April 24, 2015

Dear Fellow Stockholders:

An interesting observation about the biotech / pharmaceutical industry is that a company can be working away for years with little fanfare until—seemingly overnight—it becomes a huge success. Of course the reality is that there are no "overnight" successes in our industry. In truth, success is the result of hundreds (if not thousands) of days and nights of effort by dedicated teams of employees. To bring a drug to market that makes a real difference in patients' lives requires focus, perseverance and a dash of aggressive opportunism.

DURECT is evolving. Outsiders may historically have defined DURECT as a drug delivery company – describing our core competency as selecting existing drugs and then formulating them to improve their performance through a variety of proprietary oral, injectable and transdermal technologies. Drug delivery is one area of our expertise, to be sure, but our team also has extensive experience developing new chemical entities, and we're bringing these to bear on an exciting new program we first described publicly in March 2015, following more than three years of prior work. Since we've only recently unveiled our Epigenomics Regulator Program and its lead molecule DUR-928, we'll devote considerable attention to it in this letter. By no means does this imply that we are deemphasizing our previous pipeline of pharmaceutical candidates or are less excited by their prospects – we've just added a new opportunity with tremendous potential to the mix.

If you step back and look at it, DURECT is blessed with a rich pipeline for a small-cap company. In POSIDUR™ and REMOXY®, we have two NDA-stage product candidates that address large market opportunities in the field of pain management. Our SABER® and CLOUD™ injectable depot technologies have yielded programs such as POSIDUR, Relday™ (partnered with Zogenix) and an ophthalmic program partnered with Santen in late 2014. In addition, our ALZET® and LACTEL® product lines remain strongly cash flow positive and are valuable in their own right. And now our Epigenomic Regulator Program could yield its own pipeline of potential indications in the areas of metabolic diseases (e.g., nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH)), and acute organ injury (e.g., acute kidney injury (AKI)).

Our Epigenomic Regulator Program and lead molecule DUR-928:

We announced our Epigenomic Regulator Program in March 2015 along with the successful completion of a single-ascending-dose Phase 1 clinical trial of the program's lead product candidate DUR-928. Subsequently, we also announced the initiation of a multiple-ascending-dose Phase 1 clinical trial with DUR-928.

DUR-928 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. 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).

DURECT's Epigenomic Regulator Program is a collaborative effort, now in its fourth year, between DURECT and 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, Associate Professor of Internal Medicine at the VCU Medical Center and a recipient of multiple NIH grants for metabolic disease research. WeiQi Lin, MD, PhD, our project leader, has known Dr. Ren for over 30 years which is how we came to have this opportunity. DURECT holds the exclusive worldwide right to develop and commercialize DUR-928 and related molecules discovered in the program.

During the course of this program, a number of compounds have been identified that may have therapeutic utility for various diseases and syndromes, some orphan in nature and some affecting broader patient

populations. DUR-928, the lead compound, appears to modulate the activity of various nuclear receptors that play an important regulatory role in lipid homeostasis, inflammation and cell survival. A systems biology study involving over 23,000 genes showed that DUR-928 modulates the activity of more than 240 genes, including ACC, FAS, HMGR, Cyp7A1, LXR, PPARγ, NFκB/IκB, TNFα, IL-1α, IL-6, COX-2, PCSK9, and others.

The biological activity of DUR-928 has been demonstrated in 6 different animal disease models involving 3 animal species. Three of these models represent chronic disorders of hepatic lipid accumulation and dysfunction (NAFLD/NASH) and three represent acute toxic or ischemic organ injury (kidney and liver).

Additional pharmacokinetic and toxicity studies in mice, hamsters, rats, dogs and monkeys have shown DUR-928 to be orally bioavailable and safe at all doses tested to date. These preclinical results supported the initiation of DUR-928 into human safety trials. An oral formulation, envisioned for use in chronic conditions, is undergoing initial human testing. An initial Phase 1 single-dose trial has been successfully completed, and a multiple-ascending-dose study in healthy subjects is underway. An injectable formulation, envisioned for use in acute conditions, is currently in animal testing. We anticipate commencing human studies of the injectable formulation in the second half of 2015, starting with a single-dose trial in healthy subjects and following up with a multiple-ascending-dose Phase 1 trial. Assuming no undue negative safety signals arise from these trials, DURECT would be positioned to commence one or more Phase 2 patient trials in 2016.

We are currently evaluating potential indications for DUR-928 in order to prioritize the development program. Opportunities fall into four broad categories: (a) orphan acute indications, (b) broader acute indications, (c) orphan chronic indications, and (d) broader chronic indications. DURECT's initial Phase 2 studies will be designed to show an efficacy signal in patients suffering from an orphan acute condition, an orphan chronic condition, and/or a broad chronic indication such as NAFLD/NASH. We plan to provide more detail on the development program later this year.

Update of other selected programs:

- **POSIDUR (SABER-Bupivacaine).** POSIDUR is our investigational post-operative pain relief depot that utilizes our patented SABER technology and is intended to deliver bupivacaine (a non-opioid) to provide up to three days of pain relief after surgery. In February 2014, we received a Complete Response Letter from the FDA informing us that it would not approve the NDA in its present form, stating the NDA does not contain sufficient information to demonstrate that POSIDUR is safe when used in the manner described in the proposed label, and the FDA indicated that additional clinical safety studies would need to be conducted. We had a face-to-face meeting with the FDA in September 2014 to discuss what needs to be done to address the issues cited in the Complete Response Letter. As a result of this meeting and subsequent communications with the FDA, we have submitted to the FDA a protocol synopsis for a soft tissue Phase 3 clinical trial designed to generate the efficacy and safety data required by the FDA for product approval. We are awaiting FDA feedback on that protocol synopsis.

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

- **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. Development and commercialization rights had been held by Pfizer until October of 2014, when Pfizer notified our licensee, Pain Therapeutics, that it was returning those rights. We understand that the studies required to resubmit the NDA were completed in 2014, although we have not seen the results. Pain Therapeutics has stated that it is focused on an orderly transition of the program back from Pfizer, which they expect to be substantially completed in the second quarter of 2015, finalizing a strategy around the prospect of resubmitting the NDA, and seeking a new

commercial partner. The extended release oxycodone market is ~$2.5 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.

- **Injectable Depot Programs.** In addition to POSIDUR, we have two other disclosed programs incorporating our injectable SABER and CLOUD technologies that are worthy of review. Both of these programs began as feasibility projects and successfully matured into development agreements.
    - **Relday (Risperidone Program).** Relday is a proprietary, long-acting, once-monthly subcutaneous injectable formulation of risperidone. To provide context, an existing long-acting injectable risperidone product that achieved $1.2 billion in global net sales in 2014 requires drug reconstitution prior to use and twice-monthly, intramuscular injections. Zogenix (our licensee) has previously announced positive results from a single-dose Phase 1 clinical trial of Relday at the full dose range anticipated to be used in clinical practice. Zogenix commenced a multi-dose trial in the first quarter of 2015 and expects to have top-line data in the third quarter of 2015. Zogenix has also stated that it is targeting an end-of-Phase 2 meeting with the FDA by early 2016.
    - **Santen Ophthalmic Program.** In December 2014, we granted Santen Pharmaceutical Co., Ltd. an exclusive worldwide license to our proprietary SABER formulation platform and other intellectual property to develop and commercialize a sustained release product to deliver an ophthalmology drug. Santen controls and funds the development and commercialization program for this drug. In connection with the license agreement, Santen paid us an upfront fee of $2 million in cash and agreed to make contingent cash payments to us of up to $76 million upon the achievement of certain development and commercialization-based milestones. Santen will also pay for certain of our costs incurred during the development of the licensed product. If the product is commercialized, DURECT would also receive a tiered royalty on annual net product sales ranging from single-digit to the low double digits, determined on a country-by-country basis.
- **ALZET and LACTEL products.** The wide use and many research applications of our ALZET line of osmotic pumps are evidenced by over 15,000 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 2014, these product lines generated $11 million in revenue and $7 million in gross profit for DURECT.

Potential key drivers for DURECT over the next 12-24 months:

- Initiating and completing a Phase 3 clinical trial for POSIDUR to address the Complete Response Letter
- Conducting additional Phase 1 studies with DUR-928 such that we can commence one or more Phase 2 studies in 2016
- Supporting Pain Therapeutics as they transition the REMOXY program back from Pfizer and prepare for a potential resubmission of the NDA
- Supporting Zogenix as they conduct a multi-dose clinical study with Relday and position the program to be Phase 3 ready in 2016
- Collaborating with Santen in our new ophthalmic development program
- Advancing existing feasibility projects and potentially entering into additional feasibility studies and collaborations

On behalf of everyone at DURECT, we thank you for your continued support and look forward to reporting on our progress in 2015 and beyond.

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

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

Forward Looking Statements: The statements in this stockholder letter regarding regulatory matters, including meetings, discussions and submissions regarding POSIDUR, REMOXY and Relday and potential FDA approval of our product candidates, anticipated clinical trials (including timing and results) for POSIDUR, DUR-928, 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, including advancing and entering into feasibility projects and studies, 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 that development of REMOXY may be significantly delayed and adversely affected by Pfizer's discontinuation of its development, the risk of adverse decisions by regulatory agencies, including rejection of meeting requests, requests for additional trials of POSIDUR, requests for additional information or product non-approval or non-acceptance of the POSIDUR, REMOXY 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, 2014 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.