DURECT Completes Enrollment in Phase 2b AHFIRM Trial of Larsucosterol in Alcohol-Associated Hepatitis

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Topline data anticipated in Q4 2023

CUPERTINO, Calif., June 7, 2023 /PRNewswire/ — DURECT Corporation (Nasdaq: DRRX), a biopharmaceutical company developing epigenetic therapies for the treatment of acute organ injuries and chronic liver diseases, today announced that it has completed enrollment in its Phase 2b AHFIRM clinical trial (NCT04563026) investigating larsucosterol for the treatment of patients with severe alcohol-associated hepatitis (AH), achieving its enrollment target of 300 patients.

“We are excited to have reached this critical milestone and look forward to reporting topline data, anticipated in the fourth quarter of 2023,” said James E. Brown, D.V.M., President and Chief Executive Officer of DURECT. “We are preparing to file a New Drug Application (NDA) for larsucosterol in AH pending a positive AHFIRM trial outcome and Food and Drug Administration (FDA) guidance, and hope to expedite regulatory discussions through the Fast Track Designation that DURECT was previously granted by the FDA. In parallel, we are working on the early stages of commercial launch planning in the U.S.”

Norman Sussman, M.D., FAASLD, Chief Medical Officer at DURECT, added, “If successful, we believe that larsucosterol will represent a treatment paradigm shift as the first FDA-approved therapy for patients with this lethal disease. About one-third of severe AH patients die within 90 days of hospitalization. We look forward to building on our positive Phase 2a trial in AH and working to potentially bring a long-awaited therapy to patients and the medical community.”

About the AHFIRM Trial
AHFIRM is a 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 treat**M**ent (AHFIRM). The study is comprised of three arms evaluating a total of approximately 300 subjects, 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 received the same supportive care without steroids. In order to maintain blinding, patients in the two active arms received matching placebo capsules if the investigator prescribed steroids. The primary outcome measure will be the 90-Day incidence of death or liver transplantation for patients treated with larsucosterol compared to those treated with placebo. The Company has enrolled 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 life-threatening form of alcoholic liver disease (ALD), which can occur in individuals who chronically misuse alcohol—frequently after increased consumption—regardless of age, gender, education or income status. AH is typically characterized by severe inflammation and destruction of liver tissue (i.e., necrosis), that can lead to life-threatening complications including liver failure, acute kidney injury and multi-organ failure. There is currently no FDA or European Medicine Agency (EMA) approved treatment for AH, and novel therapeutic strategies are needed to improve survival. A retrospective analysis of 77 studies published between 1971 and 2016, which included data from a total of 8,184 patients, showed that the overall mortality from AH was 26% at 28 days and 29% at 90 days. Stopping alcohol consumption is frequently not sufficient for recovery in many AH patients. Treatments that reduce liver inflammation, such as corticosteroids, have not been shown to improve survival at 90 days or one year and have widely acknowledged contraindications. While early liver transplantation can improve survival in carefully selected patients with severe AH who do not respond to medical therapy, the procedure is costly, exceeding$875,000 in the United States on average and may be limited by the availability of donated organs. In addition, patients require lifelong immunosuppressive

therapy to prevent organ rejection.

About Larsucosterol
Larsucosterol is a synthetic form of an endogenous sulfated oxysterol and an epigenetic modulator that changes patterns of gene expression without modifying the DNA sequence. DNA hypermethylation, an example of epigenetic dysregulation, results in transcriptomic reprogramming and cellular dysfunction, and has been found to be associated with many acute (e.g., AH) or chronic diseases (e.g., NASH). Larsucosterol binds to and inhibits the activity of DNA methyltransferases (DNMT1, DNMT3a and 3b), epigenetic enzymes associated with DNA methylation. By inhibiting DNMTs, larsucosterol decreases DNA hypermethylation, thereby modulating gene expression to potentially reduce cell death, lipotoxicity and inflammation in AH. Given its proposed mechanism of action as an epigenetic modulator, there is strong scientific rationale for investigating the therapeutic potential of larsucosterol in the treatment of multiple acute organ injuries and chronic liver diseases.

About DURECT Corporation
DURECT is a biopharmaceutical company committed to transforming the treatment of acute organ injuries and chronic liver diseases by advancing novel and potentially lifesaving epigenetic therapies. Larsucosterol, DURECT's lead drug candidate, binds to and inhibits the activity of DNA methyltransferases (DNMTs), epigenetic enzymes associated with hypermethylation, found to be elevated in the livers of alcohol-associated hepatitis (AH) patients. By decreasing DNA hypermethylation, larsucosterol modulates expression of genes important in maintaining cellular functions, reducing cell death, lipotoxicity and inflammation in AH. Larsucosterol is currently being evaluated in an ongoing Phase 2b study, called AHFIRM, for the potential treatment of AH, for which FDA has granted a Fast Track Designation.

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 plan to report topline data in the fourth quarter 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 (NDA) filing and our ability to expedite the NDA process using the Fast Track Designation granted by the FDA, larsucosterol's potential to be the first FDA-approved therapy for AH, our plans to commercialize larsucosterol if approved, the potential to develop larsucosterol for AH 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 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, 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 and quarterly report on Form 10-Q for the quarter ended March 31, 2023 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: Larsucosterol 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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