that, if granted, could result in **protection until at least 2044**

3

ISSUED FAMILIES

Three patent families each include at least one **granted patent** that could provide **protection until at least 2037**

Financial Overview and Summary

Financial Overview

Nasdaq	DRRX
Market Cap	$25.4 MM[1]
Shares O/S	29.8 MM[2]
Cash & Cash Equivalents	$39.1 MM[3]
Debt	$18.7 MM[3]

Cupertino, CA headquarters

[1] As of February 12, 2024
[2] As of November 13, 2023
[3] As of September 30, 2023

Larsucosterol – Positioned for Success in AH

Compelling AHFIRM Mortality Results

- Compelling outcome on key secondary endpoint of mortality reduction at 90 days
- Pronounced reduction in mortality at 90 days in U.S. population
- Supports advancement to Phase 3 registrational trial
- Fast Track Designation

Clinical Safety

- Well tolerated, no drug-related toxicities
- Numerically fewer TEAEs in AHFIRM
- No serious AEs in AHFIRM attributed to larsucosterol
- More than 500 patients dosed in multiple Phase 1 and 2 trials

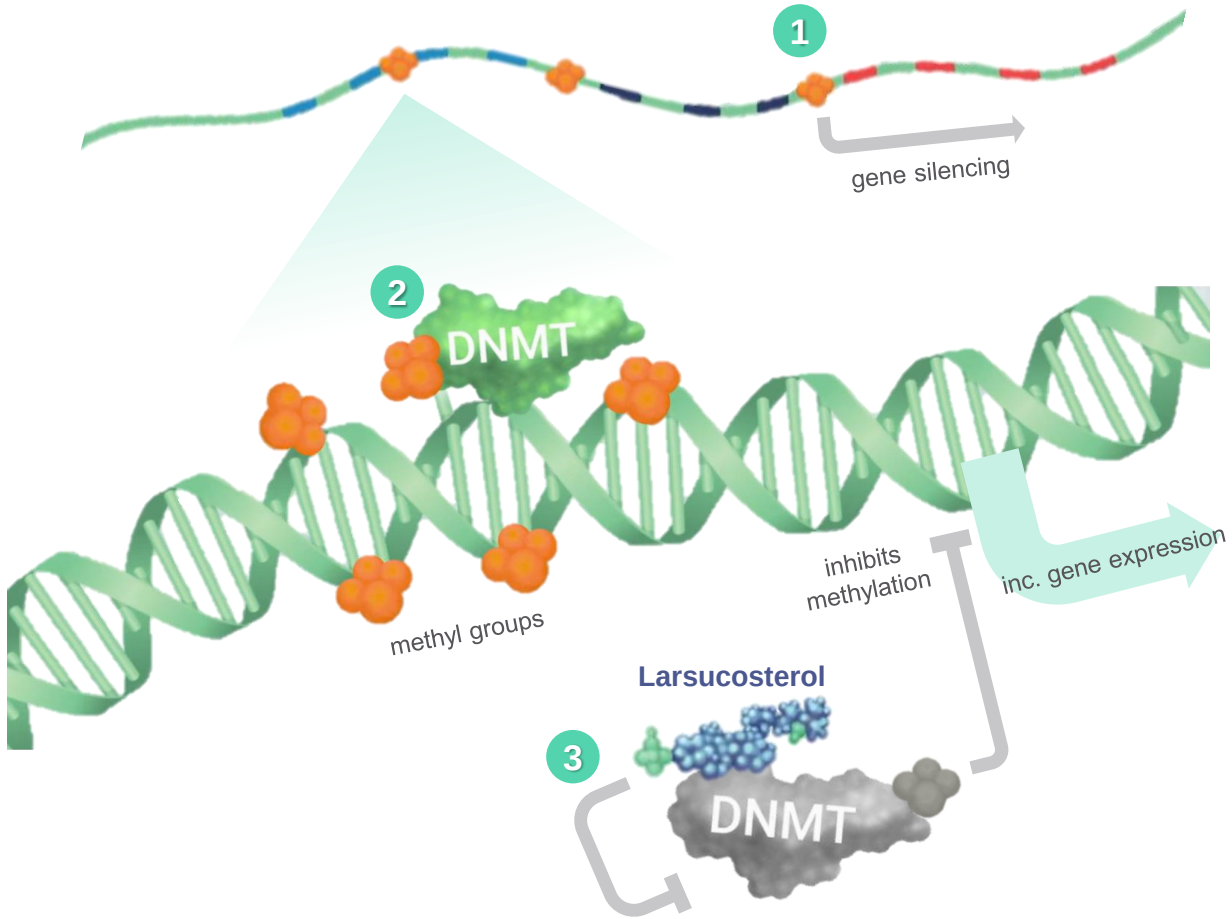
>$1 Billion Peak Sales for AH in U.S.

- ~158,000 annual hospitalizations in U.S.
- ~$10 billion annual direct hospital charges in U.S.
- No approved therapy
- Potential patent protection through at least 2044

FDA feedback on Phase 3 trial and next steps expected in Q1 2024

Appendix

Mechanism of Action Leverages Epigenetics to Impact Disease



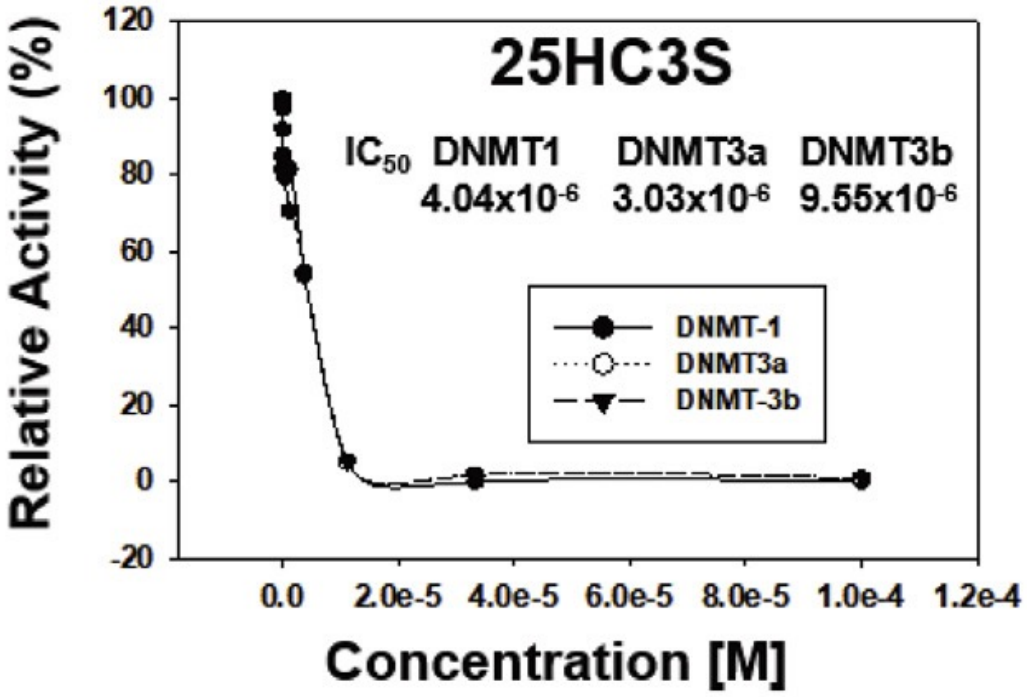
1 **Epigenetic Dysregulation in AH Patients**
Aberrant DNA hypermethylation is associated with many diseases including severe AH

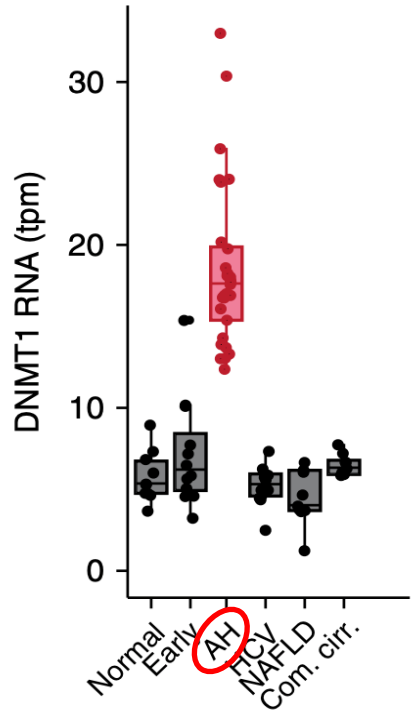
2 **Epigenetic Regulators Modulate Gene Expression**
DNA methyltransferases (DNMTs) are one such regulator that add methyl groups to certain regions of DNA, generally reducing gene expression

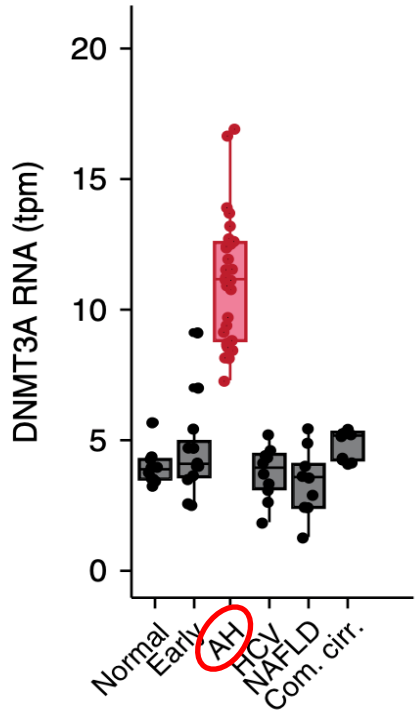
3 **Larsucosterol Inhibits DNMTs**
By inhibiting DNMTs (1, 3a, & 3b), larsucosterol reduces DNA hypermethylation, which modulates important cell signaling pathways

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