April 27, 2023

Dear fellow shareholders,

I am pleased to have the opportunity to communicate with you in the midst of a year of such magnitude for DURECT and to thank you for your ongoing support for our company. We made tremendous progress during 2022 and the first quarter of 2023 toward our collective goal of gaining approval for larsucosterol in alcohol-associated hepatitis (AH), a devastating disease with high mortality and no approved treatment. We are nearing the completion of enrollment in our ongoing Phase 2b AHFIRM trial and expect to report topline data in the second half of 2023. If AHFIRM is successful, we plan to engage in discussions with regulatory authorities in the United States and other geographies about filing an NDA based on this data. We have also made progress on a number of additional fronts; allow me to briefly outline our most important initiatives and accomplishments.

Epigenetic Modulator Program

Larsucosterol, the lead product candidate 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 works by inhibiting DNMTs to reactivate genes aberrantly silenced by hypermethylation. Data supporting this mechanism of action has been published the Journal of Lipid Research.

The primary focus of DURECT continues to be developing larsucosterol for the treatment of AH, an acute form of alcohol-associated liver disease. AH is associated with approximately 158,000 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 inadequate and there is no approved treatment for AH.

AHFIRM (*Phase 2b trial 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. As of March 2023, we have enrolled over 260 patients in a global network of clinical trial sites including leading hospitals in the U.S., Australia, E.U., and the U.K. We expect to complete dosing the last patient in the AHFIRM trial this quarter and plan to report topline data in the second half of the year.

Given the high mortality rate in severe AH patients and the absence of an approved therapeutic, we believe a successful result 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.

Published Data from Phase 2a Trial for Larsucosterol in AH in Peer-Reviewed Journal

Earlier this month, we announced the publication of an article with our Phase 2a AH data in the peer-reviewed American Journal of Gastroenterology. In addition to previously reported safety and efficacy data from our 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. We believe this new data provides further support for the promise of larsucosterol as a potential treatment for AH.

Generated $10 Million in Non-Dilutive Milestones from POSIMIR®

We licensed U.S. commercial rights for POSIMIR, our first approved therapeutic, to Innocoll in December 2021. In 2022, we earned $10 million in milestone payments from Innocoll, including $8 million in August 2022 related to the issuance a new patent extending U.S. patent coverage for POSIMIR to at least 2041 and, in September 2022, an additional $2 million milestone related to the first commercial sale of POSIMIR. These non-dilutive payments provided valuable cash infusions to help offset a portion of our expenses for 2022. Under the agreement with Innocoll, DURECT will earn low double-digit to mid teen royalties from net sales of POSIMIR and remains eligible to receive up to $122 million in additional milestone payments.

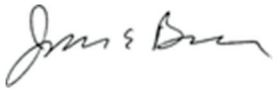
New Chair of the Board

It is my pleasure to welcome Gail Maderis to the role of Chair of the Board as announced last month. Gail has been a valuable contributor since joining the DURECT board in 2021 and we look forward to continuing to benefit from her insights in her new capacity. I also thank our outgoing Chair, Dave Hoffmann, and wish Dave all the best in his future endeavors.

Looking ahead

We continue to be focused on our primary goal of completing the AHFIRM trial and reporting data this year. A positive trial result could lead to a potential NDA filing and would be transformative for AH patients and our company. We are in the early stages of commercial launch planning in the U.S. and are preparing to capitalize on the substantial commercial potential for larsucosterol both in the U.S. and globally.

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 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 are forward looking statements. Actual results may differ materially from those contained in the forward-looking statements contained in this press release. 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 and capital expenditures, 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” and in our subsequent SEC filings. These reports are available on our website www.durect.comunder the “Investors” tab and on the SEC’s website at www.sec.gov. All information provided in this letter 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.