May 8, 2017

Dear Fellow Stockholders:

Recent progress with the development of POSIMIR® and DUR-928 gives us confidence that these innovative drugs have significant potential and that our company has reached an important inflection point as we prepare for the commercialization of POSIMIR, our first therapeutic product, and advance clinical development of DUR-928.

POSIMIR is an extended-release pain product intended to cover the first three days after surgery that may reduce the need for opioids with their attendant risks and side-effects. We expect to complete dosing patients in our pivotal Phase 3 trial (PERSIST) in the next few months and report top-line results later this year. On the basis of our clinical findings and the drug's therapeutic potential, we recently signed an agreement with Sandoz to bring this important product to patients who may benefit from it.

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 important functions of lipid homeostasis, inflammation and cell survival. As such, this small molecule may have therapeutic benefits in several metabolic and liver diseases such as nonalcoholic steatohepatitis (NASH) and primary sclerosing cholangitis (PSC), in acute organ injuries such as liver and kidney injury, and in inflammatory skin diseases such as psoriasis.

POSIMIR (SABER®-Bupivacaine):

Our recent development and commercialization agreement with Sandoz includes an upfront payment to DURECT of $20 million, with the potential for up to an additional $43 million in development and regulatory milestones, up to an additional $230 million in sales based milestones, as well as a tiered double digit royalty on product sales in the United States. DURECT will remain responsible for the completion of the ongoing PERSIST Phase 3 clinical trial for POSIMIR as well as FDA interactions through approval. Sandoz will be responsible for commercializing POSIMIR. Closing of the transaction is anticipated to occur in the second quarter of 2017 and is contingent upon Hart-Scott-Rodino (HSR) antitrust clearance.

We are nearing the completion of dosing in the Phase 3 PERSIST trial for patients undergoing laparoscopic gallbladder surgery to further evaluate the benefits and risks of POSIMIR and to generate the data necessary to support an NDA resubmission. In a previous clinical trial of 50 patients in the same surgical model (laparoscopic cholecystectomy), POSIMIR was compared with the active control bupivacaine HCl, against which POSIMIR demonstrated in a post hoc analysis an approximately 25% reduction in pain intensity on movement for the first 3 days after surgery ($p=0.024$) and for the first 2 days after surgery ($p=0.0198$), using the same statistical methodology specified for the current trial. The main cohort of the PERSIST trial consists of approximately 264 patients who will receive either POSIMIR or standard bupivacaine HCl as an active control. We expect to have top-line results from this trial in 2017, which would poise us to resubmit the NDA thereafter.

DUR-928*:*

We recently reported encouraging results at a major scientific meeting from our first patient trial utilizing DUR-928. Twenty NASH patients and 12 matched control subjects received single oral doses. DUR-928 was well tolerated in this Phase 1b study and plasma exposure was not significantly increased in NASH patients compared to matched control subjects with normal liver function. While this study was not designed to assess efficacy, treatment with a single dose of DUR-928 was associated with a decrease in cell death markers, an improvement of a biomarker of liver function, and decreases in certain biomarkers associated with inflammation. Collectively, the reduction of these biomarkers, together with results from DURECT's animal and cell culture studies, suggest potential therapeutic activity of DUR-928 in patients with liver disease.

We also conducted an initial exploratory Phase 1b trial in psoriasis patients (9 evaluable patients). The decision to proceed with clinical testing in psoriasis was based on the anti-inflammatory and cell survival properties of DUR-928, as well as the results of a psoriasis study with DUR-928 in mice. The Phase 1b trial was conducted with intradermal micro injections of DUR-928, and we feel the results demonstrated promising activity and warrant further investigation. As a result, we have developed several topical formulations of DUR-928 that we are evaluating for a topical application microplaque trial which we expect to commence this year. We believe that there is a large unmet medical need for new topical drugs for psoriasis for use prior to systemic biologic treatments which often have significant associated side effects.

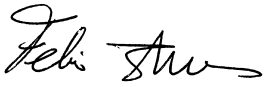
In addition, we are close to completing a Phase 1b single-ascending-dose, injectable administration trial in renal-function-impaired patients (12 chronic kidney disease and 6 matched controls). This trial is expected to enable and inform subsequent patient studies that we are designing with experts in kidney disease.

We are currently pursuing the development of DUR-928 for: (i) chronic metabolic diseases or liver diseases using an oral formulation; (ii) acute organ injury using an injectable formulation; and (iii) inflammatory skin disorders such as psoriasis using a topical formulation. Our next step in the development program involves multiple Phase 2 or other proof-of-concept studies.

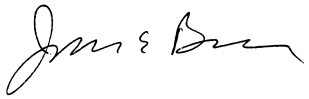
Given space constraints, just a brief mention of a few other programs and products at DURECT:

- **REMOXY® ER.** Based on DURECT's ORADUR® technology, REMOXY ER is a unique long-acting formulation of oxycodone designed to discourage common methods of tampering associated with opioid misuse and abuse. In March 2017, Pain Therapeutics (our licensee) stated that it plans to conduct two additional studies based on guidance following a meeting with the FDA. Pain Therapeutics stated that it expects to complete these studies by the end of 2017, after which they intend to have a pre-NDA meeting with the FDA followed by resubmission of the NDA. 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 ER of between 6.0% to 11.5% of net sales depending on sales volumes.
- **ORADUR-ADHD.** With our licensee in defined Asian and South Pacific countries (Orient Pharma), we are developing a drug candidate (ORADUR-methylphenidate) 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. Orient Pharma has completed dosing a Phase 3 trial in Taiwan and anticipates obtaining top-line results in the second quarter of 2017. We retain rights to all other markets in the world, notably including the U.S., Europe and Japan.
- **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 2016, these product lines generated over $11 million in revenue and over $7 million in gross profit.

We feel that DURECT has crossed several thresholds with our lead programs, with further milestones in sight. We believe that POSIMIR can be a major advance in post-surgical pain management. Our U.S. commercialization strategy is now set with the signing of our collaboration with Sandoz, and we are focused on executing the PERSIST trial and resubmitting the NDA. DUR-928 is a rare opportunity — an endogenous molecule that appears to be safe and yet with regulatory activities in the important functions of lipid homeostasis, inflammation and cell survival that could yield multiple indications. Our focus is on driving DUR-928 forward to demonstrate further proof-of-concept in different patient populations. On behalf of everyone at DURECT, we thank you for your continued support and look forward to reporting on our progress in 2017 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 anticipated submissions regarding POSIMIR and REMOXY ER, potential FDA approval of POSIMIR and REMOXY ER, anticipated clinical trials (including timing and results) for DUR-928, POSIMIR, REMOXY ER, ORADUR-ADHD and our other drug candidates, potential royalties from Sandoz and 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, and market opportunities for our products candidates 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 POSIMIR or REMOXY ER, requests for additional information or product non-approval or non-acceptance of the POSIMIR, REMOXY ER or other NDA submissions, delays and additional costs due to requirements imposed by regulatory agencies, failure of initial safety and efficacy indications for DUR-928 to be demonstrated in larger controlled trials, additional time and resources that may be required for development, testing and regulatory approval of our Epigenetic 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, 2016 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.