

Results of a Phase 2b multicenter randomized trial of larsucosterol for the treatment of severe alcohol-associated hepatitis (AHFIRM Trial)

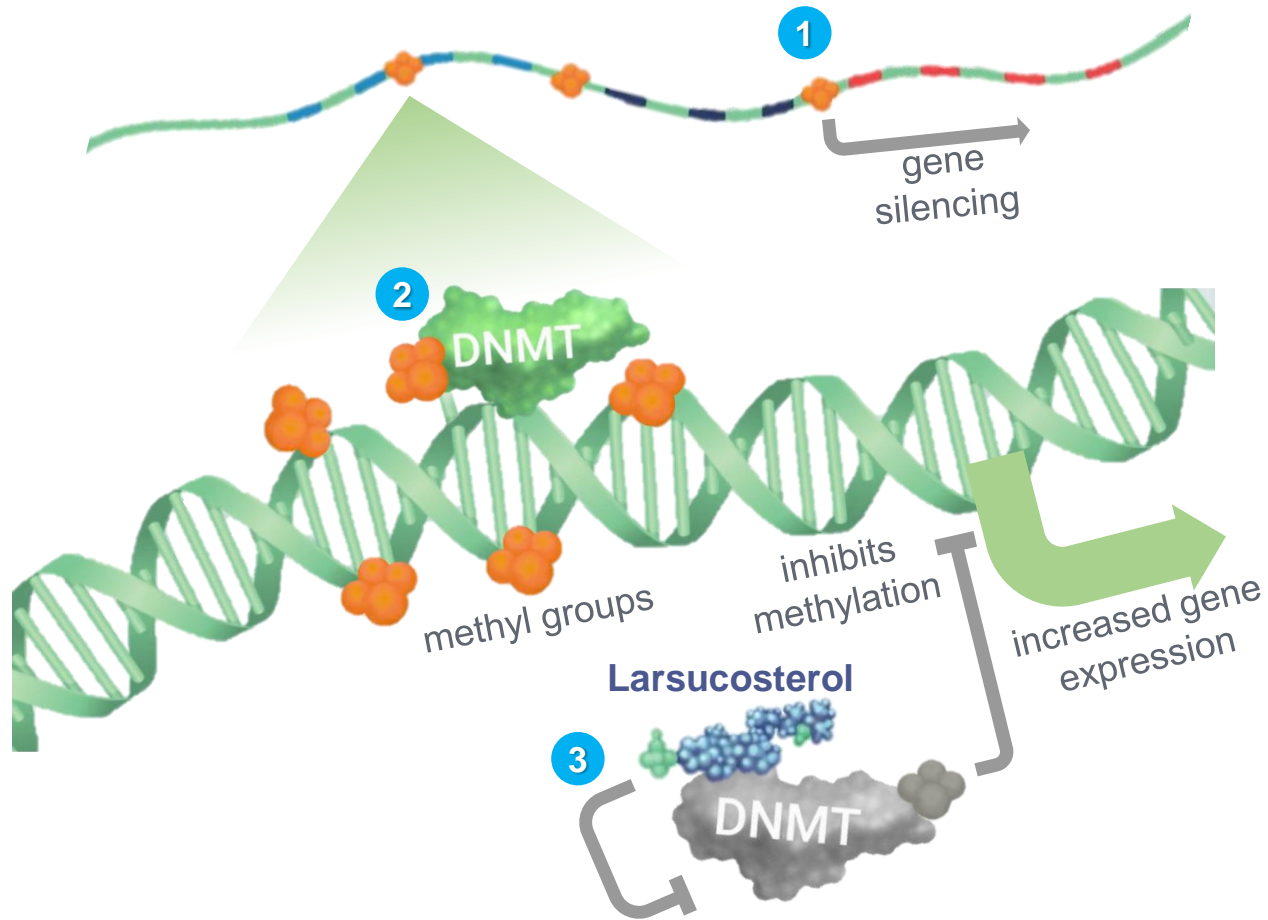
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Presented at EASL 2024, Milan, Italy

This study was funded by DURECT Corporation

Epigenetic DNMT Inhibition for Alcohol-associated Hepatitis (AH)



- There are no effective treatments for severe alcohol-associated hepatitis

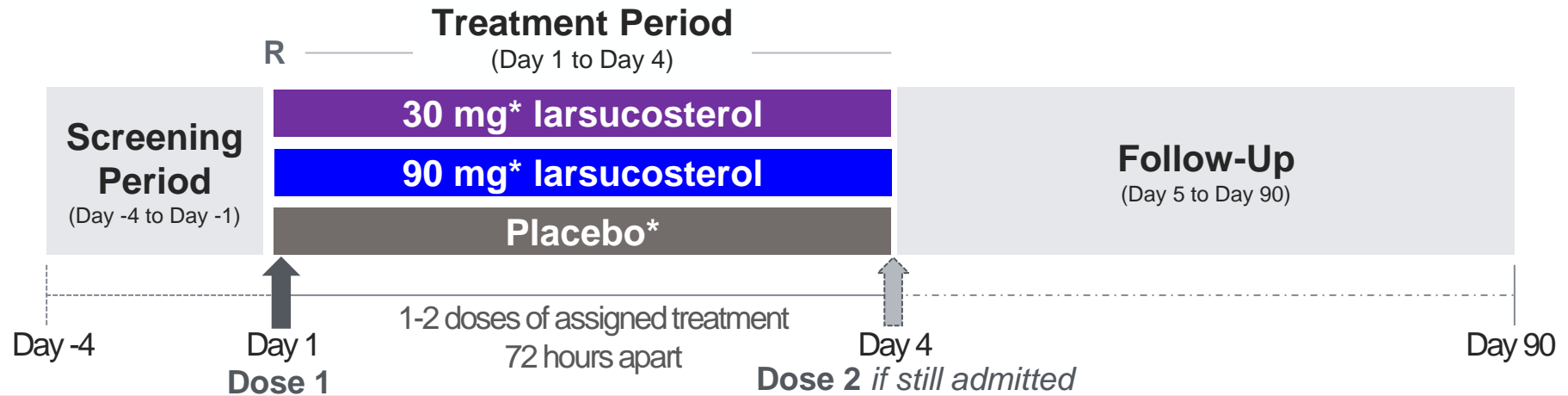
- 1 DNA methyltransferase (DNMT) activity and DNA methylation are increased in AH
- ↓
- 2 Silencing of gene activity interferes with the production of proteins that repair alcohol induced hepatocyte injury¹⁻⁵
- ↓
- 3 Larsucosterol binds to DNMTs, modulates DNA methylation, promotes downstream transcription and thereby results in improved cellular function⁶

Trial Design: Randomized, Placebo-controlled Trial at 62 Sites in US (46), EU, UK, AUS

Key Inclusion Criteria

- **Severe AH subjects** with MDF score ≥ 32 and MELD scores 21-30
- 307 subjects randomized to three groups in a 1:1:1 ratio

Study Design



Study Endpoints

- **Primary Endpoint:** 90-day mortality or liver transplant
- **Key Secondary Endpoint:** 90-day mortality

Note: Statistical analysis plan (SAP) prespecified US data would be reported separately

*All subjects receive supportive care, which for placebo subjects may include methylprednisolone capsules at the investigators' discretion. To maintain blinding, subjects in the larsucosterol arms received matching placebo capsules if the investigator prescribed steroids. MDF = Maddrey's Discriminant Function; R = randomized

Additional Inclusion Criteria

- Onset of jaundice within 8 weeks of screening
- Average daily consumption – 40 g (women) or 60 g (men)
- Less than 8 weeks of abstinence
- Bilirubin > 3.0 mg/dL, AST 50-400 IU/L, ALT < 400 IU/L, AST/ALT > 1.5
- Liver biopsy not required

Key Exclusion Criteria

- Active or high risk for developing alcohol withdrawal, seizures or DTs
- Active infection (SBP, UTI, bacteriemia, viral hepatitis, HIV, SARS-CoV2)
- Any systemic fungal infection
- Serum creatinine > 2.5 mg/dL or CRRT
- Stage 3-4 hepatic encephalopathy
- Uncontrolled GI bleeding
- Any other concomitant liver disease

Steroids

- All patients were treated according to local standard of care
- Pre-randomization steroids could not exceed 8 days in the prior 30 days
- Steroid dosing was at the discretion of the PI
- After signing consent, patients received blinded study capsules
 - Patients randomized to placebo received methylprednisolone 32 mg daily
 - Patients randomized to either larsucosterol group stopped corticosteroids and were given matching placebo capsules

Demographics and Baseline Characteristics

Baseline Characteristics (median values- full analysis set)	Placebo	Larsucosterol 30 mg	Larsucosterol 90 mg
Number of subjects randomized	103	102	102
Number of subjects with 90-day outcome data	102	99	101
Age (years)	47.0	44.0	43.0
Sex (M/F), n	51/52	69/33	48/54
Ethnicity (Hispanic/Not Hispanic) (n = 305), n	16/86	15/87	18/83
Race, n (%)			
White	86 (83.5)	83 (81.4)	83 (81.4)
Black or African American	9 (8.7)	5 (4.9)	6 (5.9)
Asian	2 (1.9)	6 (5.9)	4 (3.9)
American Indian or Native Alaskan	1 (1.0)	2 (2.0)	1 (1.0)
Multiple	1 (1.0)	0 (0.0)	2 (2.0)
Other	4 (3.9)	6 (5.9)	6 (5.9)
MELD (n =306) ¹	24.0	24.0	24.0
MDF (n =306) ¹	61.5	57.2	63.0
Bilirubin mg/dL (n = 307) ¹	18.3	17.0	17.9
INR (n = 305) ¹	1.9	1.9	1.8
Creatinine mg/dL (n =306) ¹	0.7	0.7	0.7
AST U/L (n =307) ¹	115.0	119.0	123.5
ALT U/L (n = 306) ¹	39.0	41.0	41.0
AST/ALT (n = 306) ¹	2.8	2.7	2.9
WBC Count x 1000/uL (n = 282) ²	11.6	10.0	11.3
Neutrophil/Lymphocyte (n=267) ²	6.7	6.2	6.4

¹ Data from local laboratory samples; ² Data from central laboratory samples

Results: AHFIRM Outcomes by Treatment Group (Global)

	Placebo	Larsucosterol 30 mg	Larsucosterol 90 mg
Number of subjects randomized	103	102	102
Number of subjects with 90-day outcome data - Global	102*	99	101
Deaths, n (%)	25 (24.5)	15 (15.2)	17 (16.8)
Transplants, n (%)	4 (3.9)**	6 (6.1)	9 (8.9)
Alive & Transplant-free, n (%)	73 (71.6)	78 (78.8)	75 (74.3)

*One subject was alive at Day 90 with unknown transplant status who has been counted as “Alive & Transplant-free”

**One subject was transplanted and subsequently died – classified as “died”.

Note: Excludes subjects with missing outcome data.

Results: AHFIRM Outcomes by Treatment Group (by Region)

	Placebo	Larsucosterol 30 mg	Larsucosterol 90 mg
Number of subjects with 90-day outcome data – US	77*	73	77
Deaths, n (%)	21 (27.3)	8 (11.0)	10 (13.0)
Transplants, n (%)	4 (5.2)**	5 (6.8)	8 (10.4)
Alive & Transplant-free, n (%)	52 (67.5)	60 (82.2)	59 (76.6)
Number of subjects with 90-day outcome data – France/Belgium	7	11	8
Deaths, n (%)	1 (14.3)	4 (36.4)	4 (50.0)
Transplants, n (%)	0	1 (9.1)	1 (12.5)
Alive & Transplant-free, n (%)	6 (85.7)	6 (54.6)	3 (37.5)
Number of subjects with 90-day outcome data – UK	1	5	2
Deaths, n (%)	1 (100.0)	0	1 (50.0)
Transplants, n (%)	0	0	0
Alive & Transplant-free, n (%)	0	5 (100.0)	1 (50.0)
Number of subjects with 90-day outcome data – Australia	17	10	14
Deaths, n (%)	2 (11.8)	3 (30.0)	2 (14.3)
Transplants, n (%)	0	0	0
Alive & Transplant-free, n (%)	15 (88.2)	7 (70.0)	12 (85.7)

*One subject was alive at Day 90 with unknown transplant status who has been counted as “Alive & Transplant-free”

**One subject was transplanted and subsequently died – classified as “died”.

Note: Excludes subjects with missing outcome data.

Results: Primary Endpoint 90-day Mortality or Liver Transplant*

GLOBAL

Win Probability Difference

Treatment	Win Probability Estimate (SE)	Estimate (SE)	97.5% CI ¹	Combined p-value ²
Larsucosterol 30 mg (N=102)	23.6% (3.5)	7.8% (6.1)	(-0.057, 0.214)	0.1964
Placebo (N=103)	15.8% (3.1)			
Larsucosterol 90 mg (N=102)	23.1% (3.2)	3.9% (6.2)	(-0.100, 0.178)	0.5332
Placebo (N=103)	19.2% (3.3)			

USA



Win Probability Difference

Treatment	Win Probability Estimate (SE)	Estimate (SE)	97.5% CI ¹	Combined p-value ²
Larsucosterol 30 mg (N=73)	28.1% (4.3)	15.3% (6.9)	(-0.002, 0.308)	0.0265
Placebo (N=77)	12.7% (3.2)			
Larsucosterol 90 mg (N=77)	27.4% (3.9)	10.7% (7.1)	(-0.052, 0.266)	0.1308
Placebo (N=77)	16.7% (3.5)			

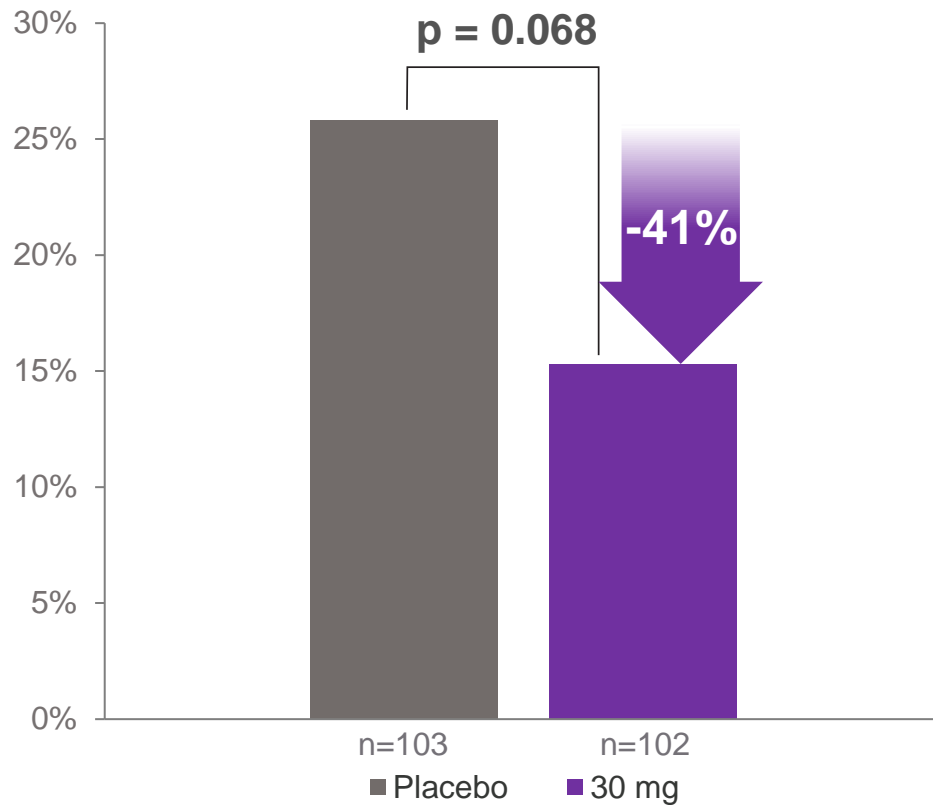
*Primary endpoint was analyzed using a hierarchical assessment of patient outcomes to calculate a win probability for each of the 30 mg and 90 mg doses of larsucosterol compared with placebo. Win probability was calculated on the hierarchy of alive and transplant-free being superior to transplant and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

1. Confidence levels for treatment comparisons have a 97.5% level to give an overall 95% level of confidence in both treatment comparisons.

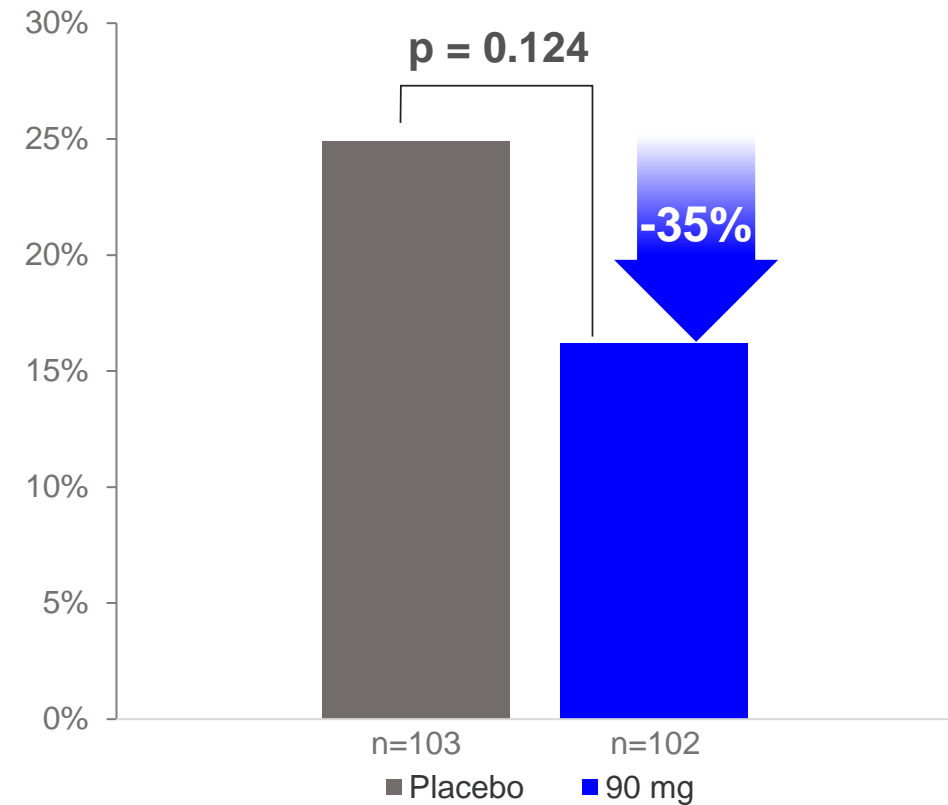
2. P-value computed by a large-sample normal test using the combined Win Probability difference divided by its standard error to test the null hypothesis that the Win probability difference between larsucosterol and placebo at Day 90 in the population is 0.

Results: Mortality at 90 Days (Global)

Mortality at 90 Days 30 mg Larsucosterol vs. Placebo



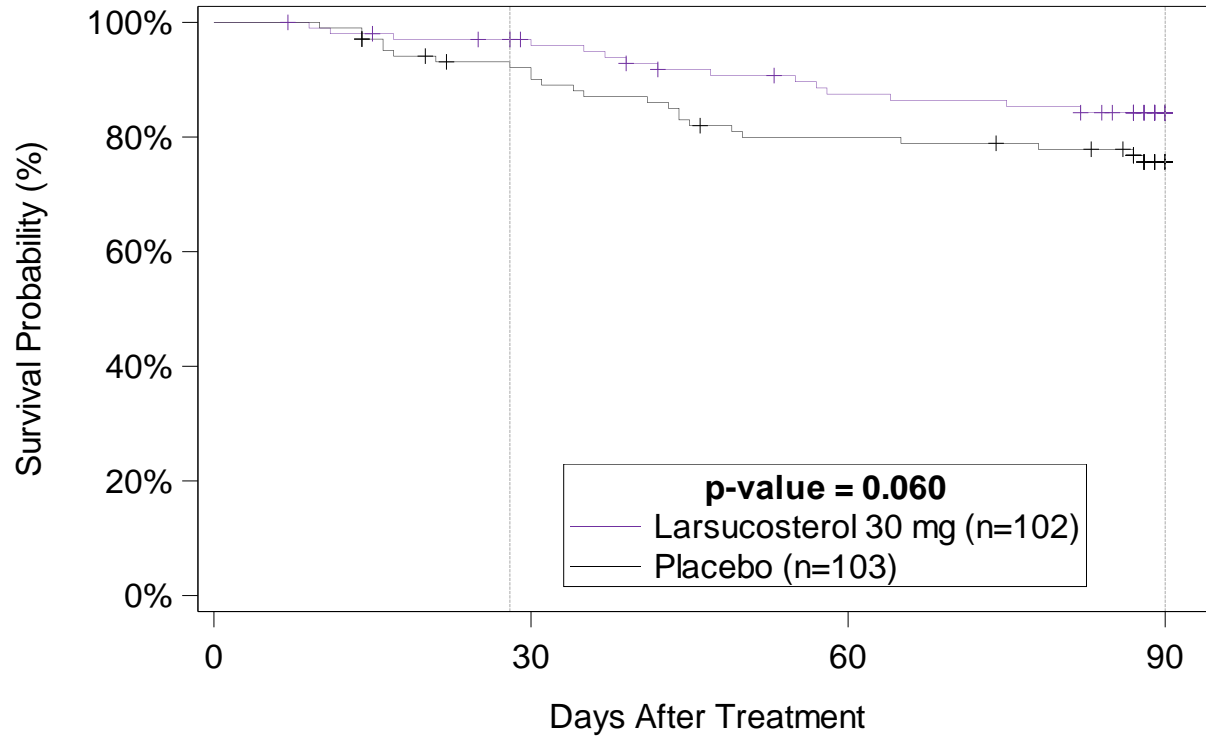
Mortality at 90 Days 90 mg Larsucosterol vs. Placebo



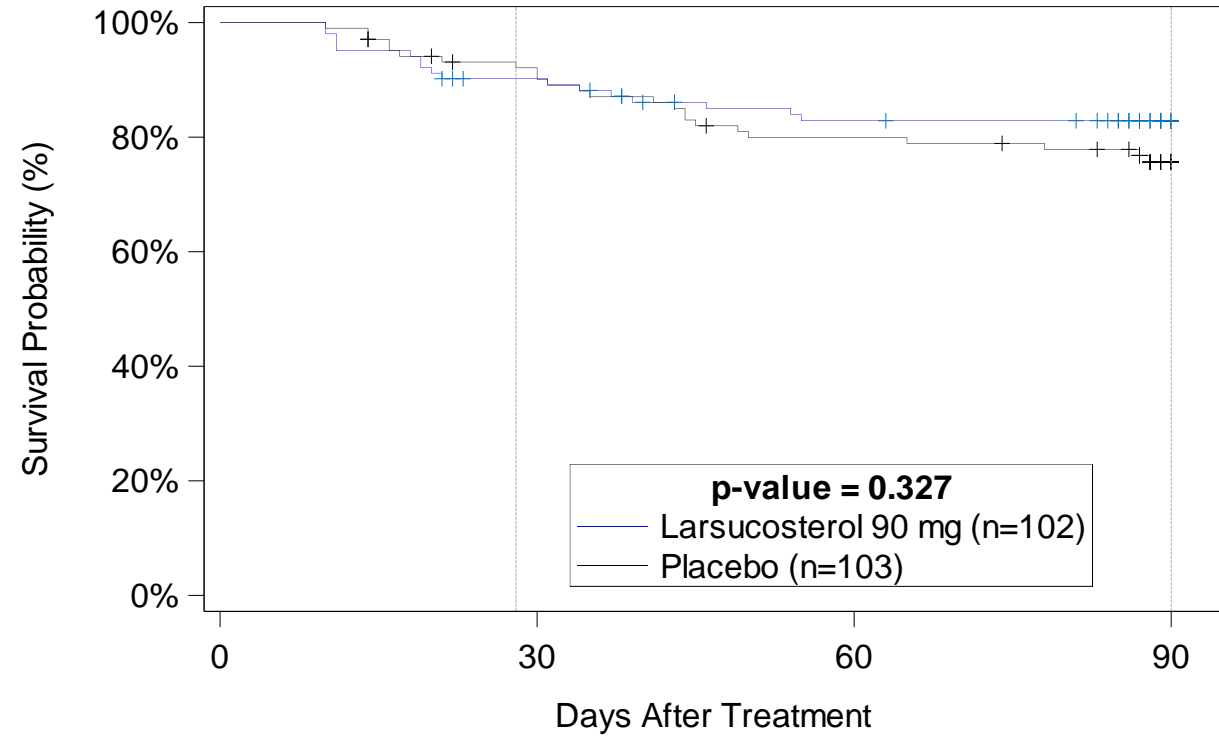
Intent-to-treat (ITT) includes patients with missing 90-day outcome data.
The analyses were adjusted to account for subjects with missing outcome data by the method of multiple imputations.

Results: 90-day Survival (Global)

Kaplan-Meier Analysis (Actual) 30 mg Larsucosterol vs. Placebo



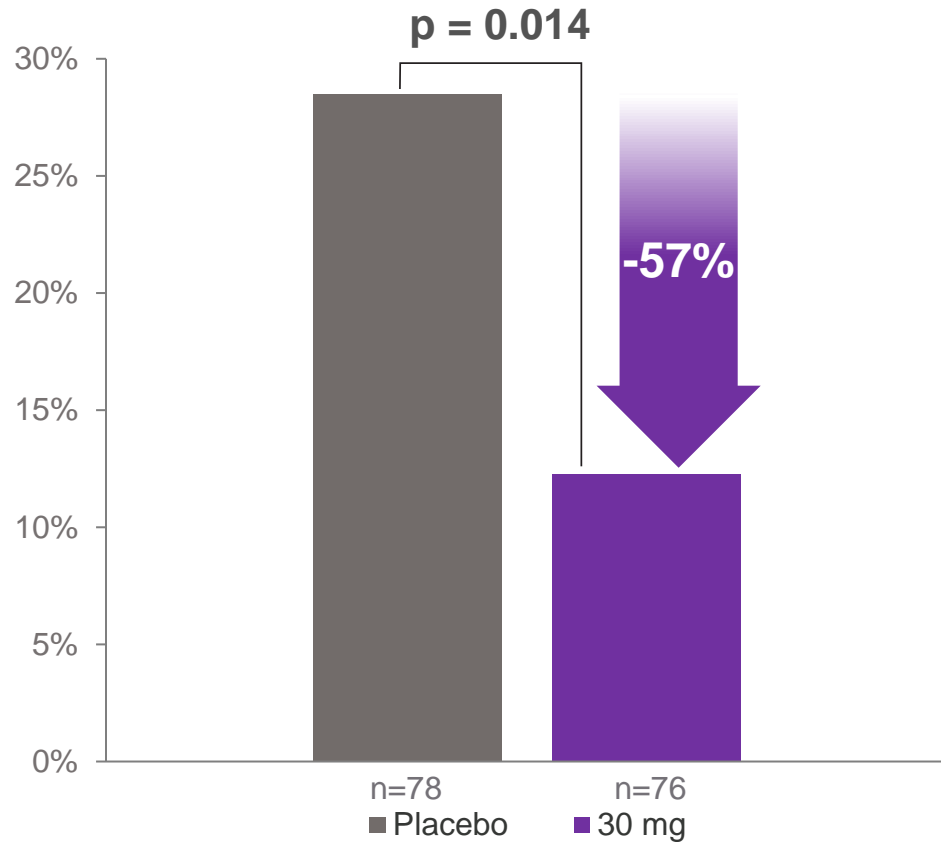
Kaplan-Meier Analysis (Actual) 90 mg Larsucosterol vs. Placebo



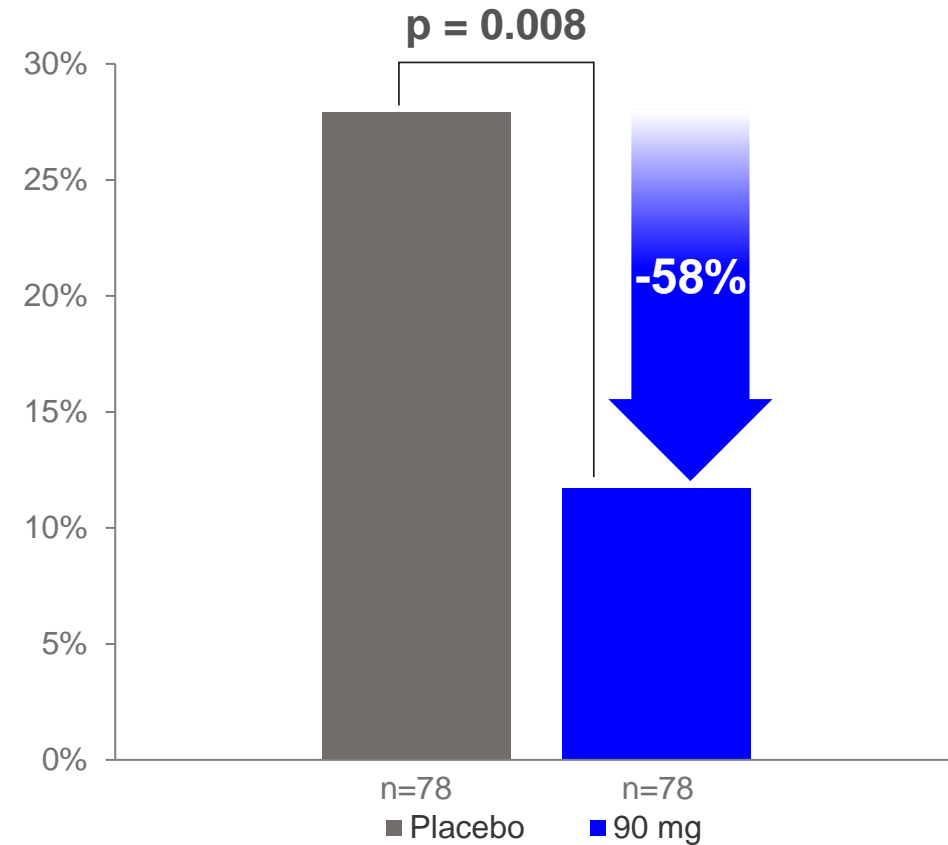
Results: Mortality at 90 Days (USA)



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



Mortality at 90 Days – U.S. Patients 90 mg LARUCOSTEROL vs. Placebo

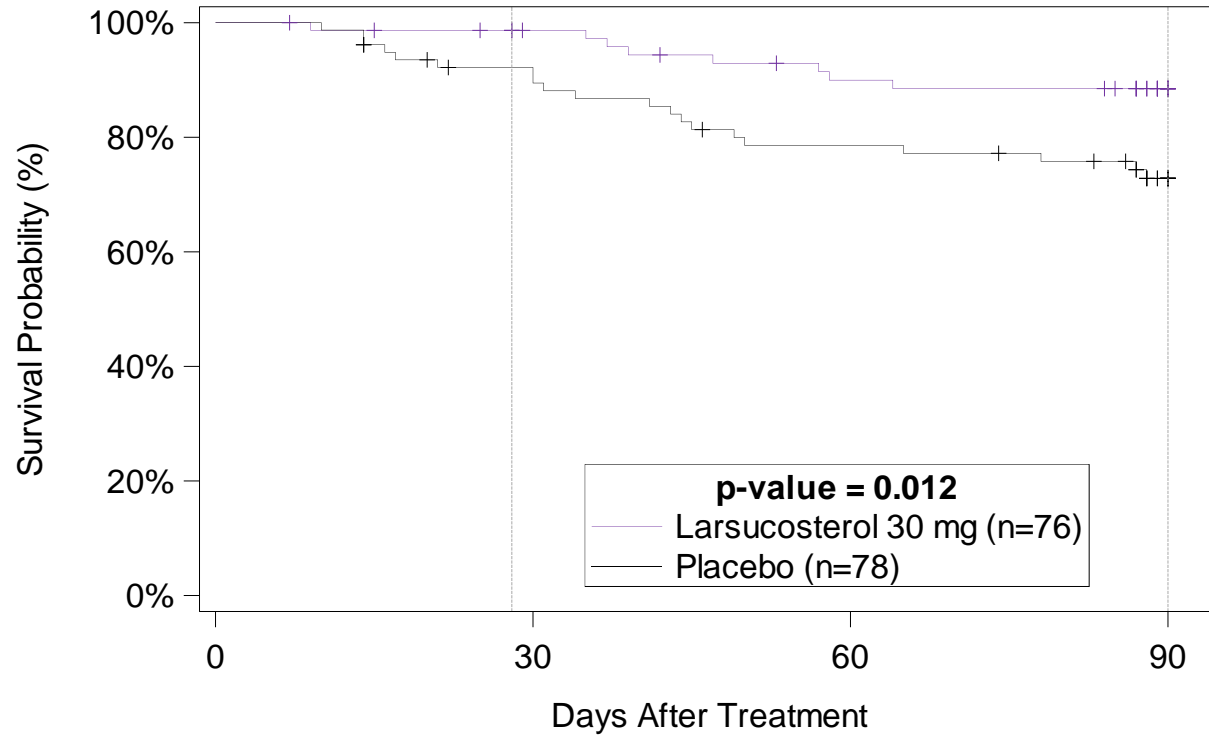


Intent-to-treat (ITT) includes patients with missing 90-day outcome data.
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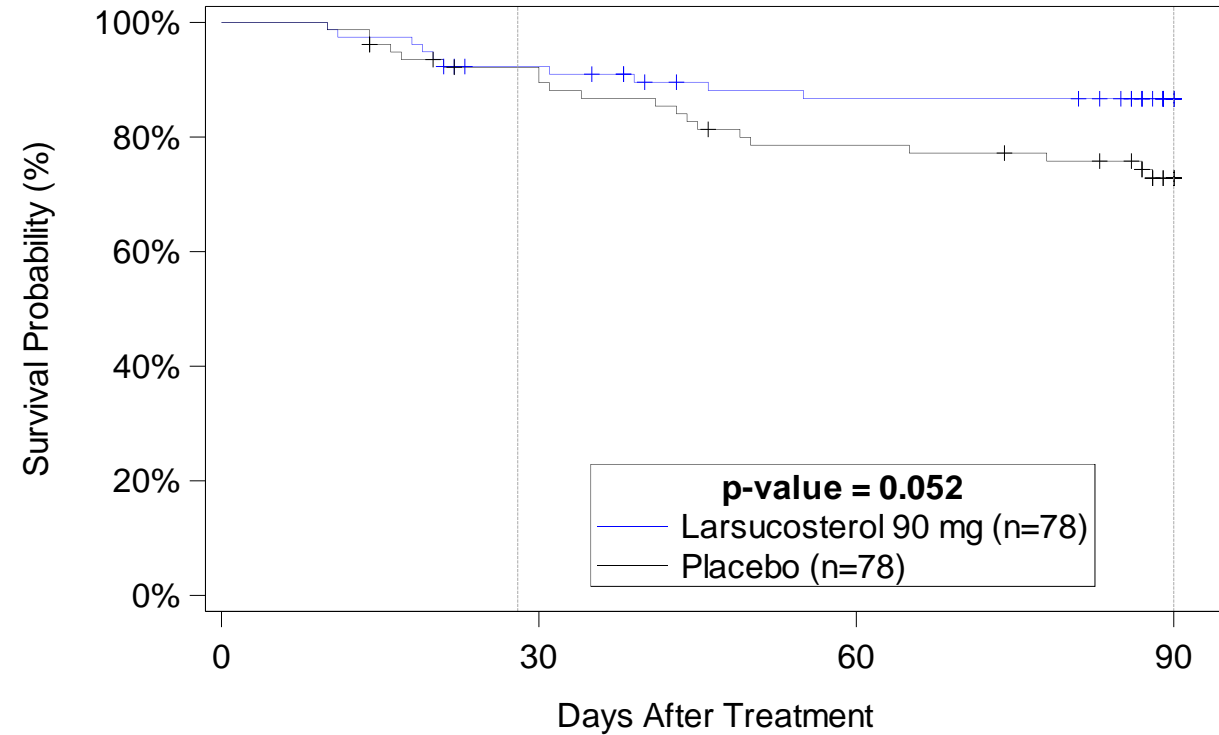
Results: 90-day Survival (USA)



Kaplan-Meier Analysis (Actual) 30 mg Lارسucosterol vs. Placebo



Kaplan-Meier Analysis (Actual) 90 mg Lارسucosterol vs. Placebo



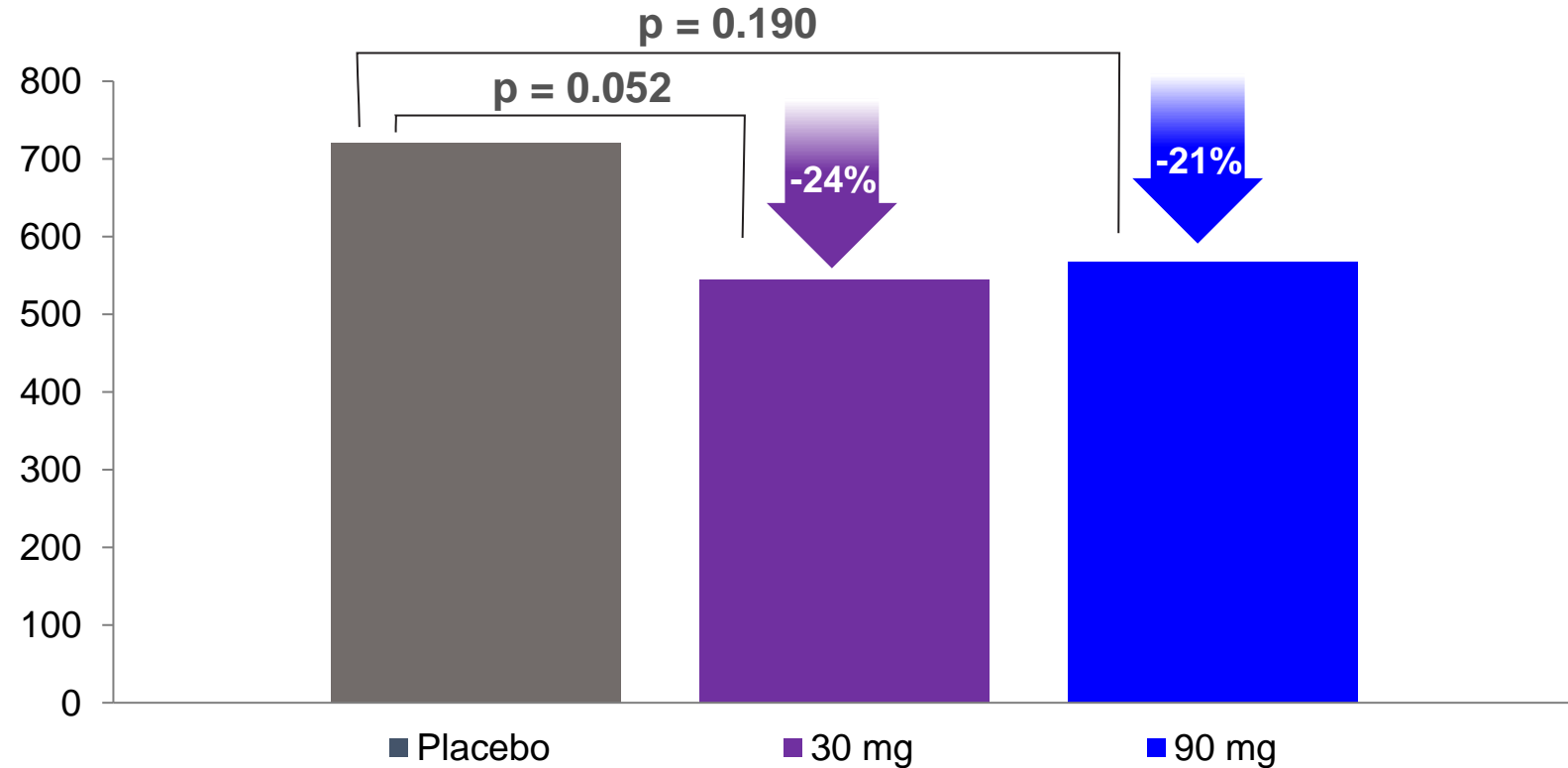
Results: Larsucosterol Treatment Emergent Adverse Events Summary

	Placebo N=102	Larsucosterol 30mg N=100	Larsucosterol 90mg N=99	
Summary of Treatment Emergent Adverse Events: Patient N (%), Events N				
>= 1 TEAE	99 (97.1), 721	92 (92.0), 545	94 (94.9), 567	
TEAE Severity Mild	21 (20.6), 378	21 (21.0), 254	23 (23.2), 257	
TEAE Severity Moderate	32 (31.4), 213	34 (34.0), 191	22 (22.2), 209	
TEAE Severity Severe	46 (45.1), 130	37 (37.0), 100	49 (49.5), 101	
Not Drug Related TEAE	54 (52.9), 551	56 (56.0), 429	57 (57.6), 463	
Unlikely Drug Related TEAE	37 (36.3), 157	27 (27.0), 103	31 (31.3), 98	
Possibly Drug Related TEAE	8 (7.8), 13	9 (9.0), 13	6 (6.1), 6	
Probably Drug Related TEAE	0 (0.0), 0	0 (0.0), 0	0 (0.0), 0	
>= 1 TESAE	60 (58.8), 111	53 (53.0), 120	63 (63.6), 115	
>= 1 Drug Related TESAE	0 (0.0), 0	0 (0.0), 0	0 (0.0), 0	
TEAE Leading to Death	28 (27.5), 39	16 (16.0), 28	22 (22.2), 31	
Non-fatal TEAE Leading to Study Withdrawal	0 (0.0), 0	0 (0.0), 0	0 (0.0), 0	
Summary of Newly-occurred Severe Liver Disease Complications: N (%)				
Day 28	Overall	49 (48.0)	39 (39.0)	43 (43.4)
	Ascites	16 (15.7)	20 (20.0)	14 (14.1)
	Gastrointestinal Bleeding (All)	13 (12.7)	5 (5.0)	12 (12.1)
	Hepatic Encephalopathy	18 (17.6)	9 (9.0)	15 (15.2)
	Acute Kidney Injury	18 (17.6)	21 (21.0)	24 (24.2)
	Sepsis	6 (5.9)	7 (7.0)	7 (7.1)
	Respiratory failure	1 (1.0)	2 (2.0)	5 (5.1)
	Multi-organ failure	1 (1.0)	0 (0.0)	0 (0.0)
Day 90	Overall	61 (59.8)	53 (53.0)	52 (52.5)
	Ascites	25 (24.5)	31 (31.0)	14 (14.1)
	Gastrointestinal Bleeding (All)	16 (15.7)	12 (12.0)	16 (16.2)
	Hepatic Encephalopathy	20 (19.6)	16 (16.0)	21 (21.2)
	Acute Kidney Injury	21 (20.6)	24 (24.0)	28 (28.3)
	Sepsis	10 (9.8)	14 (14.0)	7 (7.1)
	Respiratory failure	3 (2.9)	5 (5.0)	5 (5.1)
	Multi-organ failure	4 (3.9)	2 (2.0)	0 (0.0)

Results: Larsucosterol Safety (Global)

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

Treatment Emergent Adverse Events by Treatment Arm



Summary

- AHFIRM was a global, randomized, placebo-controlled trial in 307 subjects with severe AH in the US, EU, UK, and Australia (~75% US patients)
- AHFIRM demonstrated compelling 90-day mortality reduction with larsucosterol in both dose groups (30mg, 90mg) compared to Placebo
 - In the US, both larsucosterol groups exhibited statistically significant >50% reduction in 90-day mortality
- The primary endpoint of 90-day mortality or liver transplant did not reach statistical significance
 - In the US, the Win Ratio primary endpoint analysis in the 30mg larsucosterol group resulted in $p=0.0265$
- Larsucosterol was well-tolerated and both dose groups had numerically fewer treatment emergent adverse events than placebo
- The US Food and Drug Administration has granted Breakthrough Therapy designation to larsucosterol for the treatment of AH. A Phase 3 trial is planned.

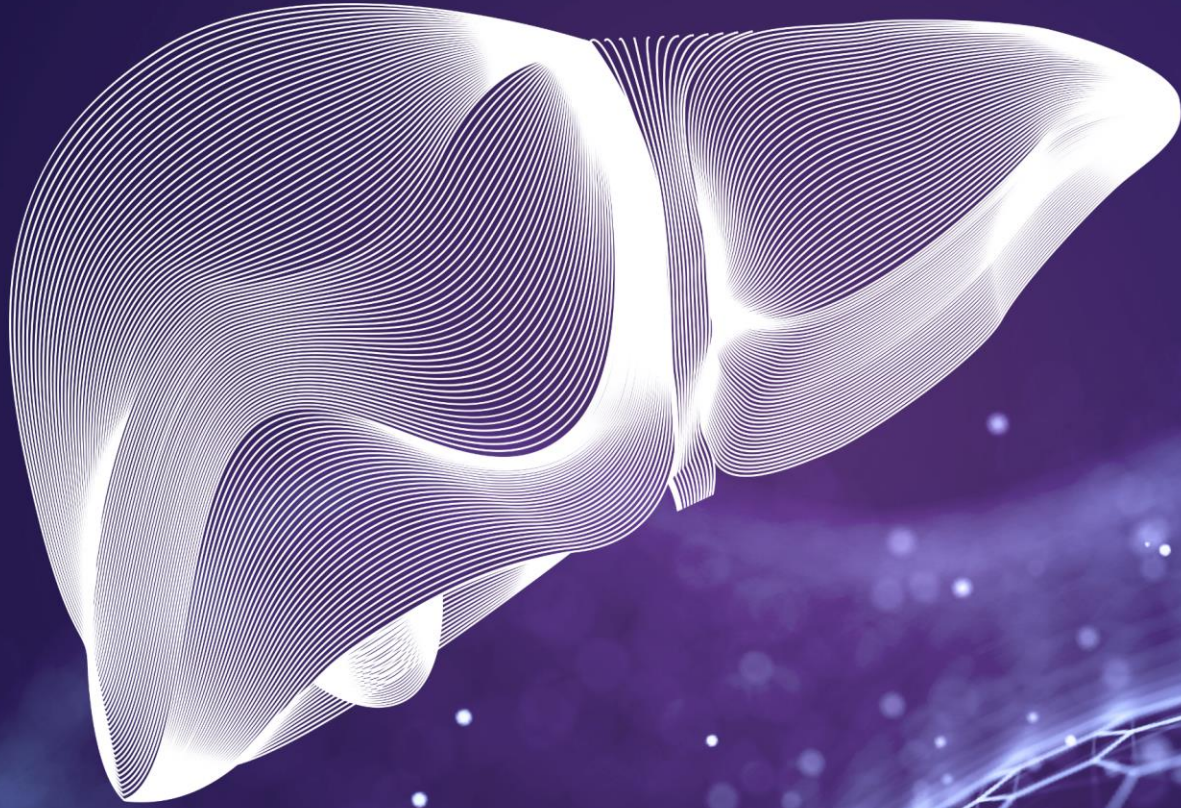
Acknowledgments

We extend our thanks to the patients, their families and all participating investigators and study teams.

AHFIRM Principal Investigators:

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This study was funded by DURECT Corporation



EASL

Milan, Italy
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Thank You