A PHASE 2B TRIAL IN ALCOHOL-ASSOCIATED HEPATITIS TO EVALUATE THE SAFETY AND EFFICACY OF LARSUCOSTEROL TREATMENT (AHFIRM)

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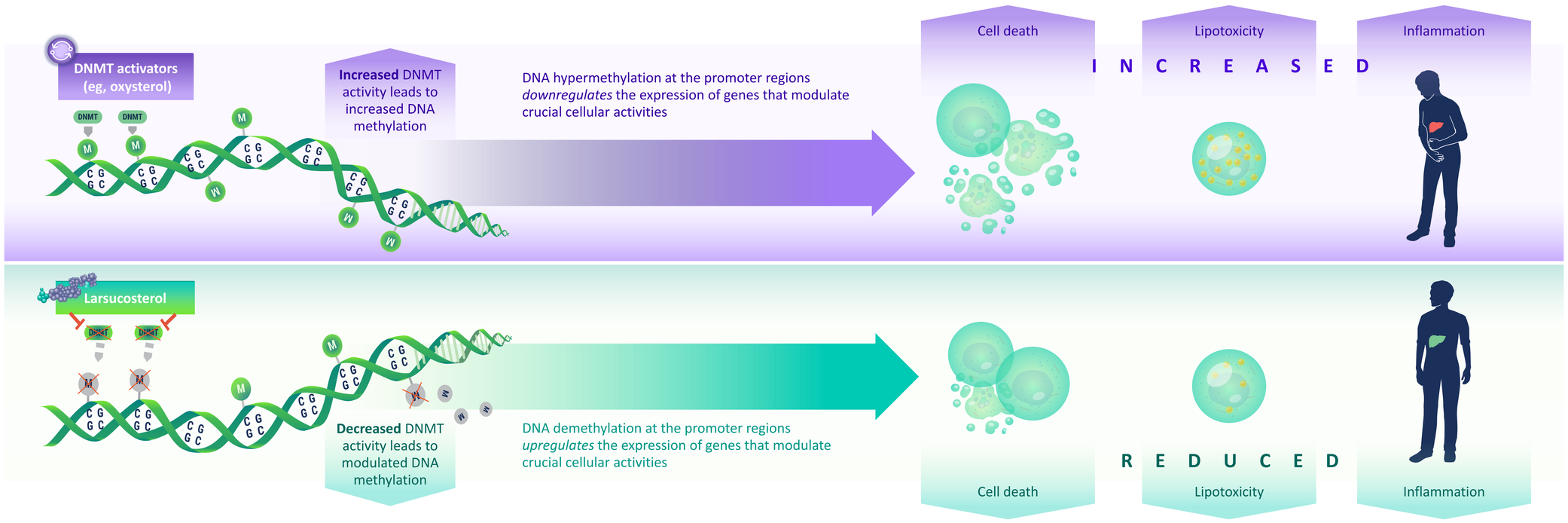
BACKGROUND

- Alcohol-associated hepatitis (AH) is an acute, life-threatening form of alcohol-associated liver disease (ALD).[1,2] AH accounted for ~137,000 hospitalizations in 2019 in the US, and approximately 30% of patients die within 90 days of hospital admission.[3,4]
- Healthcare costs and resource utilization are significant among hospitalized AH patients. The average charge for patients discharged from hospitalization was about $53,000, while the average charge for patients who died during hospitalization was about $147,000.[3]
- There are no FDA-approved therapies for AH; thus, new and innovative therapies are urgently needed.
- Larsucosterol is an endogenous, epigenetic modulator that reduces DNA hypermethylation by inhibiting the activity of methylating enzymes (known as DNA methyltransferases) (DNMT)1, DNMT3a, and DNMT3b to potentially reduce lipotoxicity, stabilize mitochondria, reduce inflammation, and improve cellular function (Figure 1).[5] These properties give it the potential to change the course of acute and chronic organ injury.
- In a phase 2a trial, larsucosterol demonstrated its potential to improve liver health and function in patients with moderate to severe AH; all patients survived through the 28-day follow-up period.[6] Larsucosterol is currently being evaluated in a phase 2b trial, AHFIRM.[7]

Figure 1. Larsucosterol Mechanism of Action[5]



STUDY DESIGN[7]

- AHFIRM is a phase 2b, randomized, double-blind, placebo-controlled, multiarm trial with approximately 70 international sites (US, Europe, UK, and Australia).
- The study has been open to accrual since January 2021 and is on track to complete enrollment in the second quarter of 2023.
- At least 300 subjects will be enrolled into 1 of 2 active arms with larsucosterol 30 mg administered intravenously (IV) or 90 mg IV vs placebo + standard of care with or without steroids at the discretion of the investigator in a 1:1:1 ratio (Figure 2).
- The study will enroll severe AH patients with Maddrey's discriminant function (Maddrey's DF) score ≥32 and Model for End-Stage Liver Disease (MELD) score 21-30.

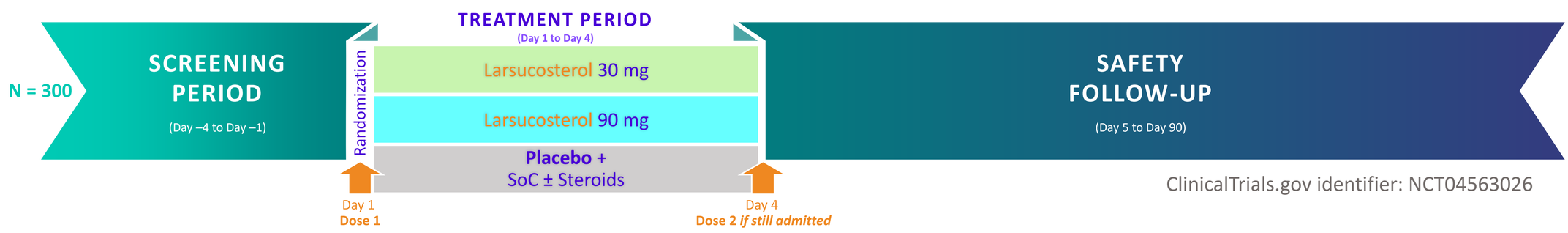
Primary Endpoint

- Difference in 90-day mortality or liver transplant between IV larsucosterol, 30 or 90 mg, and placebo

Secondary Endpoints

- Difference in 90-day mortality between IV larsucosterol, 30 or 90 mg, and placebo
- Difference in 28-day mortality or liver transplant between IV larsucosterol, 30 or 90 mg, and placebo
- Difference in 28-day mortality between IV larsucosterol, 30 or 90 mg, and placebo

Figure 2. AHFIRM Phase 2b Study Design[7]



ClinicalTrials.gov identifier: NCT04563026

KEY ELIGIBILITY CRITERIA[7]

Inclusion Criteria

- ≥18 years of age
- Onset of jaundice within prior 8 weeks
- Average daily consumption of >40 (females) or >60 (males) grams of alcohol for ≥6 months with <8 weeks of abstinence before the onset of jaundice
- The determination of AH may be based on typical serum chemistry (as determined by local laboratory) or liver biopsy at any time during the current episode of AH:
  - Serum total bilirubin >3.0 mg/dL
  - 50 < aspartate transaminase (AST) < 400 IU/L
  - Alanine aminotransferase (ALT) <400 IU/L
  - AST/ALT >1.5
- Maddrey's DF score ≥32 assuming a control prothrombin time of 12 seconds
- MELD score 21-30
- Liver biopsy not required but may be used to confirm the diagnosis of AH at the investigator's discretion. Biopsy, if used as a diagnostic criterion, must have occurred during the current episode

Exclusion Criteria

- Subjects taking systemic corticosteroids for a duration exceeding 8 days in the 30 days prior to screening
- Subjects experiencing or considered at high risk for alcohol withdrawal seizures or delirium tremens
- Active infection (such as spontaneous bacterial peritonitis, urinary tract infection, bacteremia, acute viral hepatitis, uncontrolled human immunodeficiency virus, and active SARS-CoV-2 infection)
- Serum creatinine >2.5 mg/dL
- Subjects undergoing continuous veno-venous hemodialysis
- Uncontrolled gastrointestinal bleeding
- A history of preadmission refractory ascites (defined as more than 4 paracenteses in the previous 8 weeks despite diuretic therapy)
- Liver biopsy (if carried out) with findings not compatible with AH
- Stage ≥3 hepatic encephalopathy by West Haven criteria

Note: Other protocol-defined inclusion/exclusion criteria may apply.

REFERENCES

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ACKNOWLEDGMENTS

We extend our thanks to the patients, family, friends, and caregivers, as well as to the study staff. This study was funded by the Durect Corporation.

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