Unlocking Epigenetic Therapeutics to Revolutionize Medicine

June 2024

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This presentation and various remarks we make during this presentation contain forward-looking statements of DURECT within the meaning of applicable securities laws and regulations, which are subject to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, including statements relating to the potential for larsucosterol to demonstrate a reduction in mortality or liver transplant in patients with alcohol-associated hepatitis ("AH") and to save lives, DURECT's plans, trial design and anticipated timeline for a Phase 3 trial for larsucosterol, the potential for a single Phase 3 trial of larsucosterol to show a statistically significant improvement in the treatment of AH over standard of care, the potential Federal Drug Agency (the "FDA") or other regulatory approval of larsucosterol for the treatment of AH after a Phase 3 trial, anticipated physician and hospital awareness of AH and associated product benefits and other potential uses of larsucosterol, and anticipated product markets, incident projections, value proposition and potential sales. Actual results may differ materially from those contained in the forward-looking statements contained in this presentation, and reported results should not be considered as an indication of future performance. These forward-looking statements involve risks and uncertainties that could cause actual results to differ from those in such forward-looking statements. Potential risks and uncertainties include, but are not limited to, the risk that future clinical trials of larsucosterol are delayed or do not confirm the results from subset analyses of the AHFIRM trial, including geographic or other segmentation, or of earlier clinical or pre-clinical trials, or do not demonstrate the safety or efficacy of larsucosterol in a statistically significant manner, the risk that the FDA or other government agencies may require additional clinical trials for larsucosterol before approving larsucosterol for the treatment of AH, and that larsucosterol may never be approved; risks that Innocoll may not commercialize POSIMIR successfully; and risks related to the sufficiency of our cash resources, our anticipated capital requirements and capital expenditures, our need or desire for additional financing, our ability to continue to meet the minimum bid price for continued listing on Nasdaq, our ability to obtain capital to fund our operations and expenses and our ability to continue to operate as a going concern. Further information regarding these and other risks is included in DURECT's most recent U.S. Securities and Exchange Commission ("SEC") filings, including its Annual and Quarterly Reports on Forms 10-K and 10-Q, respectively, filed with the SEC under the heading “Risk Factors.” DURECT is under no duty to update any of these forward-looking statements after the date of this presentation to conform these statements to actual results or revised expectations, except as required by law. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof and nothing (including any sale of securities by the Company after the date of this presentation) shall imply that the information contained herein or the affairs of the Company have not changed since the date hereof. Subsequent events and developments may cause DURECT’s expectations and beliefs to change.

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Company Highlights

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

- **Compelling results from 307-patient placebo-controlled Phase 2b AHFIRM trial**
  - Improvement in transplant-free survival and mortality
  - Well tolerated with no drug-related toxicities
- **Strong rationale for advancing to registrational Phase 3 trial**
  - Single pivotal trial required
- **Novel mechanism of action in hepatic disease**
  - Modulator of DNA methyltransferases (DNMTs)
- **Granted Breakthrough Therapy and Fast Track Designations by the FDA**
- **Significant unmet need: >$1 billion market opportunity in U.S.[1]**
  - 90-day mortality rate of ~30%[2]
  - No approved therapy for AH

[1] Market Research – ClearView Analysis 2023
[2] Hughes E, Hopkins LJ, Parker R. 2018. *PLOS ONE,* 13(2): e0192393

Pipeline

Program	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Marketed	Status/Timing
Epigenetic Modulator Programs							
Larsucosterol	AH (intravenous administration)						Completed Ph 2b AHFIRM trial (Q4 2023); Expect to initiate registrational Ph 3 trial (2H 2024)
NCEs[1]	Hematology/ Oncology (small molecules)						Preclinical
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
Potential in Alcohol-associated Hepatitis

Larsucosterol: Our Lead Epigenetic Modulator Program

Phase 3-ready in AH with novel mechanism of action

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 inflammation and stress response
- Promotes cell survival

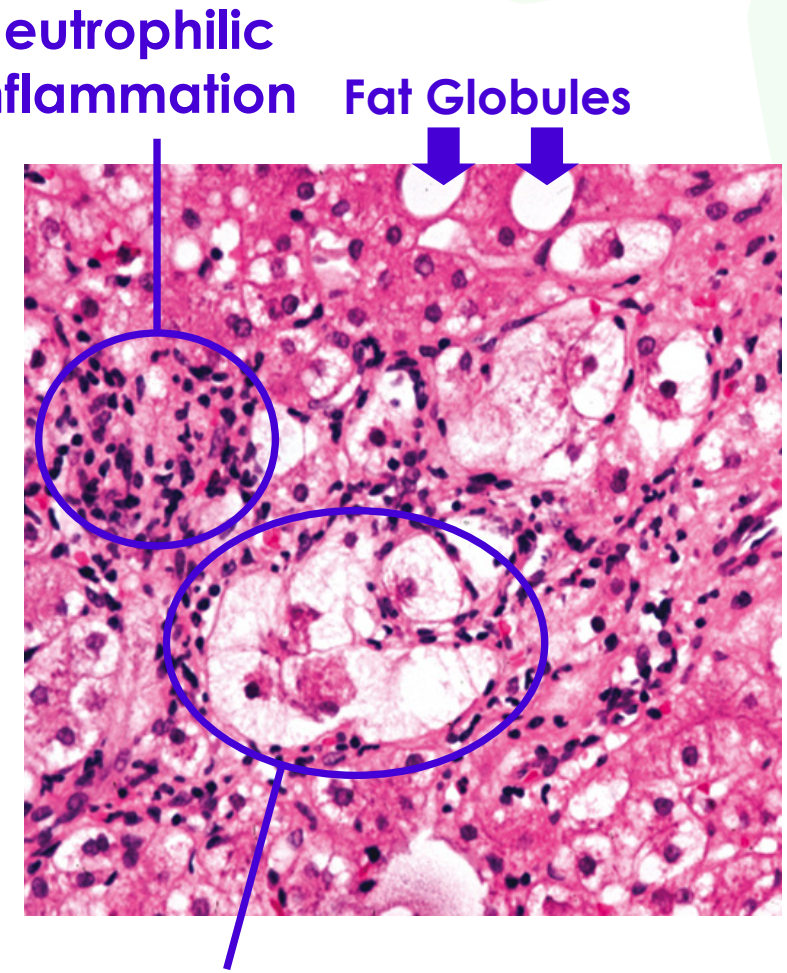
Demonstrated Clinical Efficacy and Safety

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

What is Alcohol-associated Hepatitis?

90-day mortality rate: ~30%[1]

- Life-threatening form of alcohol-associated liver disease
- Can occur in individuals who chronically misuse alcohol, frequently manifests 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)[2]
- SIRS may progress to multi-organ failure and ultimately death



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

Current Treatments for AH are Inadequate with No Approved Therapies

Corticosteroids

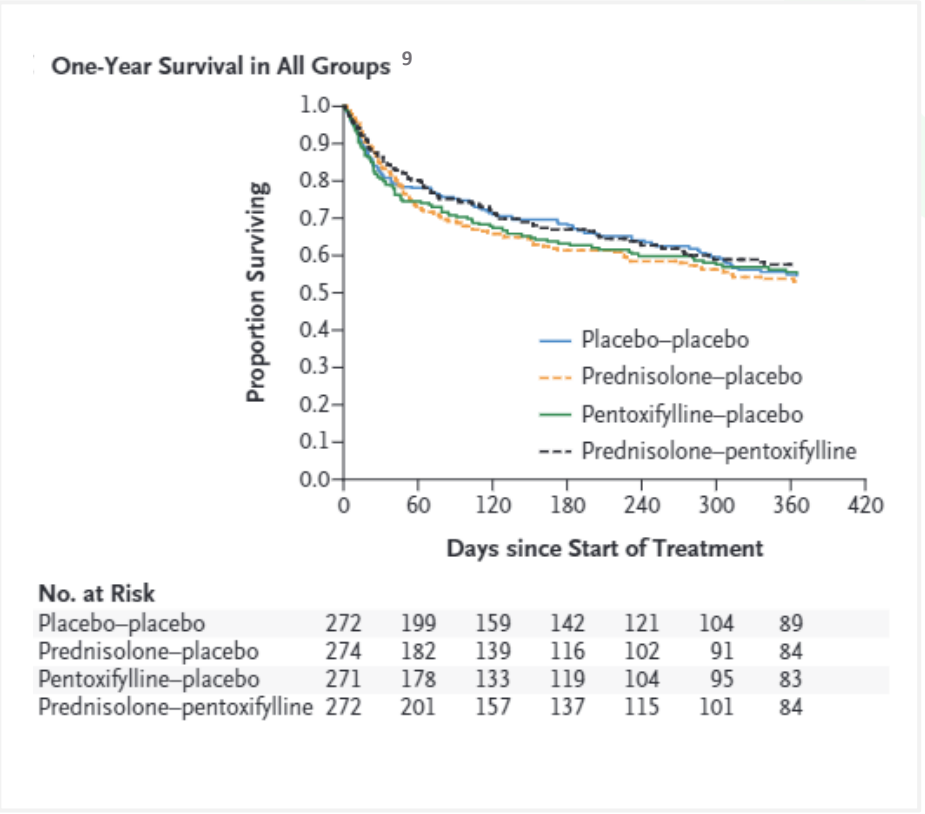
- Used as first-line treatment despite lack of demonstrated survival benefit
- Only 25% to 45% of patients are eligible for corticosteroids due to well known complications and contraindications[1,2,3,4,5,6]

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 randomized clinical trials have reduced 90-day mortality



[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.

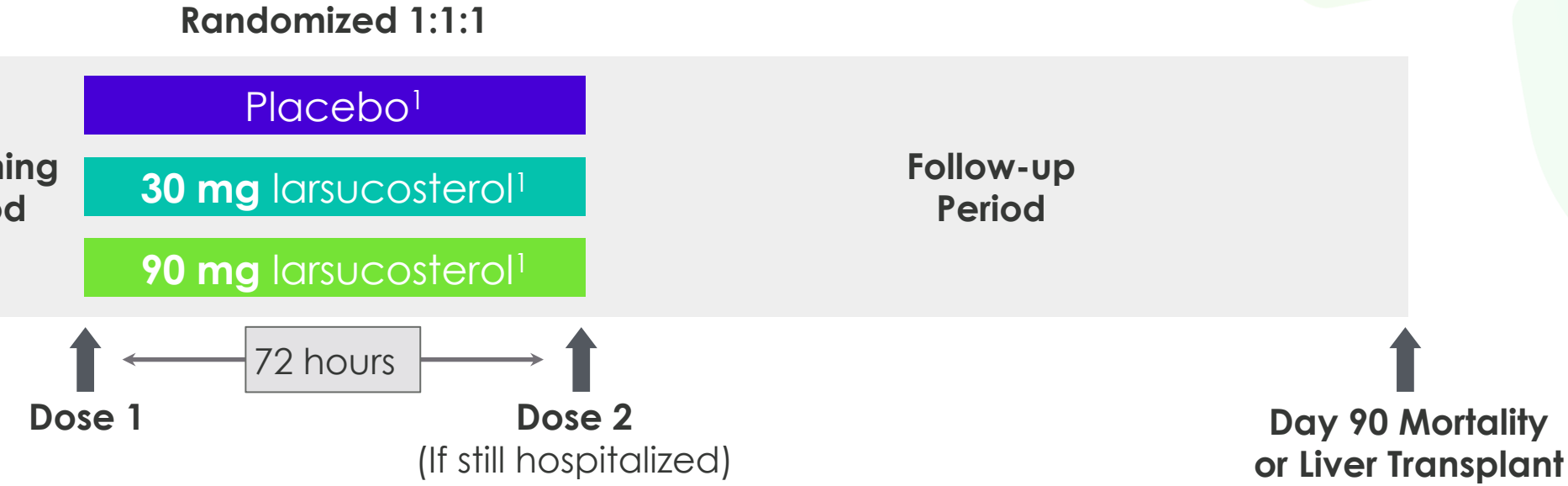
Larsucosterol

AHFIRM Trial

Phase 2b Trial in AH to Evaluate Safety and Efficacy of Larsucosterol

Phase 2b AHFIRM Trial Design

Study Design



Trial Overview

Enrolled 307 severe AH patients with MDF[2] score ≥ 32 and MELD[2] score 21-30

Primary endpoint: Mortality or liver transplant at 90 days

Key secondary endpoint: 90-day mortality

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

Placebo included active steroids at investigators' discretion[1]

[1] All patients received supportive care, which for placebo 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.

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

Median Baseline Characteristics by Arm – Global Population

	Placebo	Larsucosterol 30 mg	Larsucosterol 90 mg
Number of patients randomized	103	102	102
Number of patients with 90-day outcome data	102[1]	99	101
MELD[2]	25.0	24.0	25.0
MDF	61.5	57.2	63.0
Age	47.0	44.0	43.0

[1] One subject in placebo group was confirmed alive at Day 90 but transplant status unknown.
[2] Based on central lab MELD score.

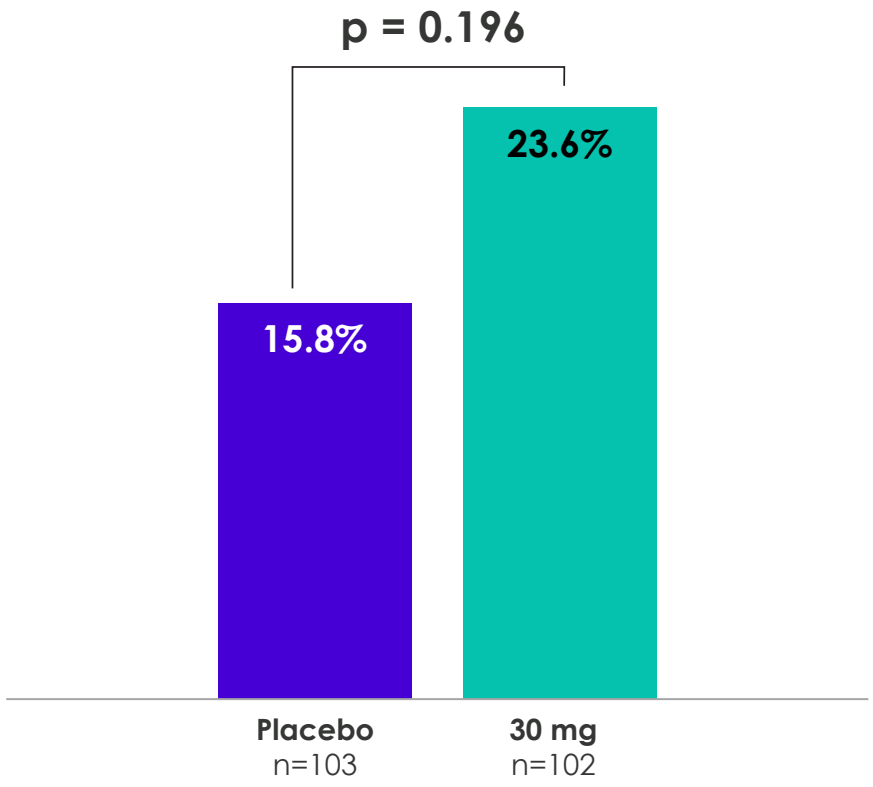
Trial Outcomes by Arm – Global Population

	Placebo[1]	Larsucosterol 30 mg	Larsucosterol 90 mg
Global:	n=102	n=99	n=101
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%)**
U.S.:	n=77	n=73	n=77
Deaths	21 (27.3%)	8 (11.0%)	10 (13.0%)
Transplants	4 (5.2%)	5 (6.8%)	8 (10.4%)
Alive & Transplant-free	52 (67.5%)	60 (82.2%)	59 (76.6%)
All Alive	**56 (72.7%)**	**65 (89.0%)**	**67 (87.0%)**

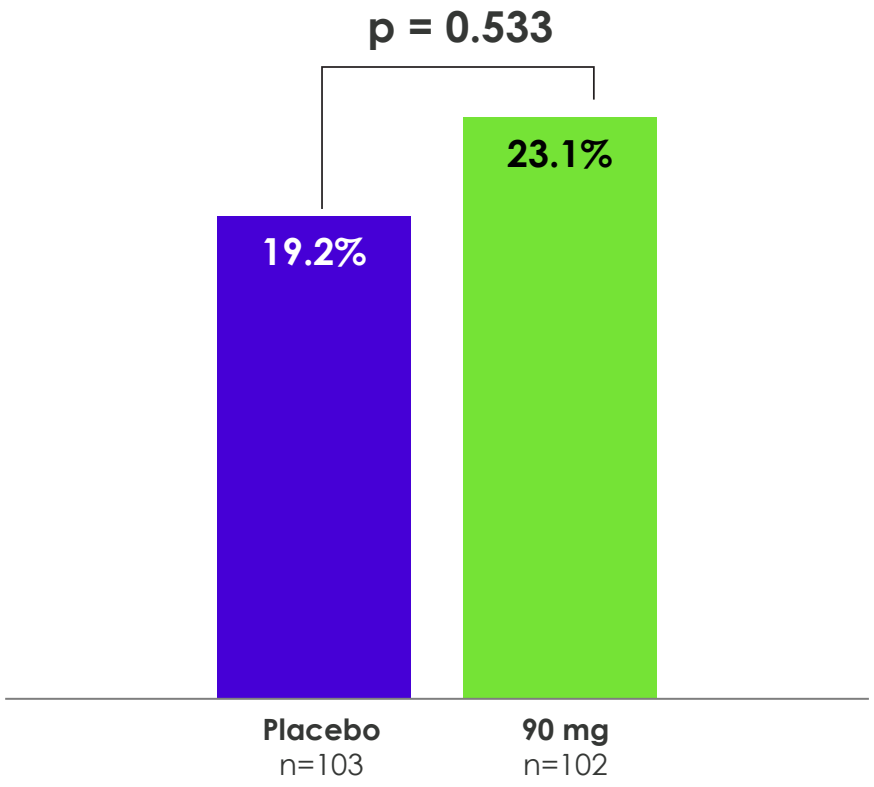
[1] One subject in placebo group was confirmed alive at Day 90 but transplant status unknown. One patient received a liver transplant and subsequently died.

Numerical Improvement in Transplant-free Survival (TFS) – Global (ITT)

Win Probability[1,2] at 90 Days
30 mg Larsucosterol vs. Placebo



Win Probability[1,2] at 90 Days
90 mg Larsucosterol vs. Placebo

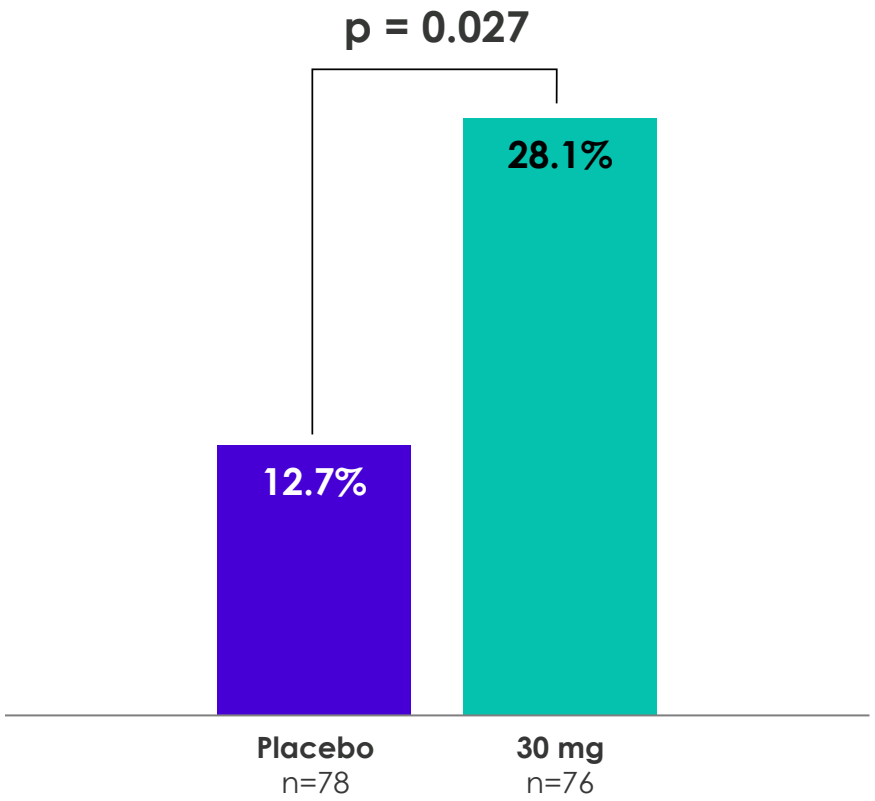


[1] Primary endpoint was analyzed using a hierarchical assessment of patient outcomes to calculate a win probability for each of the 30 mg and 90 mg doses of larsucosterol compared with placebo. Win probability was calculated on the hierarchy of alive and transplant-free being superior to transplant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

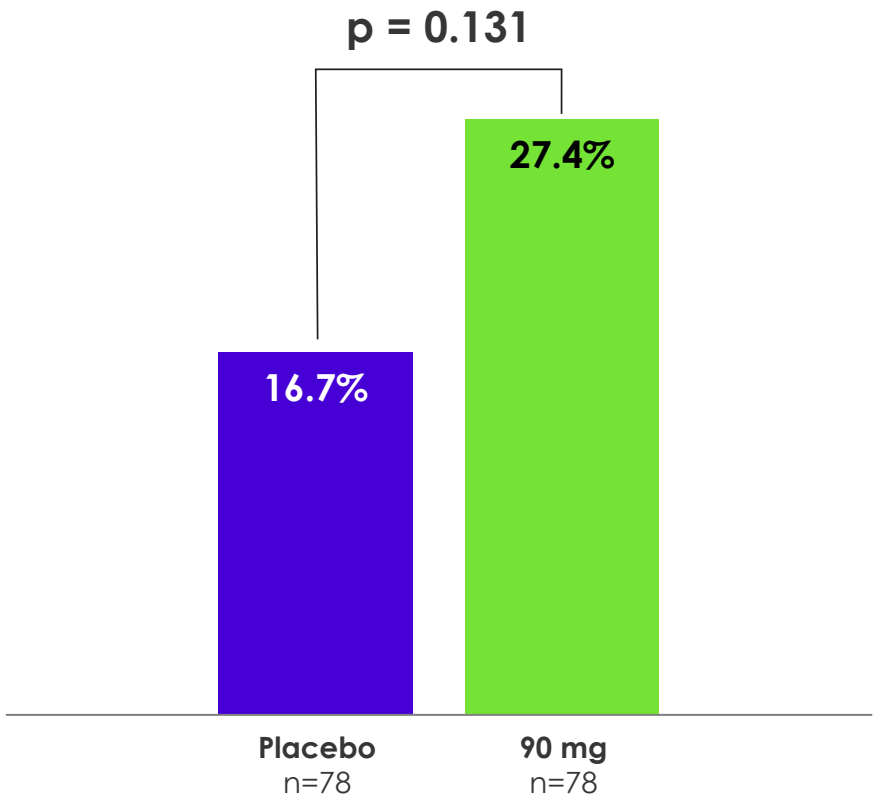
[2] Intent-to-treat (ITT) includes 5 patients with missing 90-day outcome data. The analyses were adjusted by the method of multiple imputations to account for these subjects.

TFS – U.S. Patients (ITT)

Win Probability[1,2] at 90 Days
30 mg Larsucosterol vs. Placebo



Win Probability[1,2] at 90 Days
90 mg Larsucosterol vs. Placebo

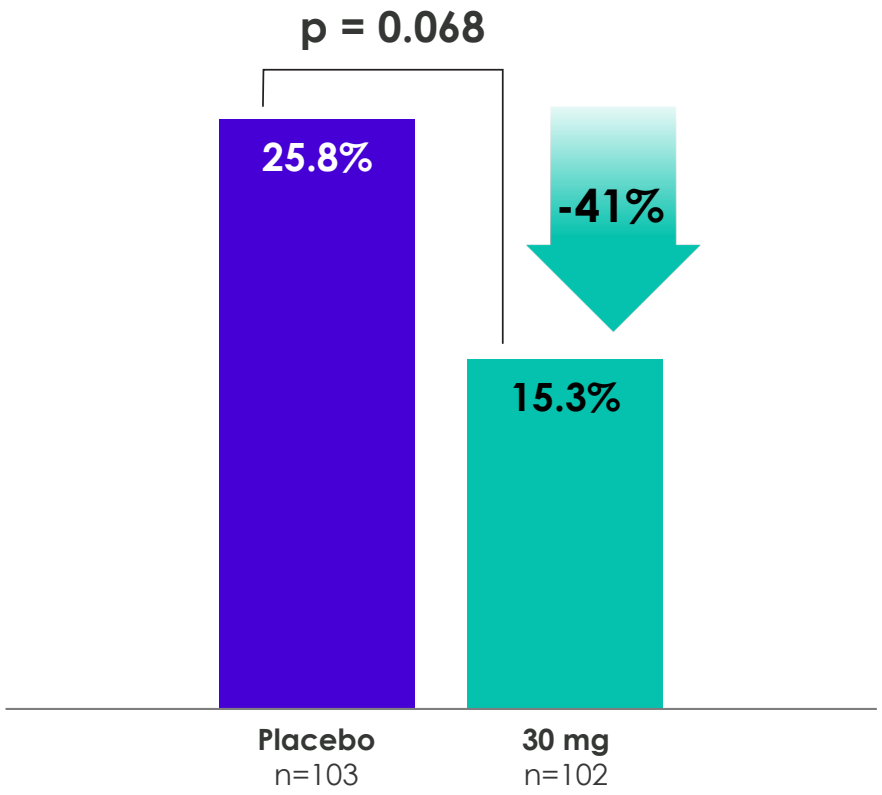


[1] Primary endpoint was analyzed using a hierarchical assessment of patient outcomes to calculate a win probability for each of the 30 mg and 90 mg doses of larsucosterol compared with standard of care. Win probability was calculated on the hierarchy of alive and transplant-free being superior to transplant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

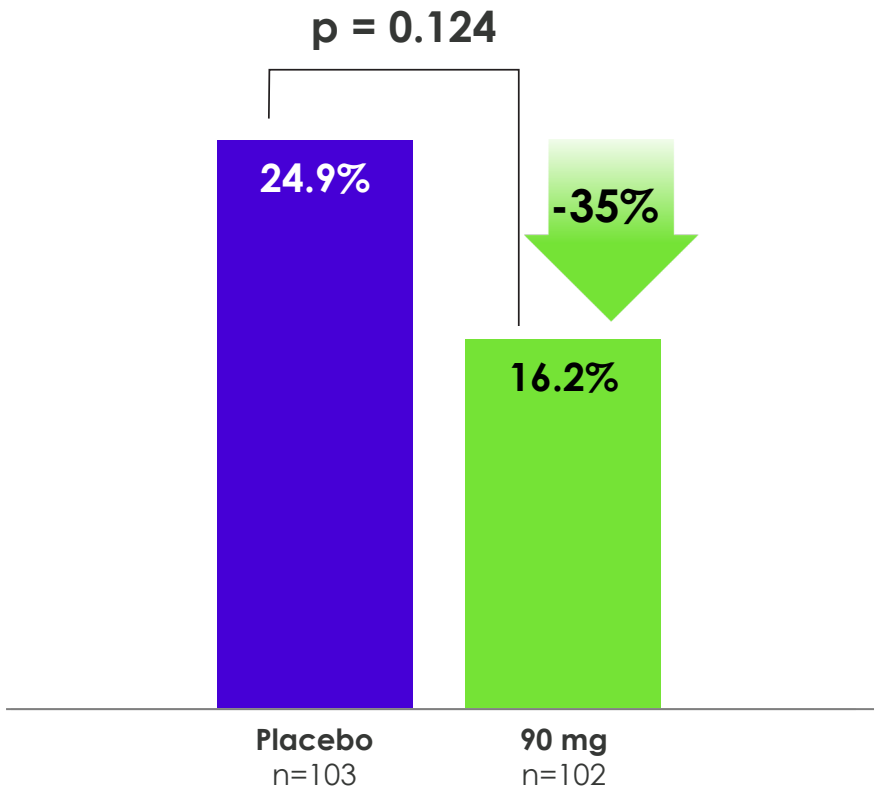
[2] Intent-to-treat (ITT) includes 5 patients with missing 90-day outcome data. The analyses were adjusted by the method of multiple imputations to account for these subjects.

Clinically Meaningful Trend Toward Reduced Mortality – Global (ITT)

Mortality at 90 Days
30 mg Larsucosterol vs. Placebo[1]



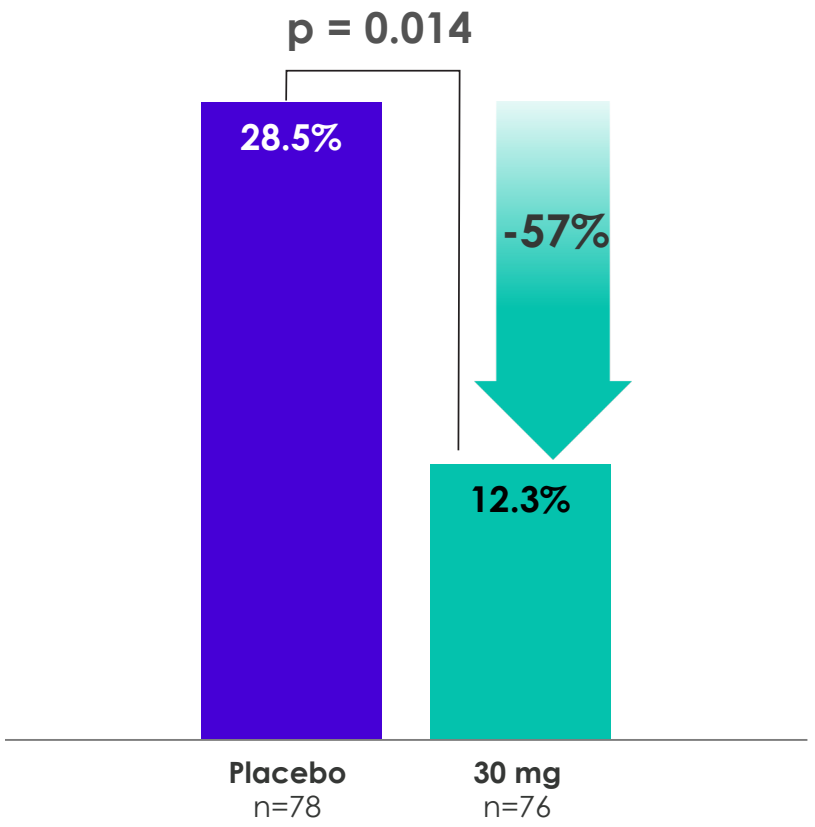
Mortality at 90 Days
90 mg Larsucosterol vs. Placebo[1]



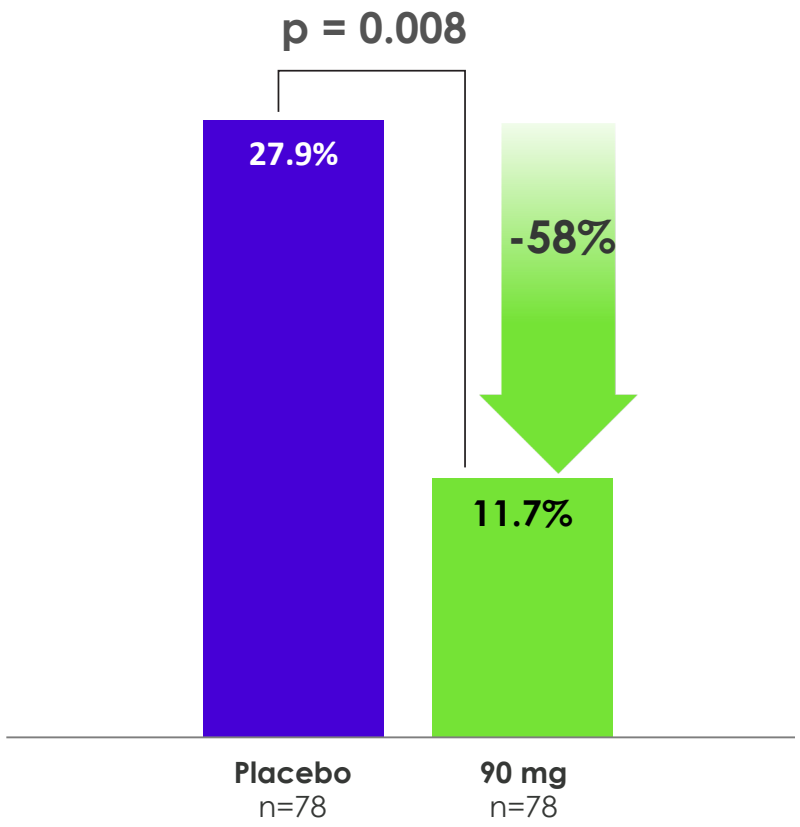
[1] Sites with enrollment <5 patients were pooled resulting in different mortality rates for placebo compared with 30 mg and 90 mg larucosterol doses.
ITT includes 5 patients with missing 90-day outcome data. The analyses were adjusted by the method of multiple imputations to account for these subjects.

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

Mortality at 90 Days – U.S. Patients 30 mg Larsucosterol vs. Placebo[1]



Mortality at 90 Days – U.S. Patients 90 mg Larsucosterol vs. Placebo[1]



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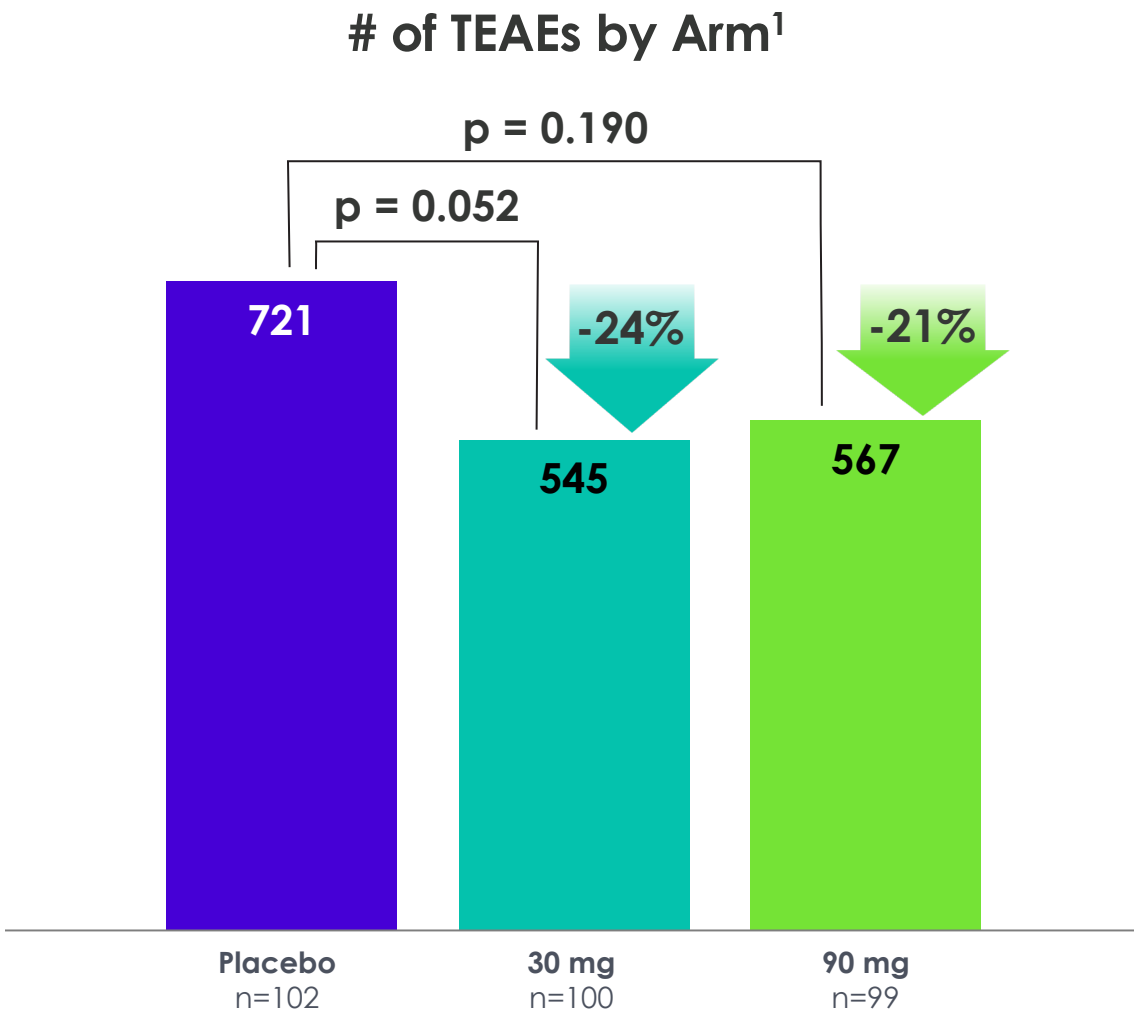
ITT includes 5 patients with missing 90-day outcome data. The analyses were adjusted by the method of multiple imputations to account for these subjects.

Larsucosterol Was Well-Tolerated

Numerically fewer TEAEs in both 30 mg and 90 mg arms compared with placebo

No meaningful difference in serious AEs and none attributed to larsucosterol



TEAEs = Treatment Emergent Adverse Events, AEs = Adverse Events

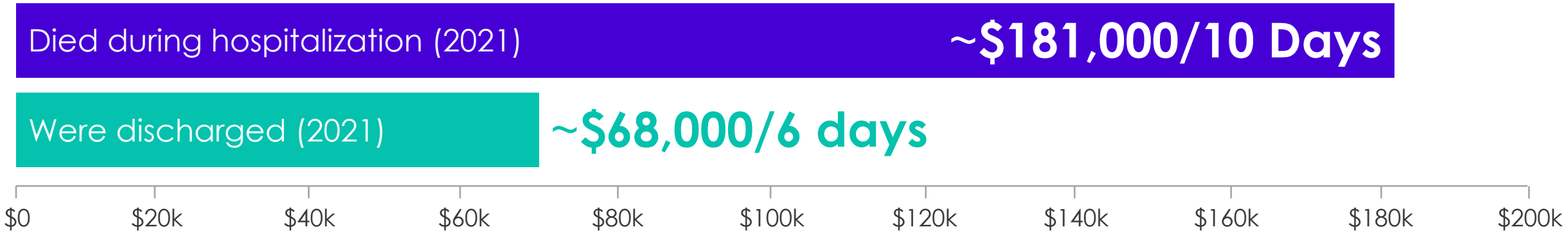
[1] Excludes 6 patients randomized but not dosed.

Larsucosterol
Commercial Opportunity in AH

AH Imposes High Economic Burden on U.S. Healthcare System

- ~164,000 U.S. hospitalizations in 2021[1]
- Incidence may result in ~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
- 88% of hospitalized AH patients are insured[1]

Each hospitalization episode with AH[1]: **Average hospital charges/length of stay**



[1] National Inpatient Sample 2021.
[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

If approved larsucosterol has the potential to become a >$1B/year 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 rate clinically meaningful

HOSPITAL COST OFFSET ECONOMICS

Reducing costly **length and frequency of ICU stays** is key for offsetting drug costs and securing favorable hospital formulary inclusion

REDUCTION IN HEALTHCARE SYSTEM COST BURDEN

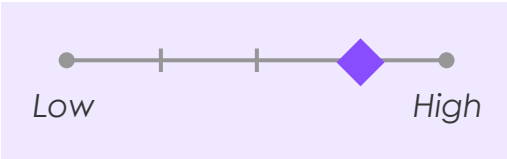
Hospital economics and payer stakeholders may use **reduction in 30-day readmissions** to assess impact on per-patient cost burden

Source: Stakeholder Interviews; ClearView Analysis 2023.

Our Market Survey Indicates Physicians Are Enthusiastic About Larsucosterol

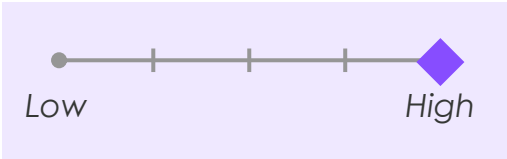
MECHANISM OF ACTION

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



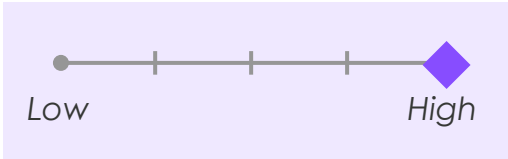
CLINICAL EFFICACY

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



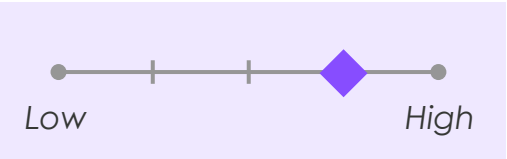
SAFETY AND TOLERABILITY

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.

Larsucosterol Intellectual Property & Regulatory Highlights

15

PATENT FAMILIES

Each include pending patent applications that, if granted, could result in protection until at least 2032 to 2044

7

ISSUED PATENTS

Seven patent families each include at least one granted patent that could provide protection until at least 2026, 2032, 2034, 2035, 2037, 2037, and 2037, respectively

BREAKTHROUGH THERAPY

DESIGNATION

Designation provides intensive guidance and organizational commitment from senior FDA managers

FAST TRACK

DESIGNATION

FDA designation for larsucosterol in the U.S. indicates the EMA could grant similar regulatory recognition in the EU

Larsucosterol – Positioned for Success in AH

Compelling AHFIRM Mortality Results

- Pronounced impact on mortality in U.S. population
- Compelling outcome on key secondary endpoint of mortality reduction at 90 days
- Breakthrough Therapy and Fast Track Designations

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.[1]

- ~164,000 annual hospitalizations in U.S.[2]
- ~$10 billion annual direct hospital charges in U.S.[2]
- No approved therapy
- Potential patent protection through at least 2044

Designing single Phase 3 trial to support NDA in U.S.

[1] Market Research – ClearView Analysis 2023.
[2] National Inpatient Sample 2021.

Financial Overview

Nasdaq	DRRX
Shares O/S	31.0 MM[1]
Cash & Cash Equivalents	$21.6 MM[2]
Debt	$14.6 MM[2]

Cupertino, CA headquarters

[1] As of May 9, 2024
[2] As of March 31, 2024

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- **Compelling results from 307-patient placebo-controlled Phase 2b AHFIRM trial**
  - Improvement in transplant-free survival and mortality
  - Well tolerated with no drug-related toxicities
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  - Single pivotal trial required
- **Novel mechanism of action in hepatic disease**
  - Modulator of DNA methyltransferases (DNMTs)
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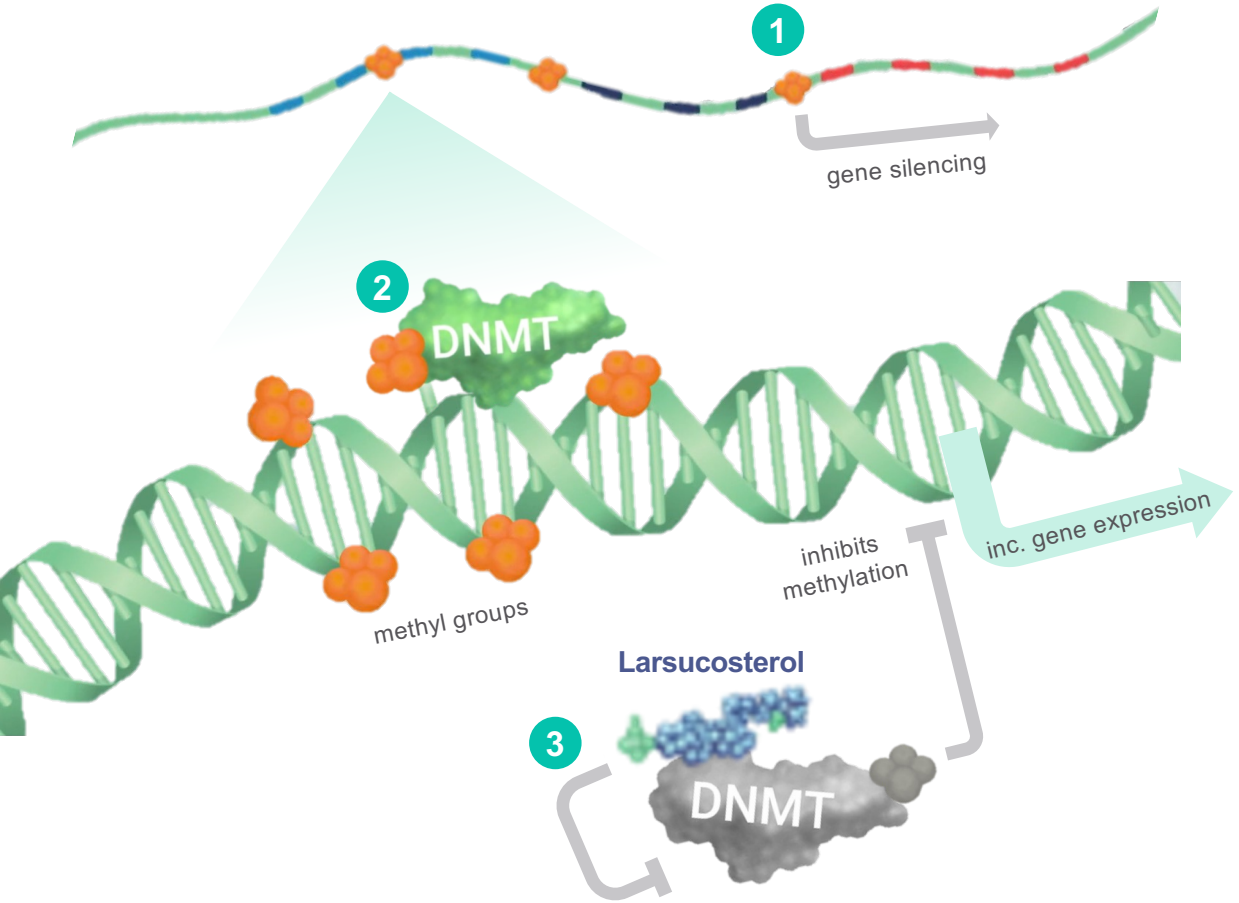
  - No approved therapy for AH

[1] Market Research – ClearView Analysis 2023
[2] Hughes E, Hopkins LJ, Parker R. 2018. *PLOS ONE,* 13(2): e0192393

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

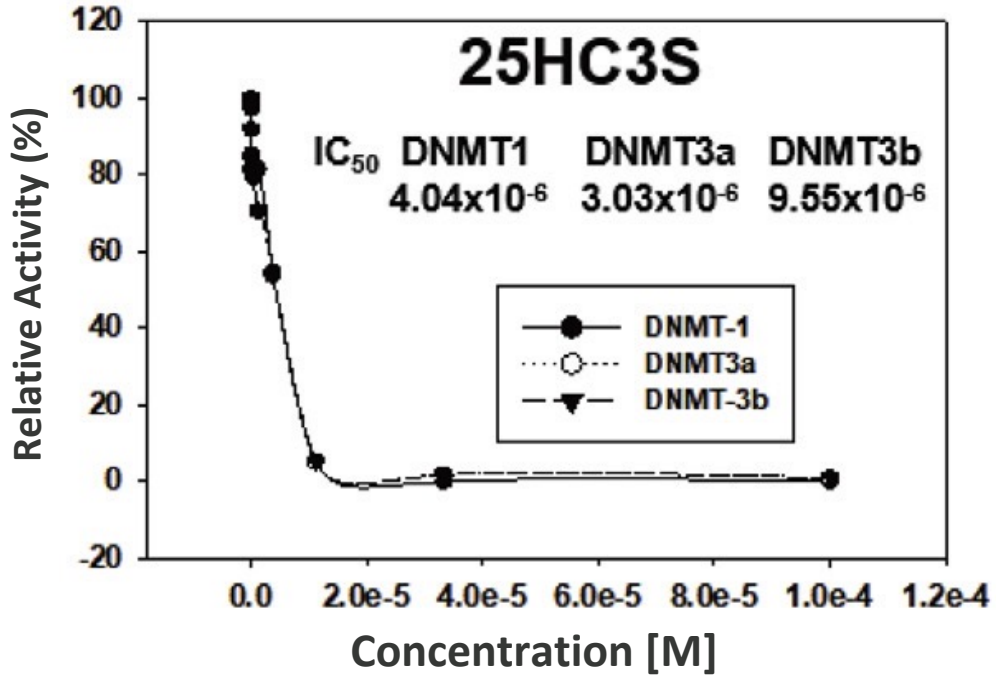
2. **Epigenetic Regulators Modulate Gene Expression**
DNA methyltransferases (DNMTs) are one such regulator that add methyl groups to certain regions of DNA, generally reducing gene expression

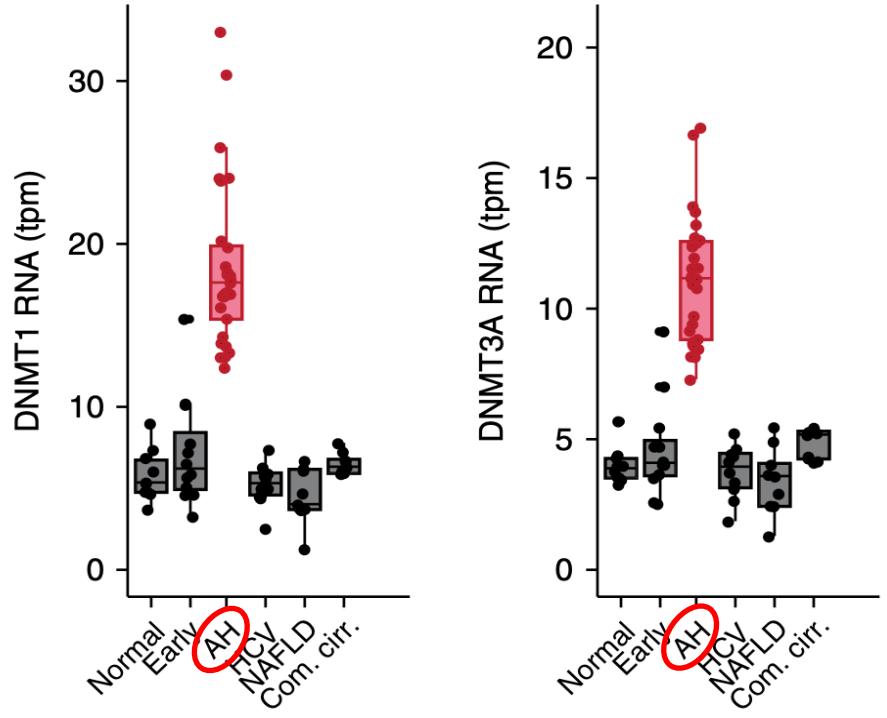
3. **Larsucosterol Inhibits DNMTs**
By inhibiting DNMTs (1, 3a, & 3b), larsucosterol reduces DNA hypermethylation, which modulates important cell signaling pathways

1. Liu et al., *Exp Mol Pathol* 2014;97(2):234-240; 2. Shen et al., *Exp Mol Pathol*. 2015;99(2):326-3293; 3. Argemi et al., *Nat Commun*. 2019;10(1):3126;
4. Niinep et al., *Front Genet*. 2021;12:750142; 5. Zheng et al., *Int J Mol Sci.* 2023;24(12):10130; 6. Wang Y, *Journal of Lipid Research*. 2021; 62: 100063

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