Larsucosterol for Treatment of Severe Alcohol-associated Hepatitis

— Impact of Hospitalization-to-Treat Time

Stein L[1] , Shiffman M[2], Da B[3], Goel A[4], Kwong A[4], Moreno C[5], Nicoll A[6], Mehta A[7], Louvet A[8], Flamm S[9], Pyrsopoulos N[10], Satapathy S[11], Kuo A[12], Ganger D[13], Aloman C[14], Strasser SI[15], Tse E[16], Russo MW[17], Rockey DC[18], Gray M[19], Mitchell M[20], Thursz M[21], Krebs W[22], Scott D[23], Blevins C[23], Ellis D[23], Brown J[23], Sussman NL[23], Lin WQ[23]

1. Piedmont Transplant Institute, 2. Bon Secours Liver Institute, 3. Northwell Health (now Merck), 4. Stanford University, 5. Université Libre de Bruxelles, 6. Eastern Health and ECRU, 7. Methodist Liver Institute, Dallas, 8. University Hospital of Lille, 9. Rush University, 10. Rutgers University (now NYU), 11. Northwell Health, 12. Cedars Sinai Medical Center, 13. Northwestern University, 14. Rush University (now Westchester Medical Center), 15. Royal Prince Alfred Hospital, 16. Royal Adelaide Hospital, 17. Atrium Health Wake Forest, 18. Medical University of S. Carolina, 19. University of Alabama, 20. University of Texas Southwestern, 21. Imperial College, 22. Consultant, 23. DURECT Corporation (Sponsor)

Poster #3040 and #3104 for additional information on AHFIRM

AASLD The Liver Meeting®

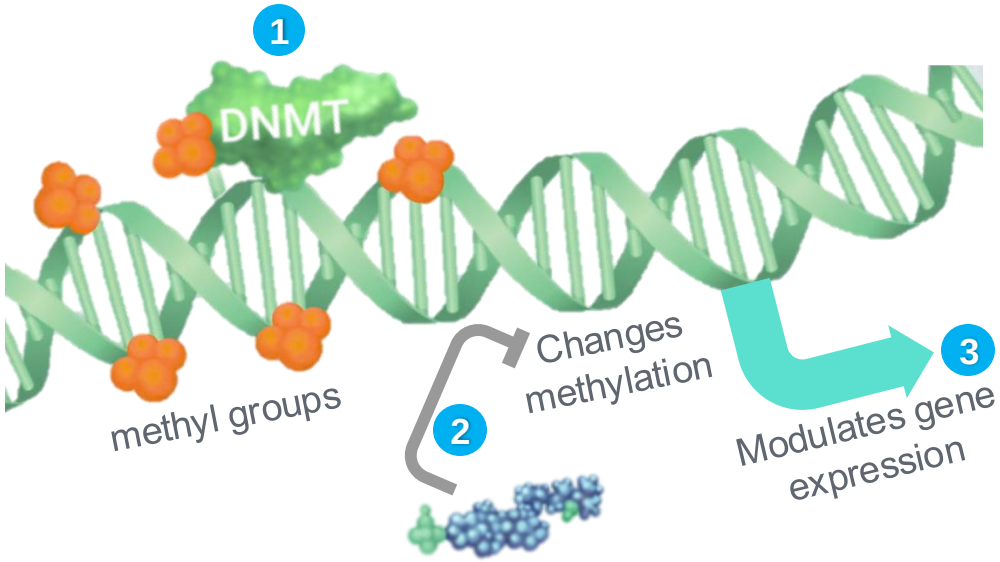
Conflict of Interest

- Research
  DURECT, Ocelot, River 2 Renal, Akero, Versantis, Novo Nordisk
- Consultant
  Intercept, Orphalan, Mallinckrodt
- Speaker
  AbbVie, Gilead, Intercept, Ipsen, Madrigal

The AHFIRM Trial was sponsored by DURECT Corporation

Larsucosterol for Alcohol-associated Hepatitis (AH)

Severe AH: an Unmet Medical Need



Alcohol Induces Epigenetic Changes:
DNA methyltransferase (DNMT) activities and DNA methylation are altered in the livers of patients with AH

1. Aberrant DNA methylation disrupts cellular functions and interactions, resulting in liver injury and failure[1-5]
2. Larsucosterol inhibits DNMTs, modulates DNA methylation and transcription
3. Improves cellular functions, including reducing lipid accumulation, regulating immune and oxidative responses, inhibiting cell death, and promoting liver regeneration.

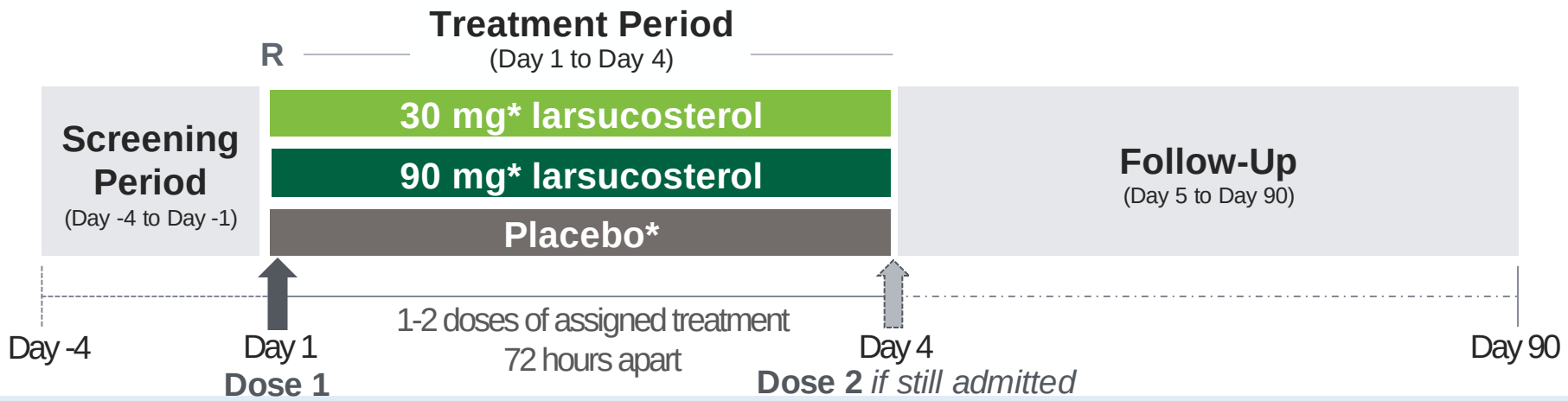
1. Liu et al., Exp Mol Pathol 2014;97(2):234-240; 2. Shen et al., Exp Mol Pathol. 2015;99(2):326-329; 3. Argemi et al., Nat Commun. 2019;10(1):3126; 4. Niinep et al., Front Genet. 2021;12:750142; 5. Zheng et al., Int J Mol Sci. 2023;24(12):10130; 6. Wang Y, Journal of Lipid Research. 2021; 62: 100063

AASLD The Liver Meeting®

AHFIRM Trial Design

- **Key Inclusion Criteria: Severe AH subjects** with MDF score ≥ 32 and MELD scores 21-30
- 307 subjects, enrolled from 62 sites in US, EU, AU, and UK, 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

AASLD The Liver Meeting®

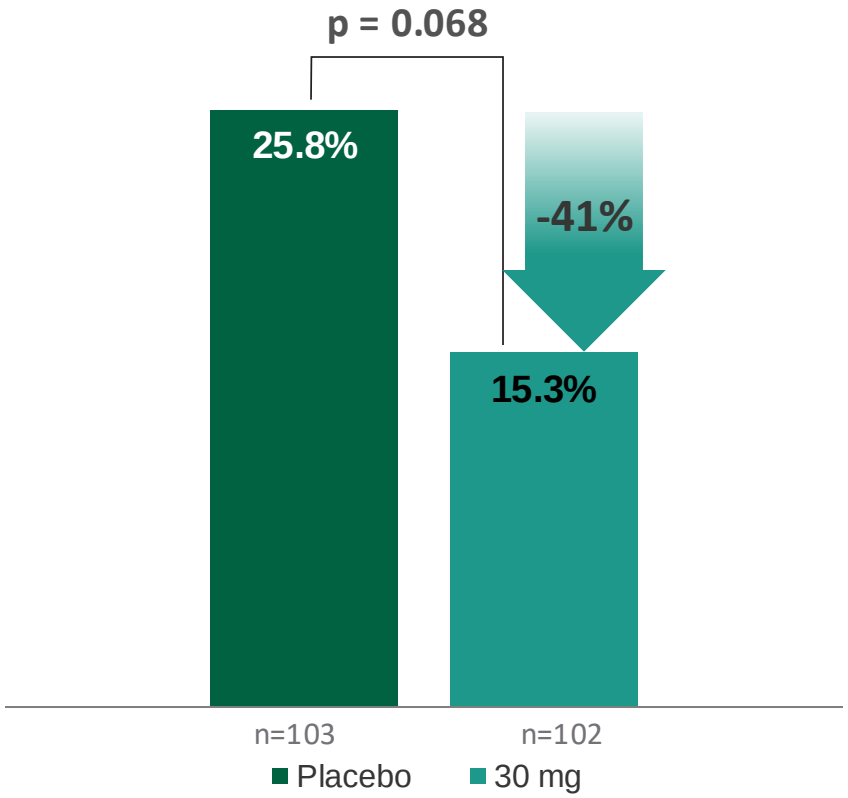
Enrollment by Treatment Group & Region

N (%)	Placebo	Larsucosterol 30 mg	Larsucosterol 90 mg
Total	**102**	**99**	**101**
US	77 (75.5)	73 (73.7)	77 (76.2)
EU	7 (6.9)	11 (11.1)	8 (7.9)
UK	1 (1.0)	5 (5.1)	2 (2.0)
AU	17 (1.7)	10 (10.1)	14 (13.9)

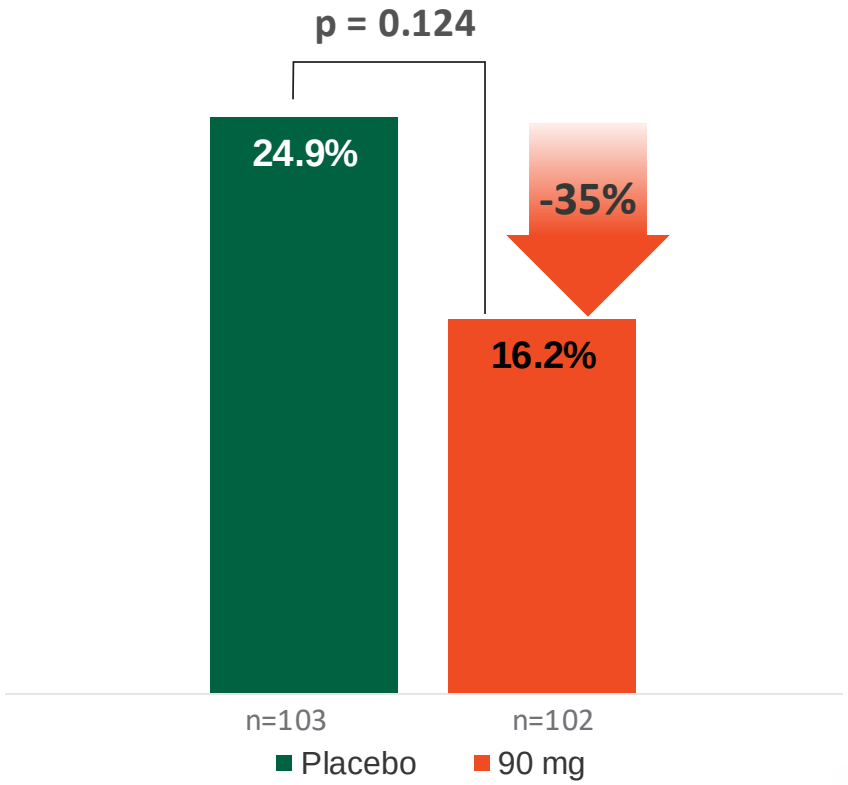
The trial did not meet statistical significance for the primary endpoint, 90-day death or liver transplant

Reduction of 90-Day Mortality – Global (ITT)

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



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

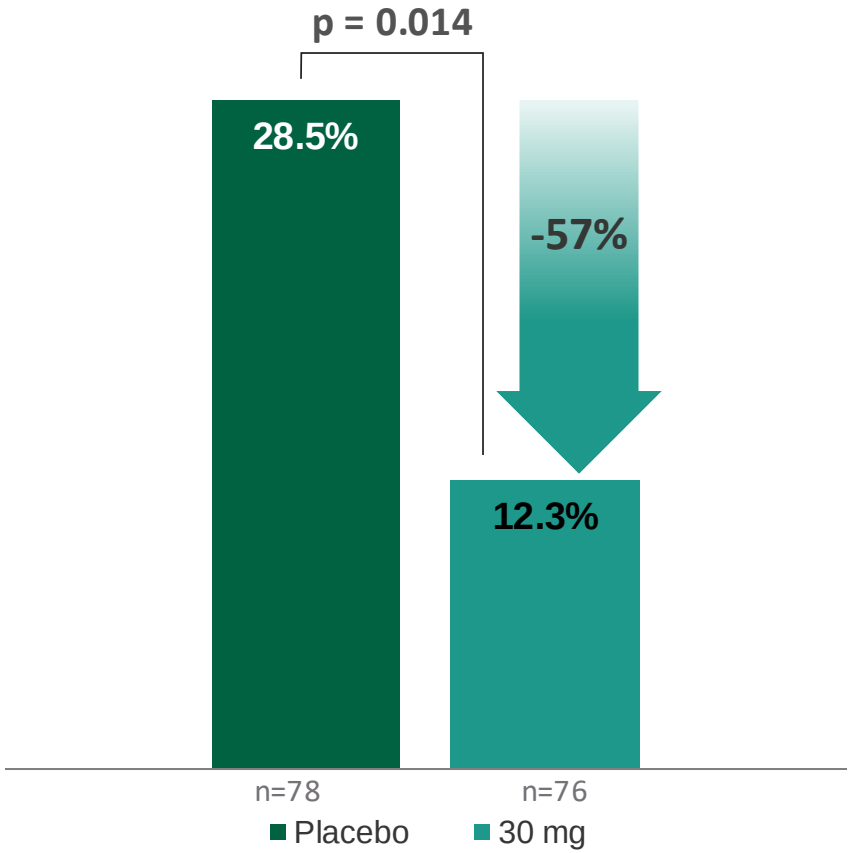


[1] Sites with enrollment <5 patients were pooled resulting in different mortality rates for placebo compared with 30 mg and 90 mg larucosterol doses. ITT includes 5 patients with missing 90-day outcome data. The analyses were adjusted by the method of multiple imputations to account for these subjects.

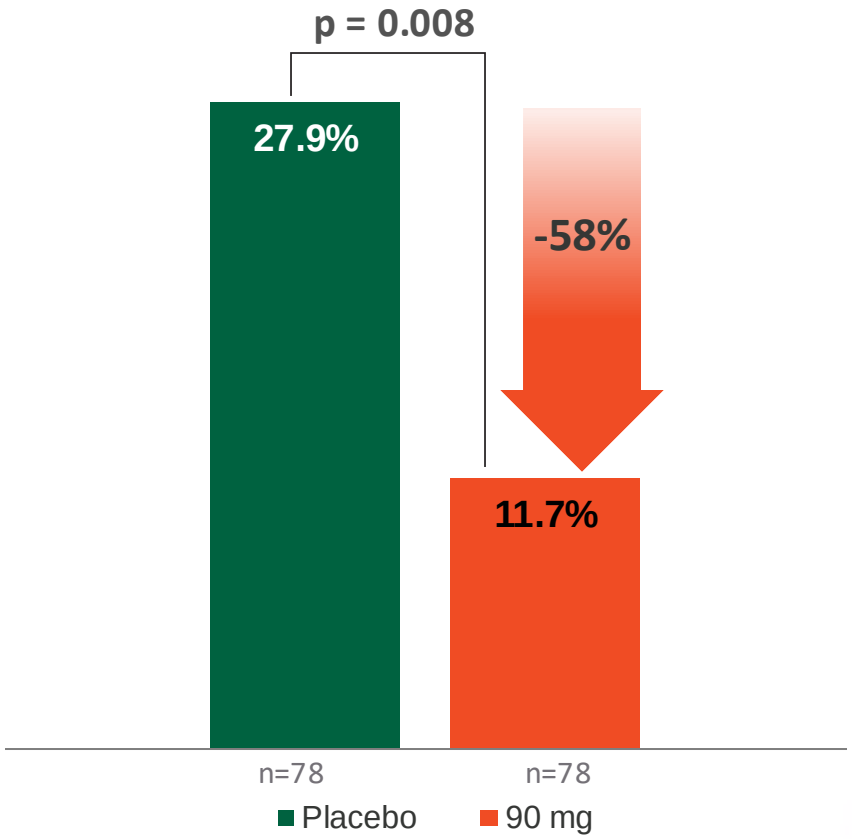
AASLD The Liver Meeting®

Reduction of 90-Day Mortality – 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]



[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.

AASLD The Liver Meeting®

AHFIRM Trial Outcomes

- The trial did not meet statistical significance for the primary endpoint
- The key secondary endpoint, 90-day mortality, was reduced
- Larsucosterol was well tolerated (fewer TEAEs than in Placebo)
- Considerable regional differences were observed

Observed Regional Differences

- Small sample sizes in non-US regions
- Asymmetric randomization in non-US regions
- Patient characteristics such as age & ethnicity
- Patient drinking behavior
- Days from hospital admission to the first dose of treatment

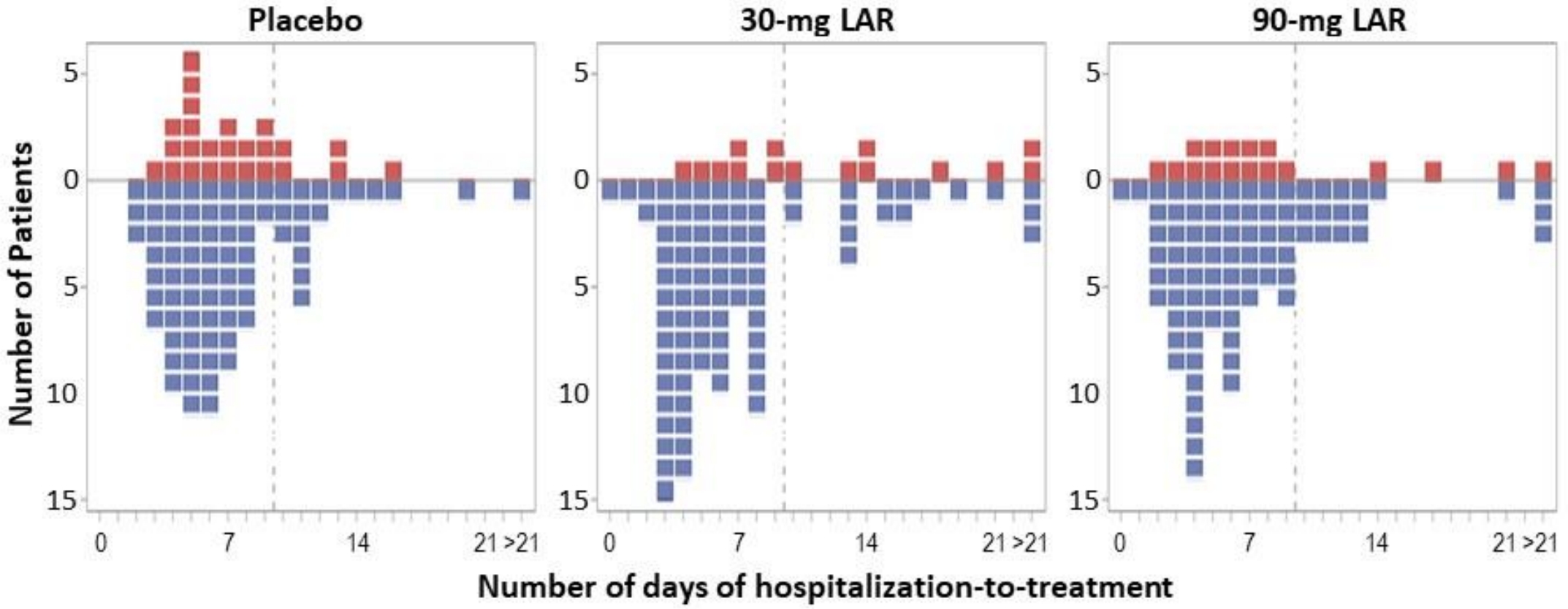
Hospitalization-to-Treatment Days by Region

Region	N	Minimum	1st Quartile	Median	3rd Quartile	Maximum
United States	232	1	4	**5**	9	58
European Union	26	4	8	**13**	15	19
Great Britain	8	3	7	**11**	18	34
Australia	41	2	6	**7**	9	47

Among all patients, 75% were treated <10 days of hospitalization.

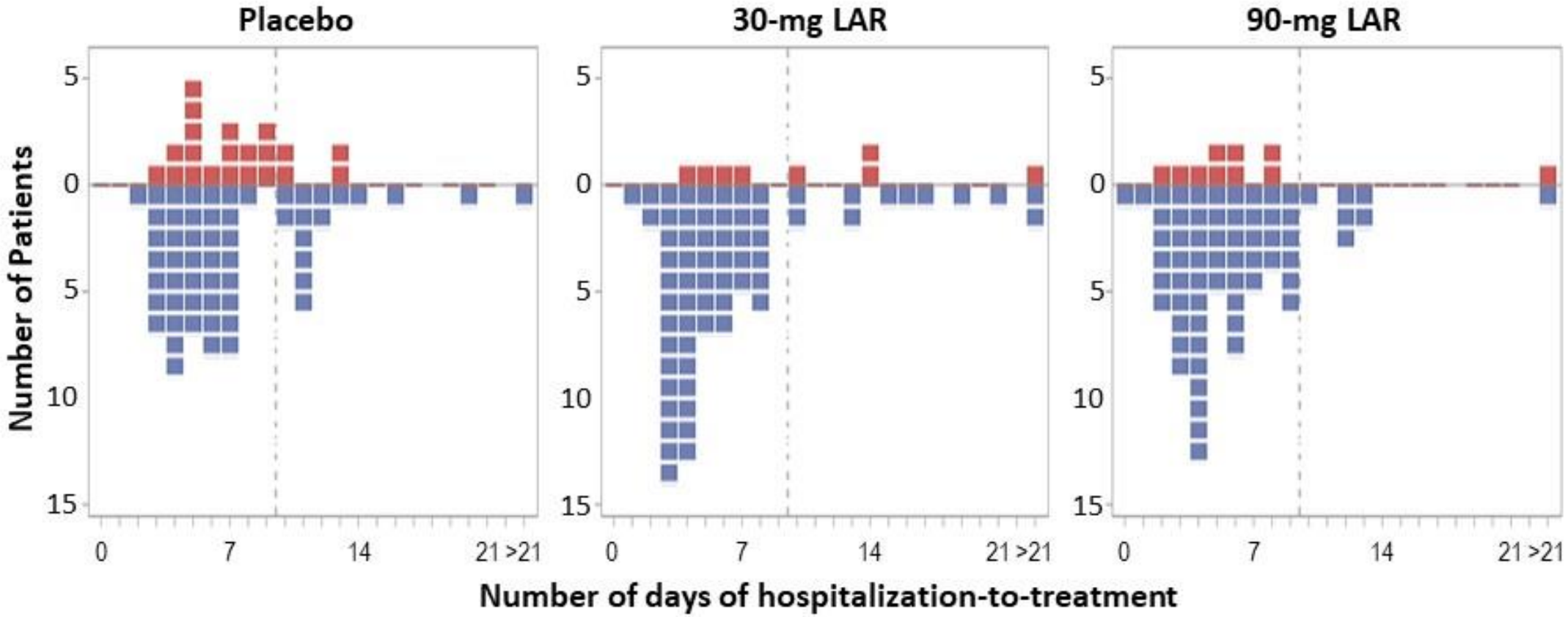
AASLD The Liver Meeting®

Hospitalization-to-Treatment — Global Data



The Liver Meeting®

Hospitalization-to-Treatment — US Data



The Liver Meeting®

Outcomes of Patients Treated in <10 Days of Hospitalization

Global Data			
	Placebo	**30-mg LAR**	**90-mg LAR**
Number	79	74	77
Death (%)	20 (25.3)	7 (9.5)	13 (16.9)
Transplant (%)	2 (2.5)	5 (6.8)	7 (9.1)
90-day Death or Transplant **p-value**		**0.053**	**0.602**
90-day Mortality **p-value**		**0.010**	**0.197**
US Data			
Number	57	57	66
Death (%)	17 (29.8%)	4 (7.0)	9 (13.6)
Transplant (%)	2 (3.5)	5 (8.8)	7 (10.6)
90-day Death or Transplant **p-value**		**0.015**	**0.155**
90-day Mortality **p-value**		**0.002**	**0.028**

Summary

- Both larsucosterol-treated groups had better 90-day survival rates than the placebo group
- One of the obvious regional differences observed was the time from hospital admission to the first dose of larsucosterol
  - The median number of days from hospital admission to the 1st dose was shortest in the US
  - Patients treated <10 days of admission had the better outcomes, especially in the 30-mg larsucosterol group

Conclusions and Next Steps

- Larsucosterol is well tolerated in patients with severe AH
- Larsucosterol improves survival in patients with severe AH
- The efficacy of larsucosterol is further improved by early treatment
- The Phase 3 trial will include a requirement for treatment in <10 days after index hospital admission

Acknowledgements

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

AHFIRM Principal Investigators:

Laura Alba, Costica Aloman, Amon Asgharpour, Sumeet Asrani, Marc Bourlière, Robert Brown, Stephen Caldwell, Matt Cave, Paul Clark, Ben Da, Srinivasan Dasarathy, Janet Dearden, Ashwin Dhanda, Steve Flamm, Juan Gallegos, Daniel Ganger, Aparna Goel, Russell Goodman, Stuart Gordon, Meagan Gray, Ahmet Gurakar, Tarek Hassanein, Gene Im, Rajiv Jalan, Vandana Khungar, Kevin Korenblat, Alexander Kuo, Charles Landis, Alexandre Louvet, Gerry Macquillan, Ashwini Mehta, Fernando Membreno, Mack Mitchell, Tim Mitchell, Christophe Moreno, Kate Muller, Amanda Nicoll, Gulshan Parasher, Nikolaos Pyrsopoulos, Vikrant Rachakonda, K Gautham Reddy, Fredric Regenstein, Fedja Rochling, Don Rockey, Natasha Von Roenn, Mark Russo, Sanjaya Satapathy, Rohit Sawhney, Esperence Schaefer, Courtney Sherman, Kirti Shetty, Mitchell Shiffman, Coleman Smith, Margaret Sozio, Lance Stein, Simone Strasser, Rise Stribling, Vinay Sundaram, Norah Terrault, Thierry Thevenot, Julie Thompson, Mark Thursz, Edmund Tse, Hugo Vargas, David Victor III, Martin Weltman

This study was funded by DURECT Corporation

AASLD The Liver Meeting®