May 2, 2019

Dear Fellow Stockholders:

2019 has the potential to be a transformative year for DURECT. With respect to DUR-928, our flagship program, we have accomplished several important development milestones this year, including achieving encouraging preliminary data in alcoholic hepatitis patients and initiating dosing in NASH and psoriasis clinical trials. We have also made significant progress toward finalizing a response to the POSIMIR® Complete Response Letter (CRL), which we expect to submit to the FDA this quarter, and strengthened our board with the addition of two new members who bring valuable experience and perspective. As a result of the productive start to the year, we have four potential major catalysts ahead of us this year: data from the three ongoing DUR-928 clinical trials and a potential approval for POSIMIR.

Epigenetic Regulator Program

DUR-928, 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 homeostasis, inflammation and cell survival. As such, this small molecule may have therapeutic benefits in several acute organ injuries such as alcoholic hepatitis, hepatic diseases such as nonalcoholic steatohepatitis (NASH), and inflammatory skin diseases such as psoriasis and atopic dermatitis.

Alcoholic Hepatitis (AH)

DURECT is conducting a Phase 2a clinical trial with intravenously administered DUR-928 in patients with AH. This is an open label, dose escalation (30, 90 and 150 mg), multi-center U.S. study that is enrolling patients with moderate and severe AH. Dose escalation may occur following review of safety and pharmacokinetic (PK) results of the prior dose level by a Dose Escalation Committee (DEC). The target number of patients for the study is 4 moderate and 4 severe patients per dose group. The objectives include assessment of safety, PK and pharmacodynamic (PD) signals, including liver chemistry and biomarkers.

After completing the low-dose 30 mg cohort in moderate AH patients, the DEC approved commencement of the 90 mg cohort in moderate AH patients while simultaneously commencing recruitment of severe AH patients with the 30 mg dose. Enrollment of severe AH patients has been more rapid than that of moderate patients. Upon completion of the 30 mg cohort in severe AH patients, the DEC approved advancement to the 90 mg dosing in severe AH patients. We are now enrolling both moderate and severe AH patients for the 90 mg cohorts.

Preliminary data from this trial has been encouraging, and we have received strong encouragement and support from our key expert advisors and clinical trial investigators.

Non-Alcoholic Steatohepatitis (NASH)

In March 2019 we began enrolling patients in a Phase 1b randomized and open-label clinical study in the U.S. to evaluate safety, pharmacokinetics and signals of biological activity of DUR-928 in NASH patients with stage 1-3 fibrosis. Three doses of DUR-928 will be administered orally for 28 consecutive days with 20 patients per dose group for a total of 60 patients in the trial. Key endpoints include safety and PK, clinical chemistry and biomarkers (e.g., bilirubin, lipids, liver enzymes, CK-18s, and inflammatory cytokines) as well as liver imaging (e.g., MRI-PDFF). We expect to announce initial data from this study in the second half of 2019.

In our previous Phase 1b NASH study, reported at the European Association for the Study of the Liver (EASL) in April 2017, exploratory biomarker analysis demonstrated that a single oral dose of DUR-928 in NASH patients, at both dose levels tested (50 mg and 200 mg), resulted in statistically significant reductions from baseline of both full-length and cleaved cytokeratin-18 (CK-18), bilirubin, hsCRP and IL-18.

Psoriasis

In March 2019 we began enrolling patients in a Phase 2a, randomized, double-blind, vehicle-controlled proof-of-concept clinical trial in which DUR-928 is applied topically once-daily for four weeks in patients with mild to moderate plaque psoriasis. The trial is being conducted at multiple clinical sites in the U.S. Twenty patients are planned to be enrolled to obtain 15 evaluable patients. Patients serve as their own controls, applying DUR-928 to the plaque on one arm and the vehicle to a similar plaque on the other arm. After the treatment period, patients will be followed for an additional four weeks. The primary efficacy endpoint is the change in local psoriasis scores from baseline in the DUR-928-treated plaques compared to that in the vehicle-treated plaques. We expect to announce top line data from this study in the second half of 2019.

We previously conducted an exploratory Phase 1b trial in psoriasis patients (9 evaluable patients) in Australia. The trial was randomized, double-blinded, placebo and self-controlled, using a micro-plaque assay with intralesional injections of DUR-928. The results were encouraging and warranted advancing into the current proof-of-concept trial with topically applied DUR-928.

POSIMIR® (extended-release bupivacaine solution). POSIMIR is our investigational post-operative pain relief depot that utilizes our patented SABER® technology and is designed to deliver bupivacaine to provide up to three days of pain relief after surgery. After a comprehensive review of the POSIMIR program in light of the issues raised by the FDA in our communications with them, including the CRL, we are planning to submit a full response to the CRL this quarter. As the submission will be a response to a CRL, we expect a 6-month FDA review period.

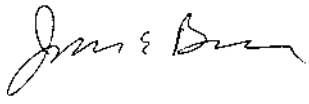
The effort to evaluate the program, develop a strategy for filing the response, and the actual writing of key sections of the response, has been under the direction of our consultant, Dr. Lee Simon, who was formerly the FDA's Division Director of Analgesic, Anti-inflammatory and Ophthalmologic Drug Products.

We believe that the completed inguinal hernia and subacromial decompression (shoulder) clinical trials support the efficacy of POSIMIR in post-operative pain and meet the requirements to be considered as adequate and well-controlled pivotal clinical trials. Both trials demonstrated a significant decrease in pain and opioid use over the 0-72 hour period following surgery as compared to placebo.We have completed 16 clinical trials in the POSIMIR program, involving more than 1,400 patients, over 850 of whom received POSIMIR with the remainder in control groups. We believe this is a sufficiently sized safety database. We believe that, with the PERSIST safety data included, we now have sufficient data to address FDA's issues raised in the CRL and that the data package meets the requirements for FDA approval.

In addition, the following products are cash flow positive for us:

- **PERSERIS™ and Methydur**. PERSERIS is a once-monthly, risperidone-containing long-acting injectable (LAI), which was launched in the U.S. by Indivior, PLC. in February 2019. We assigned certain of our U.S. patent rights to Indivior, including granted patents extending into at least 2026. Indivior has paid us $17.5 million in upfront and milestone payments and also pays us quarterly earn-out payments based on a single digit percentage of U.S. net sales of PERSERIS. Indivior has stated that its peak year net revenue goal for PERSERIS is $200 million to $300 million. Our partner, Orient Pharma has stated that it expects to launch Methydur (ORADUR®-Methylphenidate ER) in Taiwan in 2019 for treatment of ADHD, while pursuing approvals and commercial partnerships in China and other countries in Southeast Asia.
- **ALZET® and LACTEL® products.** The wide use and many research applications of our ALZET line of osmotic pumps are supported by over 16,000 references in the scientific literature. We also design, develop and manufacture a line of biodegradable polymers under the LACTEL brand name, and several of these polymers are incorporated in FDA-approved therapeutics. In 2018, these product lines generated over $10 million in revenue for DURECT and over $6 million in gross profit.

We are pleased with the productive start to the year for our flagship DUR-928 program, having achieved encouraging preliminary data in AH patients and having initiated key clinical trials in NASH and psoriasis patients. We look forward to multiple data read-outs from these DUR-928 trials and a potential approval for POSIMIR this year. On behalf of everyone at DURECT, we thank you for your continued support and look forward to reporting on our progress in 2019 and beyond.



James E. Brown, D.V.M.
President and Chief Executive Officer

Forward-Looking Statements: The statements in this stockholder letter regarding future events, including anticipated timing and results for ongoing clinical trials of DUR-928 in AH, NASH and psoriasis, potential FDA approval of POSIMIR, potential earn-out payments from Indivior, potential launch of Methydur and the potential revenues and profits from ALZET and LACTEL 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 risk of delays in the enrollment or completion of the ongoing clinical trials of DUR-928, failure of initial safety and efficacy indications for DUR-928 to be demonstrated in ongoing clinical trials, and the failure of such trials to meet their endpoints, unexpected delays in the regulatory review of, or adverse decisions by, the FDA, for POSIMIR, potential adverse effects arising from the testing or use of DUR-928, the potential failure of Indivior to obtain anticipated revenues for PERSERIS, the potential failure of Orient Pharma to launch Methydur, the potential loss of revenues or increases in expenses for ALZET and LACTEL, and risks related to our ability to avoid infringing patents held by other parties and secure and defend patents of our own, and manage and obtain capital to fund operations and expenses. Further information regarding these and other risks is included in DURECT's Annual Report on Form 10-K for the year ended December 31, 2018 filed with the Securities and Exchange Commission on March 8, 2019, under the heading "Risk Factors."