April 29, 2022

Dear fellow shareholders,

We have made considerable progress in 2021 and the early part of 2022 in a number of important areas as we increasingly focus on driving forward the development of Larsucosterol (also known as DUR-928), while deriving value from our legacy drug delivery programs. Let me briefly outline our most important initiatives and accomplishments.

Epigenetic Regulator Program

Larsucosterol, the lead product in our Epigenetic Regulator Program, is a naturally occurring small molecule that plays an important regulatory role in the vital functions of lipid metabolism, cellular stress and inflammatory responses, cell survival and death. Larsucosterol would be a first-in-class treatment for alcohol-associated hepatitis (AH). Last year the mechanism of action for larsucosterol was published in the Journal of Lipid Research; it works by inhibiting DNMTs to reactivate genes aberrantly silenced by hypermethylation.

The primary focus of our company is developing larsucosterol for the treatment of AH. AH is an acute form of alcohol-associated liver disease. AH is associated with approximately 137,000 US hospitalizations per year, and there is a significant unmet medical need for the treatment of AH given the high, short-term mortality of this condition of 20-26% at 28 days and 29-31% at 90 days. The standard of care for the treatment of AH is ineffective, and there is no approved drug to treat it.

AHFIRM (*Phase 2b study in subjects with AH to evaluate saFety and effIcacy of laRsucosterol treatMent*)

After completing a Phase 2a trial where 100% of AH patients treated with larsucosterol survived the 28-Day study period, we are now conducting a ~300-patient, double-blind, placebo-controlled Phase 2b clinical trial, AHFIRM, in which we are evaluating larsucosterol's life saving potential compared to placebo plus the current standard of care in patients with severe AH. We have nearly achieved our goal of 60+ clinical trial sites now open at leading hospitals in the U.S., Australia, E.U., and the U.K., and as of early March 2022 we had enrolled over 100 patients. At the pace of enrollment achieved in the first quarter of 2022, we would complete dosing the last patient in the AHFIRM trial in mid-2023; we expect the pace of enrollment should improve through our clinical site expansion, clinical trial engagement activities and the potential lessening of the impact of COVID on the hospitals participating in AHFIRM.

Given the high mortality rate in severe AH patients and the absence of an approved therapeutic, we believe demonstration of a robust survival benefit in the AHFIRM trial may support an NDA filing. The FDA has granted larsucosterol Fast Track Designation for the treatment of AH. The FDA grants Fast Track Designation to facilitate development and expedite the review of therapies with the potential to treat a serious condition where there is an unmet medical need. A therapeutic that receives Fast Track Designation may benefit from early and frequent communication with the agency in addition to a rolling submission of the marketing application, with the objective of getting important new therapies to patients more quickly.

POSIMIR® Approval and Out-licensing for U.S. Commercialization

In February 2021, our first therapeutic was approved when POSIMIR was granted U.S. FDA approval in adults for administration into the subacromial space under direct arthroscopic visualization to produce post-surgical

analgesia for up to 72 hours following arthroscopic subacromial decompression. Full Prescribing Information, including the Boxed Warning, is available at www.POSIMIR.com. In December 2021, we signed an exclusive U.S. licensing agreement with Innocoll Pharmaceuticals Limited. Under the agreement, DURECT will earn low to mid double-digit royalties from net sales of POSIMIR and is eligible to receive up to $136 million in upfront and milestone payments, including the $4 million upfront license fee received in January 2022, and a $2 million milestone payment upon the first commercial sale of POSIMIR, which is anticipated in Q2 2022.

Additional Accomplishments

During 2021, larsucosterol's mechanism of action was published in a peer-reviewed journal. Without having the time to fully describe the science, the take home message is that the mechanism of action of larsucosterol is fully consistent with the activity we've seen to date in AH. At the corporate level, over the last 18 months we have appointed three new highly experienced biopharmaceutical board members whose fresh perspective has been invaluable. I am proud of our team and what we have accomplished over the past year, particularly while dealing with all of the challenges presented by COVID.

Looking ahead

Our ruthless focus is on the execution of the AHFIRM trial, where a positive trial outcome would be transformative for AH patients and our company. DURECT's medical affairs team has been substantially increasing our AH market outreach and education efforts to amplify larsucosterol awareness and facilitate AHFIRM enrollment efforts. We also believe that there are several other indications in which larsucosterol can be impactful, and expect to be in a position to determine and announce next steps in another indication later this year.

To our shareholders, employees, clinical trial participants and collaborators, thank you for your continued support.

James E. Brown
President and CEO

DURECT Forward-Looking Statement: The statements in this stockholder letter regarding plans to complete enrollment of the AHFIRM trial in mid-2023, plans to increase the number of clinical trial sites in the AHFIRM trial, the potential for the AHFIRM trial to support an NDA, the expected commercial launch of POSIMIR by Innocoll, potential future payments we may receive from Innocoll, and the potential to develop larsucosterol for other indications are forward-looking statements involving risks and uncertainties that can cause actual results to differ materially from those in such forward-looking statements. Potential risks and uncertainties include, but are not limited to, the risks that the AHFIRM trial takes longer to conduct than anticipated due to COVID 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 or the life-saving potential of larsucosterol in a statistically significant manner, the risk that the FDA or other regulatory agencies may require additional clinical trials of larsucosterol before granting regulatory approval, risks that Innocoll may not commercialize POSIMIR successfully, if at all, and risks related to our ability to obtain capital to fund operations and expenses. Further information regarding these and other risks is included in DURECT's Form 10-K for the year ended December 31, 2021 and Form 10-Q for the quarter ended March 31, 2022 when filed with the Securities and Exchange Commission under the heading "Risk Factors." These reports are available on our website www.durect.com under the "Investors" tab. These reports are available on our website www.durect.com under the "Investors" tab. Forward-looking statements contained in this stockholder letter are made as of this date, and DURECT undertakes no duty to update such information except as required under applicable law.