April 24, 2016

Dear Fellow Stockholders:

Transforming Medicine. Simply put, that is our mission. Whether taking aim at improved drug formulations or bringing to market therapies based on completely novel molecules and avenues of research, the men and women of DURECT strive to fulfill a fundamental promise to patients, physicians, corporate partners and investors: create best-in-class pharmaceuticals with enduring value – measured most directly by their potential to make real, palpable differences in the lives of those who need them.

2015 was a transformative year for DURECT as we announced and made solid progress with our Epigenomics Regulator Program (lead molecule: DUR-928), and our late stage pain management product candidates (REMOXY® and POSIMIR®) advanced in meaningful ways. DURECT is extremely fortunate to have these programs and product candidates that seek to address major medical needs and which also entail meaningful commercial opportunities.

Because of its regulatory role in lipid homeostasis, inflammation and cell survival, DUR-928 may yield multiple clinical indications (in both oral and injectable formulations) ranging from chronic liver and kidney diseases to acute organ injury. In 2015, we added to our varied animal studies that are suggestive of DUR-928 utility, completed five Phase 1 clinical trials dosing over 75 healthy volunteers with either our oral or injectable formulations, and saw no serious or treatment-related adverse events. These activities enabled us to initiate our first DUR-928 patient trials in 2016.

REMOXY and POSIMIR represent two late stage product candidates that address large market opportunities in the field of pain management. These two product candidates address a major medical need driven by the widespread use (including abuse and misuse) of opioids, but in different ways. REMOXY is designed to provide effective opioid treatment for chronic pain sufferers, but in a tamper-resistant formulation. We developed POSIMIR as an extended release pain product intended to cover the first full three days after surgery while also significantly reducing the need for opioids and their attendant risks and side-effects in this important patient setting.

Throughout 2015 and early 2016, we supported our licensee, Pain Therapeutics, as they prepared the REMOXY NDA resubmission. That resubmission occurred on schedule in March 2016, a target PDUFA date of September 25, 2016 has been set by the FDA, and we look forward to potentially receiving our first product approval in 2016. In November 2015, we began recruiting patients in PERSIST, our POSIMIR pivotal Phase 3 clinical trial. Based on further input from the FDA received subsequent to the start of the trial, we are amending the PERSIST study, which will add to the time and cost to complete the trial; however, we believe that a positive outcome from this revised trial design would result in a stronger NDA filing and potentially provide commercial advantages.

Our Epigenomic Regulator Program and lead molecule DUR-928:

DURECT's Epigenomic Regulator Program involves a multi-year collaborative effort with the Department of Internal Medicine at Virginia Commonwealth University (VCU), the VCU Medical Center and the McGuire VA Medical Center. The discoveries driving this program are the result of more than 20 years of lipid research by Shunlin Ren, MD, PhD, Professor of Internal Medicine at the VCU Medical Center and a recipient of multiple NIH grants for metabolic disease research. DURECT holds the exclusive worldwide right to develop and commercialize DUR-928 and related molecules discovered in the program.

DUR-928, our lead compound in this program, is an endogenous, small-molecule new chemical entity (NCE). “Endogenous” means that DUR-928 is naturally produced in the body. It is also present in all animal species we’ve studied in very similar plasma concentrations. Examples of other endogenous molecules that have become important drugs include insulin, corticosteroids, thyroid hormone, growth hormone, erythropoietin and granulocyte-colony stimulating factor (G-CSF).

DUR-928 is a sulfated oxysterol. In contrast to other oxysterols, DUR-928 appears to have the ability to modulate at a very high level the activities of various nuclear receptors that play an important regulatory role in lipid homeostasis, inflammation and cell survival. As such, it may have broad applicability in several metabolic diseases such as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), and in acute organ injuries such as acute liver and kidney injury. The biological activity of DUR-928 has been demonstrated in 8 different animal disease models involving 3 animal species. Four of these models represent chronic disorders of hepatic lipid accumulation and dysfunction (e.g., NAFLD and NASH) and four represent acute organ injuries (endotoxin shock, kidney, liver and brain).

Additional pharmacokinetic and toxicity studies in mice, hamsters, rats, dogs and monkeys have shown DUR-928 to be orally and parenterally bioavailable and safe at all doses tested to date. These preclinical results supported the initiation of DUR-928 into human safety trials. In 2015, we completed five Phase 1 clinical trials dosing over 75 healthy volunteers with either our oral or injectable formulations and saw no serious or treatment-related adverse events, including when the doses resulted in plasma levels more than 100-fold higher than endogenous levels. There was no food effect observed, no accumulation in plasma concentrations with repeated dosing and dose proportionality was observed.

We are currently pursuing the development of DUR-928 through two broad programs for: (i) chronic metabolic diseases using an oral formulation, and (ii) acute organ injury using an injectable formulation. We are also actively exploring additional indications beyond these broad programs.

We are currently conducting a single-ascending-dose Phase 1b clinical trial with DUR-928 in patients with biopsy-confirmed NASH. This study, which is primarily a safety and pharmacokinetic trial, is being conducted in Australia, and we anticipate that we will obtain results from this trial starting in the second quarter of 2016. We anticipate that the single-ascending-dose Phase 1b clinical trial described above will enable and inform a multiple-dose study in NASH patients or patients with other liver function impairment.

In addition, we are commencing a Phase 1b single-ascending-dose, injectable administration trial in renal function impaired patients in the second quarter of 2016, with data available from the study expected in 2016. This trial is also designed as a single-site, open-label safety and pharmacokinetics study. This trial is expected to enable and inform subsequent patient studies in acute kidney injury and/or other kidney function impairment.

Update of other selected programs:

- **REMOXY.** Based on DURECT’s ORADUR® technology, REMOXY is a unique long-acting formulation of oxycodone designed to discourage common methods of tampering associated with opioid misuse and abuse. Opioid drugs such as oxycodone are an important treatment option and widely used by patients with severe chronic pain. However, oxycodone abuse and diversion remains a serious, persistent public health problem which the FDA recently described as an epidemic.

  Throughout 2015 and early 2016, we supported our licensee, Pain Therapeutics, as they prepared the REMOXY NDA resubmission. That resubmission occurred on schedule in March 2016. In April 2016, Pain Therapeutics announced that the FDA had determined that the NDA was sufficiently complete to permit a substantive review, and September 25, 2016 is the target action date under the Prescription Drug User Fee Act (PDUFA).

  The extended release oxycodone market is greater than $2 billion in the U.S. alone, and we are eligible for a potential royalty on REMOXY of between 6.0% to 11.5% of net sales depending on sales volumes.

- **POSIMIR (SABER®-Bupivacaine).** POSIMIR is an investigational post-operative pain relief depot that utilizes our patented SABER technology and is intended to deliver bupivacaine (a non-opioid) to provide three days of pain relief after surgery. We feel that there is an unmet medical need for a product with POSIMIR's extended duration of action and potential to reduce the need for opioids (with their associated side-effects and costs).

  In February 2014, we received a Complete Response Letter from the FDA. Based on the Complete Response Letter and subsequent communications with the FDA, we are conducting a new POSIMIR Phase 3 clinical trial (the PERSIST trial) consisting of patients undergoing laparoscopic cholecystectomy (gallbladder removal) surgery to further evaluate the benefits and risks of POSIMIR. In a previous trial of 50 patients undergoing laparoscopic cholecystectomy, POSIMIR demonstrated an approximately 25% reduction in pain intensity on movement for the first 3 days after surgery (p=0.024) against the active control bupivacaine HCl, using the same statistical methodology specified for the PERSIST trial. We began recruiting patients for this trial in November 2015 with an intent to compare POSIMIR to placebo. Based on advice from the FDA received subsequent to the start of the trial, in April 2016, we decided to amend the PERSIST trial including by incorporating standard bupivacaine HCl as an active control. This change will add to the time and cost to complete the PERSIST trial, but we believe that a positive outcome from this trial design would result in a stronger NDA filing and potentially commercial advantages. This clinical trial is designed to generate data necessary to support an NDA resubmission.

  We are in discussions with potential partners regarding the licensing of development and commercialization rights to POSIMIR, for which we hold worldwide rights. Simultaneous with these activities, we are preparing to be in a position to commercialize POSIMIR ourselves in the U.S. in the event that we determine that is the preferred route of commercialization.

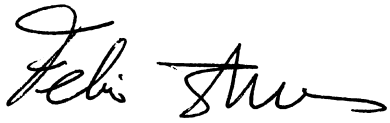
- **Other Programs.** Given space constraints, just a brief mention of three other programs at DURECT.
  - **ORADUR- ADHD.** With our licensee, Orient Pharma, we are developing a drug candidate (ORADUR-methylphenidate) incorporating our ORADUR technology to treat patients with Attention Deficit Hyperactivity Disorder (ADHD). ADHD drugs, much like opioids, are often abused so we believe the tamper-resistant features of ORADUR may be highly beneficial in the ADHD field. Orient Pharma is conducting a Phase 3 trial in Taiwan and anticipates completing it in 2016.
  - **Relday® (Risperidone Program).** Relday is a proprietary, long-acting, once-monthly subcutaneous injectable formulation of risperidone, intended to treat schizophrenia patients. In 2015, our licensee, Zogenix, announced that they had completed a multi-dose Phase 1b trial with results consistent with the profile of risperidone and a previous single-dose Phase 1 trial with Relday. Zogenix has stated that it is seeking a partner for Relday and that Relday is well-positioned to begin a Phase 3 program once a partner is secured.
  - **Santen Ophthalmic Program.** In 2015, we worked with our licensee, Santen Pharmaceutical, to develop a sustained release product utilizing our SABER formulation platform to deliver an ophthalmology drug. Santen controls and funds the development and commercialization program for this drug candidate which is in pre-clinical development.

- **ALZET and LACTEL products.** The wide use and many research applications of our ALZET line of osmotic pumps are evidenced 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 2015, these product lines generated over $11 million in revenue and over $7 million in gross profit for DURECT.

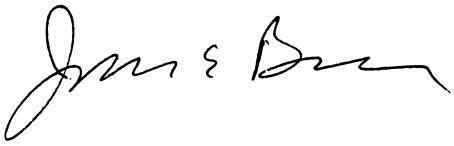
Concluding remarks:

Developing meaningful medicine is not for the faint of heart. However, history suggests that one break-through product can absolutely transform a company. We remain convinced that REMOXY, not far from potential approval now, incorporates best-in-class tamper-resistance to address the public health crisis that is opioid misuse and abuse. We believe that POSIMIR can be a major advance in post-surgical pain management, and we are focused on executing the PERSIST trial, resubmitting the NDA and defining our commercial strategy. Perhaps dwarfing REMOXY and POSIMIR in terms of potential patient impact and ability to deliver value for DURECT is DUR-928, where our focus is on demonstrating proof-of-concept in patients in one or more of multiple indications where it may prove efficacious. We are blessed to have this pipeline and want to assure you that the employees of DURECT are dedicated to making these product candidates a reality.

On behalf of everyone at DURECT, we thank you for your continued support and look forward to reporting on our progress in 2016 and beyond.



Felix Theeuwes, D.Sc.
Chairman and
Chief Scientific Officer



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

Forward Looking Statements: The statements in this stockholder letter regarding regulatory matters, including meetings, discussions and submissions regarding POSIMIR, REMOXY and Relday and potential FDA approval of our product candidates, anticipated clinical trials (including timing and results) for POSIMIR, DUR-928, ORADUR-ADHD, Relday and our other drug candidates, the potential of our Epigenomic Regulator Program and other development programs, potential royalties from Pain Therapeutics, potential milestone payments from our licensees, the potential benefits and uses of our drug candidates and pipeline of products, collaborations with third parties, potential business development, licensing and commercialization activities, market opportunities for our products candidates and cash flows and other results of operations 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 unexpected delays in the regulatory review of, or adverse decisions by, the FDA, for REMOXY, requests for additional information or product non-approval or non-acceptance of the REMOXY, POSIMIR or other NDA submissions, delays and additional costs due to requirements imposed by regulatory agencies, additional time and resources that may be required for development, testing and regulatory approval of our Epigenomic Regulator Program, potential adverse effects arising from the testing or use of our drug candidates, the potential failure of clinical trials to meet their intended endpoints, our potential failure to maintain our collaborative agreements with third parties or consummate new collaborations and risks related to our (and our third party collaborators where applicable) ability to design, enroll, conduct and complete clinical trials, complete the design, development, and manufacturing process development of product candidates, manufacture and commercialize product candidates, obtain marketplace acceptance of product candidates, 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, 2015 under the heading "Risk Factors."

For additional information on DURECT, please refer to our SEC filings, including our Annual Report on Form 10-K and Quarterly Reports on Forms 10-Q, our website (www.durect.com), or call us at any time.