DURECT Corporation Announces Phase 3 Registrational Trial Design for Larsucosterol in Alcohol-associated Hepatitis

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– Type B meeting with FDA held under Breakthrough Therapy designation resulted in agreement on key aspects of Phase 3 trial design

– Single Phase 3 trial designed to enroll 200 U.S. patients with a 90-day survival primary endpoint;topline results expected within two years of trial initiation

– Protocol for Phase 3 trial builds on data from the AHFIRM Phase 2b trial; 30 mg and 90 mg doses of larsucosterol reduced 90-day mortality in U.S. patients by 57% and 58%, respectively, compared with placebo

CUPERTINO, Calif. , Sept. 25, 2024 /PRNewswire/ — DURECT Corporation (Nasdaq: DRRX), a late-stage biopharmaceutical company pioneering the development of epigenetic therapies to transform the treatment of serious and life-threatening conditions such as acute organ injury, today provided details on the design of its upcoming registrational Phase 3 trial which will evaluate larsucosterol for the treatment of patients with severe alcohol-associated hepatitis (AH).

“We are pleased with the collaborative interactions with the U.S. Food and Drug Administration (FDA), including our recent Type B meeting held under Breakthrough Therapy designation, that allowed us to reach agreement on key elements of the protocol for the upcoming Phase 3 trial,” said James E. Brown, D.V.M., President and Chief Executive Officer of DURECT. “We believe the primary endpoint of 90-day survival is clinically meaningful and provides the greatest probability of success based on the AHFIRM data. In the completed AHFIRM trial, larsucosterol showed the ability to reduce mortality in AH patients compared to standard of care, particularly in the U.S., where we observed nearly 60% lower mortality at 90-days in both the 30 mg and 90 mg dose groups. We look forward to initiating the Phase 3 trial as soon as possible, subject to obtaining sufficient funds, which should enable us to report topline data within two years of trial initiation. The FDA also agreed that a single Phase 3 trial would be sufficient to support a New Drug Application (NDA). Larsucosterol’s Breakthrough Therapy designation for the treatment of AH gives us the opportunity to file an NDA as a rolling submission. As we continue to advance our development program for larsucosterol in AH, we look forward to additional discussions with the FDA under this designation.”

Norman Sussman, M.D., FAASLD, Chief Medical Officer of DURECT, added, “As cases of AH continue to rise, there is an urgent need for an effective therapy to significantly reduce the high mortality rate, which is approximately 30% at 90 days. Based on our Phase 2b AHFIRM data, we believe larsucosterol has the potential to save the lives of tens of thousands of patients yearly who currently have very limited options. We have ongoing discussions with a range of U.S. clinical sites and hepatologists, including those who participated in AHFIRM, to streamline the process of initiating our Phase 3 trial. We are pleased to have the opportunity to work again with a high quality network of sites and investigators who are enthusiastic about larsucosterol and eager to participate in the Phase 3 trial.”

The proposed Phase 3 trial design incorporates feedback from the Type B meeting held with the FDA under the Breakthrough Therapy designation. It is designed as a randomized, double-blind, placebo-controlled, multi-center study conducted in the U.S., which will evaluate the safety and efficacy of larsucosterol for the treatment of patients with severe AH. The primary outcome measure will be a 90-day survival endpoint. The Phase 3 trial is planned to enroll approximately 200 patients randomized in a 1:1 ratio across two arms: 1) larsucosterol (30 mg) or 2) placebo, which will be added to the current standard of care, with or without methylprednisolone capsules at the investigators’ discretion. Patients enrolled in the trial will be followed for a total of up to 180 days to collect additional safety and outcomes data.

Data from the AHFIRM trial showed a compelling efficacy signal in favor of larsucosterol in the key secondary endpoint of mortality at 90 days. Both the 30 mg and 90 mg larsucosterol doses demonstrated clinically meaningful trends in reduction of mortality at 90 days with mortality reductions of 41% (p=0.068) in the 30 mg arm and 35% (p=0.124) in the 90 mg arm compared with placebo. The

reductions in mortality at 90 days were more pronounced in U.S. patients, who comprised 76% of the trial population, with reductions of 57% (p=0.014) in the 30 mg arm and 58% (p=0.008) in the 90 mg arm compared with placebo. The numerical improvement in the primary endpoint of mortality or liver transplant at 90 days did not achieve statistical significance for either dose of larsucosterol. Reflecting the life-threatening nature of AH and the lack of therapeutic options, the FDA granted larsucosterol Fast Track and Breakthrough Therapy designations for the treatment of AH.

About Alcohol-associated Hepatitis (AH)

AH is an acute form of alcohol-associated liver disease (ALD) associated with long-term heavy alcohol intake, often following a recent period of increased consumption (i.e., a binge). AH is typically characterized by severe inflammation and liver cell damage, 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 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 necessary, but frequently not sufficient for recovery in many moderate (defined as MELD scores of 11-20) and severe (defined as MELD scores >20) patients, and therapies that reduce liver inflammation, such as corticosteroids, are limited by contraindications, 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 total number of such transplants is still relatively small and limited by organ availability. Average costs for a liver transplant exceed $875,000, and patients require lifelong immunosuppressive therapy to prevent organ rejection.

About the AHFIRM Trial

AHFIRM was a Phase 2b randomized, double-blind, placebo-controlled, international, multi-center study conducted in subjects with severe alcohol-associated hepatitis (AH) to evaluate the saFety and effIcacy of laRsucosterol treatMent (AHFIRM). The study was comprised of three arms and enrolled 307 patients, with approximately 100 patients in each arm: (1) Placebo, which consists of standard of 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. The primary outcome measure was the 90-day incidence of mortality or liver transplantation for patients treated with larsucosterol compared to those treated with placebo, and the key secondary endpoint was 90-Day survival. The Company enrolled patients at clinical trial sites across the U.S., EU, U.K., and Australia. In November 2023, the Company announced topline data for the AHFIRM Trial. 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 and Breakthrough Therapy Designation for the treatment of AH. For more information, refer to ClinicalTrials.gov Identifier: NCT04563026.

About Larsucosterol

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 has been reported in many acute (e.g., AH) and chronic diseases (e.g., metabolic dysfunction-associated steatohepatitis (MASH)). As an inhibitor of DNA methyltransferases (DNMT1, DNMT3a and 3b), larsucosterol inhibits DNA methylation, which subsequently modulates the expression of genes that are involved in cell signaling pathways associated with stress responses, cell death and survival, and lipid biosynthesis. 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 acute organ injury and certain chronic diseases.

About DURECT Corporation
DURECT is a late-stage biopharmaceutical company pioneering the development of epigenetic therapies that target dysregulated DNA methylation to transform the treatment of serious and life-threatening conditions, including acute organ injury. Larsucosterol, DURECT's lead drug candidate, binds to and inhibits the activity of DNA methyltransferases, epigenetic enzymes that are elevated and associated with hypermethylation found in AH patients. Larsucosterol is in clinical development for the potential treatment of AH, for which the FDA has granted a Fast Track and a Breakthrough Therapy designation; MASH 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 is exclusively licensed to Innocoll Pharmaceuticals for sale and distribution in the United States. For more information about DURECT, please visit www.durect.com and follow us on X (formerly Twitter) at https://x.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 initiate and enroll patients in a Phase 3 trial of larsucosterol in AH in 2024 and present top-line data in the second half of 2026, our ability to confirm the efficacy and safety of larsucosterol in AH patients to support an NDA filing with the FDA, the potential benefits of Breakthrough Therapy designation, and the potential uses of laruscosterol to treat patients with AH and potentially other indications. 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 future clinical trials of larsucosterol are delayed or do not confirm the results from subset analyses of the AHFIRM trial, including geographic or other segmentation, or of earlier clinical or pre-clinical trials, or do not demonstrate the safety or efficacy of larsucosterol in a statistically significant manner; the risk that we do not raise sufficient capital to commence or complete the Phase 3 trial of larsucosterol in patients with AH or continue to fund our operations, the risk that the FDA or other government agencies may require additional clinical trials for larsucosterol before approving larsucosterol for the treatment of AH, the risk that Breakthrough Therapy designation does not expedite the process for FDA approval and that larsucosterol may never be approved; and risks related to the sufficiency of our cash resources, our anticipated capital requirements, our ability to continue to meet the minimum bid price for continued listing on Nasdaq, 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, 2023 and quarterly report on Form 10-Q for the quarter ended June 30, 2024, 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 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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