# DURECT Announces Peer-Reviewed Article Accepted for Publication with Additional Data from Previously Completed Phase 2a Study of Larsucosterol in Alcohol-Associated Hepatitis

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*Data expands upon previously reported results, including individual patient data, additional liver biomarkers, and comparisons to matching arms from a contemporaneous study*

*Company on track to report data from ongoing Phase 2b AHFIRM trial in 2H 2023*

CUPERTINO, Calif., April 10, 2023 /PRNewswire/ — DURECT Corporation (Nasdaq: DRRX), a biopharmaceutical company focused on developing epigenetic modulator programs for the treatment of acute organ injury and chronic liver diseases, today announced that additional data from the company's previously completed Phase 2a trial evaluating larsucosterol in alcohol-associated hepatitis (AH) has been accepted by the peer-reviewed journal *American Journal of Gastroenterology*. In addition to previously reported safety and efficacy data from the 19-patient, open label Phase 2a trial, the publication includes cross-study comparisons of severe AH patients from the Phase 2a trial with two matching comparison arms from a contemporaneous study conducted by the DASH (Defeat Alcoholic Steatohepatitis) Consortium. The two well-matched comparison arms consist of an 8-patient observational arm (Observational Arm) and a separate 16-patient steroid-treated arm (Study-Steroid Arm). Both comparison arms received standard-of-care including corticosteroids. The full article, entitled "Safety, Pharmacokinetics, & Efficacy Signals of Larsucosterol (DUR-928) in Alcohol-associated Hepatitis," can be accessed here. Supplemental tables and figures referred to in the article will be available in the final print publication.

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Lille scores from 8 severe AH patients who received 30 or 90 mg of larsucosterol were compared with patients from two study arms, the observational arm (n=8) and a larger parallel comparison arm (n=16) in the contemporaneous NIH-funded DASH study. Patients from both comparative arms were diagnosed with AH and screened for inclusion and exclusion criteria that were similar to the larsucosterol trial and treated with standard-of-care, including corticosteroids. In addition, they were matched by MELD score to the 8 severe AH patients who received 30 or 90 mg of larsucosterol. **Represents p<0.01 by T-test.

"The Phase 2a study showed very promising efficacy signals of larsucosterol in AH patients, with all patients surviving the 28-day follow-up period," said Tarek Hassanein, M.D., Professor of Medicine at University of California San Diego Health, Medical Director of Southern California Research Center, and the lead author of the study. "This is an extremely encouraging result considering that approximately a quarter of AH patients entering hospitals don't survive longer than a month, an outcome that has not improved in the past 50 years."

Craig McClain, M.D., Professor of Departments of Medicine and Pharmacology & Toxicology, Distinguished University Scholar at University of Louisville, and co-corresponding author of the article, commented, "The efficacy signals from this Phase 2a study compared favorably with two matched arms of AH subjects treated with standard of care, including steroids, from a contemporaneous study of the DASH Consortium. We hope that this novel drug, larsucosterol, will provide much needed treatment for a disease process having very high morbidity and mortality for which there is currently no FDA-approved therapy."

James E. Brown, D.V.M., President and CEO of DURECT, added “We are excited to announce the acceptance of this peer-reviewed publication of our Phase 2a AH trial which provides further expert support of the data and larsucosterol’s potential for the treatment of AH patients. We look forward to building upon this positive safety and efficacy data as we complete our ongoing Phase2b AHFIRM trial. We are approaching our target enrollment of 300 patients and anticipate topline data in 2H 2023. Larsucosterol’s mechanism of action as an epigenetic modulator is different from any other treatment previously evaluated for AH, tying directly into the biology of the disease. We believe AHFIRM, if it is successful, has the potential to support an NDA filing. With FDA Fast Track Designation, our goal is to advance larsucosterol to approval as quickly as possible in the U.S. and other regions.”

**Key results from the article are highlighted below:**

- **Survival:** 100% of patients (n=19) treated with larsucosterol, including 12 patients with severe AH, survived the 28-day follow-up period compared to a historical 28-day mortality rate of 26%.
- **Safety**: Larsucosterol was well-tolerated and safe at the three doses studied (30, 90, and 150 mg) when administered as one or two intravenous infusions in subjects with moderate or severe AH. The drug exposure was not affected by the disease severity and was dose proportional.
- **Time to discharge:** 74% of patients treated with larsucosterol were discharged in under 4 days after a single dose.
- **Serum bilirubin:** Rapid reductions from baseline of serum total bilirubin levels were observed at both Day 7 and Day 28 after larsucosterol dosing, including significant reductions from baseline in moderate AH patients at day 7 and in severe AH patients at day 28.
- **Model of End Stage Liver Disease (MELD) Score:** Reductions of MELD scores from baseline were observed at Day 7 and Day 28. At Day 28, patients with moderate AH had statistically significantly lower MELD scores at Day 28 and those with severe AH had MELD scores that decreased from baseline at Day 28 but did not achieve statistical significance.
- **Lille score:** All 8 severe AH patients in the 30 or 90 mg dose cohorts were treatment responders (Lille score <0.45) and their Lille scores were statistically lower than those of well-matched patients from the Observational Arm and Study-Steroid Arm of the DASH Consortium trial in a cross-study comparison (see figure).
- **Liver biomarkers:** Both AST and ALT enzymes decreased rapidly in severe AH patients in the 30 or 90mg dose cohorts, with ALT being statistically significantly lower than those in the DASH patients in a cross-study comparison.

**About the Larsucosterol AH Phase 2a Trial**
Patients with moderate and severe AH were treated with larsucosterol intravenously in this open label, dose escalation, U.S. multi-center, Phase 2a clinical trial. Final enrollment was 19 patients and comprised of: 8 patients (4 moderate and 4 severe) who received 30 mg, 7 patients (3 moderate and 4 severe) who received 90 mg, and 4 patients (4 severe) who received 150 mg of larsucosterol. The study objectives included assessment of safety, pharmacokinetics (PK) and efficacy signals, including liver chemistry and biomarkers.

**About the AHFIRM Trial**
Enrollment is ongoing in our Phase 2b randomized, double-blind, placebo-controlled, international, multi-center study in subjects with severe acute alcohol-associated hepatitis (**AH**) to evaluate sa**F**ety and eff**I**cacy of la**R**sucosterol (DUR-928) treat**M**ent (AHFIRM). The study is comprised of three arms targeting enrollment of 300 total patients, with approximately 100 patients in each arm: (1) Placebo plus supportive care, with or without methylprednisolone capsules at the investigators’ discretion; (2) larsucosterol (30 mg); and (3) larsucosterol (90 mg). Patients in the larsucosterol arms receive the same supportive care without steroids. In order to maintain blinding, patients in the two active arms receive matching placebo capsules if the investigator prescribes steroids. The primary outcome measure will be the 90-Day incidence of mortality or liver transplantation for patients treated with larsucosterol compared to those treated with placebo. DURECT is enrolling patients at more than 60 clinical trial sites across the U.S., EU, U.K., and Australia. Reflecting the life-threatening nature of AH and the lack of therapeutic options, the U.S. Food and Drug Administration (FDA) has granted larsucosterol Fast Track Designation for the treatment of AH. We believe a positive outcome in the AHFIRM trial could support a New Drug Application filing. For more information, refer to ClinicalTrials.gov Identifier: NCT04563026.

**About Alcohol-associated Hepatitis (AH)**
AH is an acute form of alcohol-associated liver disease (ALD), associated with long-term heavy intake of alcohol and often occurs after a recent period of increased alcohol consumption (i.e., a binge). AH is typically characterized by severe inflammation and destruction of liver tissue (i.e., necrosis), potentially leading to life-threatening complications including liver failure, acute kidney injury and multi-organ failure. There are no FDA approved therapies for AH and a retrospective analysis of 77 studies published between 1971 and 2016, which included data from a total of 8,184 patients, showed the overall mortality from AH was 26% at 28 days, 29% at 90 days and 44% at 180 days. A subsequent global study published in December 2021, which included 85 tertiary centers in 11 countries across 3 continents, prospectively enrolled 2,581 AH patients with a median Model of End-Stage Liver Disease (MELD)

score of 23.5, reported mortality at 28 and 90 days of approximately 20% and 31%, respectively. Stopping alcohol consumption is frequently not sufficient for recovery in many AH patients and treatments that reduce liver inflammation, such as corticosteroids, are limited by contraindications and have not been shown to improve survival at 90 days or one year, and have demonstrated an increased risk of infection. While liver transplantation is becoming more common for ALD patients, including AH patients, the procedure is available to a minority of AH patients, costs exceed $875,000 on average, and patients require lifelong immunosuppressive therapy to prevent organ rejection.

**About Larsucosterol (DUR-928)**
Larsucosterol is an endogenous sulfated oxysterol and an epigenetic modulator. Epigenetic regulators are compounds that regulate patterns of gene expression without modifying the DNA sequence. DNA hypermethylation, an example of epigenetic dysregulation, results in transcriptomic reprogramming and cellular dysfunction, and is reportedly associated with many acute (e.g., AH) or chronic diseases (e.g., NASH). As an inhibitor of DNA methyltransferases (DNMT1, DNMT3a and 3b), larsucosterol inhibits DNA hypermethylation, which subsequently modulates expression of genes that are involved in cell signaling pathways associated with stress responses, cell death and survival, liver regeneration, and lipid metabolism. This may ultimately lead to improved cell survival, reduced inflammation, and decreased lipotoxicity. As an epigenetic modulator, the proposed mechanism of action provides further scientific rationale for developing larsucosterol for the treatment of certain acute organ injuries and chronic diseases.

**About DURECT Corporation**
DURECT is a biopharmaceutical company committed to transforming the treatment of acute organ injury and chronic liver diseases by advancing novel and potentially lifesaving therapies based on its endogenous epigenetic regulator program. Larsucosterol (also known as DUR-928), DURECT's lead drug candidate, binds to and inhibits the activity of DNA methyltransferases (DNMTs), DNA-modifying enzymes that are elevated and associated with the hypermethylation found in patients with alcohol-associated hepatitis (AH). Larsucosterol is in clinical development for the potential treatment of AH, for which FDA has granted a Fast Track Designation. Non-alcoholic steatohepatitis (NASH) is also being explored. In addition, POSIMIR® (bupivacaine solution) for infiltration use, a non-opioid analgesic utilizing the innovative SABER® platform technology, is FDA-approved and has been exclusively licensed to Innocoll Pharmaceuticals for commercialization in the United States. For more information about DURECT, please visit www.durect.com and follow us on Twitter https://twitter.com/DURECTCorp.

**DURECT Forward-Looking Statements**
This press release contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, relating to: our plans to complete enrollment of the AHFIRM trial in the second quarter of 2023 and report topline data in the second half of 2023, the potential FDA approval of larsucosterol for the treatment of AH, the ability of a positive outcome in the AHFIRM trial to support a New Drug Application filing, the commercialization of POSIMIR by Innocoll, the potential to develop larsucosterol for AH, NASH or other indications, and the potential benefits, if any, of our product candidates. Actual results may differ materially from those contained in the forward-looking statements contained in this press release, and reported results should not be considered as an indication of future performance. The potential risks and uncertainties that could cause actual results to differ from those projected include, among other things, the risks that the AHFIRM trial takes longer to conduct than anticipated due to COVID-19 or other factors, the risk that ongoing and future clinical trials of larsucosterol do not confirm the results from earlier clinical or pre-clinical trials, or do not demonstrate the safety or efficacy of larsucosterol in a statistically significant manner, the risk that the FDA or other government agencies may require additional clinical trials for larsucosterol before approving it for the treatment of AH even if the results of the AHFIRM trial are successful, risks that Innocoll may not commercialize POSIMIR successfully, and risks related to the sufficiency of our cash resources, our anticipated capital requirements, our need or desire for additional financing, our ability to obtain capital to fund our operations and expenses and our ability to continue to operate as a going concern. Further information regarding these and other risks is included in DURECT's most recent Securities and Exchange Commission (SEC) filings, including its annual report on Form 10-K for the year ended December 31, 2022 under the heading "Risk Factors." These reports are available on our website www.durect.com under the "Investors" tab and on the SEC's website at www.sec.gov. All information provided in this press release and in the attachments is based on information available to DURECT as of the date hereof, and DURECT assumes no obligation to update this information as a result of future events or developments, except as required by law.

NOTE: POSIMIR® is a trademark of Innocoll Pharmaceuticals, Ltd. in the U.S. and a trademark of DURECT Corporation outside of the U.S. SABER® is a trademark of DURECT Corporation. Other referenced trademarks belong to their respective owners. Larsucosterol (DUR-928) is an investigational drug candidate under development and has not been approved for commercialization by the U.S. Food and Drug Administration or other health authorities for any indication.

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