What is Acute Alcoholic Hepatitis (AH)?

- A **life-threatening acute alcoholic liver disease** (ALD) caused by chronic heavy alcohol use[1] and a recent increase in alcohol consumption (e.g., a binge)
- Characterized by **severe inflammation and destruction of liver tissue** (i.e., necrosis)
- AH **may occur suddenly** after binge drinking, potentially leading to life-threatening complications, including liver failure, acute renal injury and multi-organ failure

AH causes more than 122,000 US hospitalizations per year[2]

The cost related to treating AH is estimated at >$50,000 per patient in the first year[3]

A larger number of younger adults have been diagnosed in recent years as a result of increasing heavy drinking and binge drinking prevalence[6]

Prognosis: Average 28-day overall mortality rate of 26%[4]

AH can affect both women and men

More than half of the people diagnosed with AH are between 40 and 60 years old[5]

AH patients typically have a history of daily alcohol use of:

>40g alcohol/day (female), which is about 3 standard drinks, for 6 months or longer[7,8]

or

>60g alcohol/day (male), which is about 4 standard drinks, for 6 months or longer[7,8]

What is a Standard Drink?*

12 fl oz of regular beer
about 5% alcohol

8-9 fl oz of malt liquor
about 7% alcohol

5 fl oz of table wine
about 12% alcohol

1.5 fl oz shot of distilled spirits
about 40% alcohol

Individuals with a sudden increase in alcohol intake or intermittent heavy drinking may also be affected[7,8]

AH can also be developed in patients with a much shorter history of heavy alcohol use[7,8]

Common symptoms include

- Nausea
- Vomiting blood
- Loss of appetite
- Fever
- Fatigue and weakness
- Rapid onset of jaundice (yellowing of skin or eyes)
- Negative changes in mental state

Acute severe cases may lead to life-threatening complications, including acute renal injury, liver failure and multi-organ failure associated with systemic inflammatory responses

Current treatments are limited and/or generally ineffective

No FDA approved therapies

Stopping alcohol consumption is not sufficient for recovery in many moderate and severe patients[9]

Treatments to reduce liver inflammation, such as corticosteroids, have no benefit in survival shown at 90 days or 1 year, and have demonstrated an increased risk of infection (STOPAH trial); only 25 to 45% of AH patients are eligible for these drugs[10]

Liver transplantation is becoming more common for alcoholic liver disease patients, including AH patients; the procedure involves a long waiting period, a burdensome selection process and costs more than $800,000[11]

No improvement in AH mortality in > 4 decades[12]

[1]Singal, et al., 2018, American Journal of Gastroenterology, 175-194.
[2]US Department of Health and Human Services' Healthcare Cost and Utilization Project reports https://hcupnet.ahrq.gov (accessed Oct 2020).
[3]Thompson, et al., 2018, Alcohol, 57-63.
[4]Hughes, et al., 2018, PLOS ONE.
[5]Alcoholic hepatitis. Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/17853-alcoholic-hepatitis.
[6]Dwyer-Lindgren, et al., 2015, American Journal of Public Health, 1120-1127.
[7]Friedman, et al., 2018, UptoDate.
[8]Diagnosis and Treatment of Alcohol-Related Liver Diseases, 2019, Practice Guidance from the American Association for the Study of Liver Diseases, 48.
[9]Gastroenterol Hepatol (N Y). 2017 Jul; 13(7): 425–427.
[10]Singal, et al., 2018, Journal of Hepatology, 534-543.
[11]Bentley, T.S. and Phillips, S.J. 2017 U.S. organ and tissue transplant cost estimates and discussion (Milliman Research Report, 2017).
[12]National Institute of Alcohol Abuse and Alcoholism, accessed April 2, 2019.

Each beverage portrayed above represents one drink (or one alcohol drink equivalent), defined in the United States as any beverage containing 0.6 fl oz or 14 grams of pure alcohol. The percentage expressed here as alcohol by volume (alc/vol) varies within and across beverage types. Although the standard drink amounts are helpful for the following health guidelines, they may not reflect customary serving sizes.

DURECT

DUR-928 – DURECT's Drug Candidate for AH with Demonstrated Therapeutic Potential

- DUR-928: an endogenous sulfated oxysterol and an epigenetic regulator
- 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
- DUR-928 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

Encouraging Results of DUR-928 in a Phase 2a Study in AH[13] - Phase 2b Clinical Trial Planned to Start in 2020

The open label, multi-center, dose escalation Phase 2a clinical study demonstrated DUR-928's potential to improve liver health and function for AH patients:

Survival	100% of patients (n=19) treated with DUR-928, including 15 patients with severe AH (DF ≥ 32*), survived the 28-day follow-up period vs 26% historical 28-day mortality rate
Safety	Well tolerated at 30, 90 or 150 mg doses (administered intravenously once or twice during the study period) with no drug-related serious adverse events
Time to Discharge	74% of patients treated with DUR-928 discharged within 4 days or less of treatment after 1 dose
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 (Bilirubin levels are used as a marker of liver health. Higher than normal levels of total bilirubin are an indicator of liver dysfunction.)

Prognostic Indicators of Mortality	**MELD** (Model for End-Stage Liver Disease):
	• 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[14]
	Median reduction from baseline in MELD among all DUR-928 treated patients was over 2 points and among those with baseline bilirubin levels >8 mg/dL was 5 points by day 28
	
	LILLE: AH patients with Lille <0.45 have an 85% 6-month survival rate (SR) vs. 25% SR when Lille >0.45[15]
	• Lille overall response rate: superior response rate (RR) in hospitalized AH patients for DUR-928: 89%[12] vs. standard of care RR: 53%[16]
	• Lille in severe AH patients:
	  • Significantly lower Lille scores in severe AH patients (MELD 21-30) treated with 30mg or 90mg of DUR-928 vs. historical control severe AH patients treated with steroids[17]
	  • MELD 21-30: 83% overall RR including all doses and 100% RR at 30mg or 90mg dose of DUR-928
	  • DF ≥ 32*: 87% overall RR including all doses and 100% RR at 30mg or 90mg dose of DUR-928

*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%[18].

[13]Hassanein, et al. 2019, Late-Breaking Presentation at AASLD The Liver Meeting®.
[14]Questions and answers for transplant candidates about MELD and PELD. United Network for Organ Sharing. https://unos.org/wp-content/uploads/unos/MELD_PELD.pdf.
[15]Louvet, et al., 2007, Hepatology, 1348-1354.
[16]Historical control from contemporaneous Univ. of Louisville study in 15 similar AH patients treated with standard of care.
[17]McClain, et. al., 2019, AASLD The Liver Meeting® poster presentation.
[18]Akriviadis, et al., 2000, Gastroenterology, 1637–1648.

DURECT

DUR-928 is an investigational product and has not been approved by the FDA for marketing in the U.S. for any indication