Larsucosterol (DUR-928) – DURECT's Drug Candidate for Alcohol-Associated Hepatitis (AH)[1,2]

- Larsucosterol: an endogenous sulfated oxysterol and an epigenetic regulator[1,2]
- Endogenous epigenetic regulators are naturally occurring compounds in the body that operate within the nucleus of the cell to modulate gene expression without modifying the underlying DNA sequence[1]
- Larsucosterol epigenetically modulates the expression of multiple clusters of master genes that are involved in many important cell signaling pathways, through which it stabilizes mitochondria, reduces lipotoxicity, regulates inflammatory or stress responses, and promotes cell survival[1]

Encouraging Results of Larsucosterol in a Phase 2a Study in AH[3] - Phase 2b Trial (AHFIRM) Ongoing[4]

Survival	100% of patients (n=19) treated with larsucosterol, including 15 patients with severe AH (DF ≥32*), survived the 28-day follow-up period vs 26% historical 28-day mortality rate[3,5]
Safety	No drug-related SAEs at 30, 90, or 150 mg doses (administered intravenously once or twice during the study period) with no drug-related serious adverse events[3]
Time to Discharge	74% of patients treated with larsucosterol discharged in under 4 days after a single dose[3]
Bilirubin	Patients with the most elevated bilirubin at baseline (serum bilirubin >8 mg/dL) had a median reduction from baseline of 25% by day 7 and 48% by day 28[3] (Bilirubin levels are used as a marker of liver health. Higher than normal levels of total bilirubin are an indicator of liver dysfunction.)[6]

Prognostic Indicators of Mortality	**MELD** (Model for End-Stage Liver Disease)[7]
	• Patients with MELD scores of 11-20 are classified as having moderate AH
	• Patients with MELD scores of 21-30 are classified as having severe AH
	• Patients with MELD scores of 15 or higher are candidates for liver transplant[8]
	Median reduction from baseline in MELD among all larsucosterol-treated patients was over 2 points and among those with baseline bilirubin levels >8 mg/dL was 5 points by day 28[3]
	
	Lille: AH patients with Lille <0.45 have an 85% 6-month survival rate (SR) vs 25% SR when Lille >0.45[9]
	• Lille overall response rate: superior response rate (RR) in hospitalized AH patients for larsucosterol: 89% vs standard of care RR: 53%[2]
	• Lille in severe AH patients[3]
	  • Significantly lower Lille scores of severe AH patients (MELD 21-30) treated with 30 mg or 90 mg of larsucosterol vs historical control of severe AH patients treated with steroids[10]
	  • MELD 21-30: 83% overall RR including all doses and 100% RR at 30 mg or 90 mg dose of larsucosterol
	  • DF ≥ 32*: 87% overall RR including all doses and 100% RR at 30 mg or 90 mg dose of larsucosterol
	*DF (Maddrey's discriminant function) is the traditional model for evaluating the severity and prognosis in alcoholic hepatitis. DF ≥32 implies poor outcome with steroid treatment with one-month mortality ranging between 35% to 45%[11].

Larsucosterol is an investigational product and has not been approved by the FDA for marketing in the U.S. for any indication.

1. Wang Y, et al. *J Lipid Res.* 2021;62:1-14. **2.** DURECT. Data on file. **3.** Hassanein T, et al. Presented at: AASLD 2019. November 8-12, 2019. **4.** ClinicalTrials.gov identifier: NCT04563026. Accessed February 22, 2022. **5.** Hughes E, et al. *PLoS One*. 2018;13:1-10. **6.** Guerra Ruiz AR, et al. *Adv Lab Med.* 2021;2:352-361. **7.** Singal AK, et al. *J Hepatol.* 2018;69:534-543. **8.** UNOS. Questions & answers for transplant candidates about MELD and PELD. Accessed February 22, 2022. https://www.unos.org/wp-content/uploads/unos/MELD_PELD.pdf. **9.** Louvet A, et al. *Hepatology*. 2007;45:1348-1354. **10.** McClain C, et al. Presented at: AASLD 2019. November 8-12, 2019. Poster 1376. **11.** Akriviadis E, et al. *Gastroenterology*. 2000;119:1637-1648.