UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2021

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission file number: 000-31615

DURECT CORPORATION

(Exact name of registrant as specified in its charter)

Delaware	**94-3297098**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

10260 Bubb Road
Cupertino, CA 95014
(Address of principal executive offices, including zip code)
Registrant's telephone number, including area code: (408) 777-1417

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Trading Symbol(s)	Name of Each Exchange on Which Registered
Common Stock $0.0001 par value per share	**DRRX**	**The NASDAQ Capital Market LLC**

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES ☐ NO ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15 of the Act. YES ☐ NO ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period than the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. YES ☒ NO ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). YES ☒ NO ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	☐	Accelerated filer	☐
Non-accelerated filer	☒	Smaller reporting company	☒
Emerging growth company	☐		

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). YES ☐ NO ☒

The aggregate market value of the voting stock held by non-affiliates of the registrant was approximately $322,943,320 as of June 30, 2021 based upon the closing sale price on The Nasdaq Global Market reported for such date. Shares of Common Stock held by each officer and director and by each person who may be deemed to be an affiliate have been excluded. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

There were 227,694,015 shares of the registrant's Common Stock issued and outstanding as of March 3, 2022.

DOCUMENTS INCORPORATED BY REFERENCE

Part III incorporates information by reference from the definitive Proxy Statement for the 2021 annual meeting of stockholders, which is expected to be filed not later than 120 days after the Registrant's fiscal year ended December 31, 2021.

DURECT CORPORATION

ANNUAL REPORT ON FORM 10-K

FOR THE FISCAL YEAR ENDED DECEMBER 31, 2021

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PART I

Item 1. Business.

Overview

We are a biopharmaceutical company advancing novel and potentially lifesaving investigational therapies derived from our Epigenetic Regulator Program. Larsucosterol (also known as DUR-928), a new chemical entity in clinical development, is the lead candidate in our Epigenetic Regulator Program. An endogenous, orally bioavailable small molecule, larsucosterol has been shown in both *in vitro* and *in vivo* studies to play an important regulatory role in lipid metabolism, stress and inflammatory responses, and cell death and survival. Alcohol-associated hepatitis (AH) is a life-threatening acute liver condition with no approved therapeutics and a 28-day and 90-day historical mortality rate of 20%-26% and 29%-31%, respectively. 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 called 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. If the AHFIRM trial is successful, it may support an NDA filing and we may decide to develop our own commercial, sales and marketing organization. We have also investigated larsucosterol in patients with nonalcoholic steatohepatitis (NASH) and are considering further development for this indication. In March 2021, a peer-reviewed research paper describing the binding sites and proposed mechanism of action of larsucosterol was published in The Journal of Lipid Research. The publication shows that larsucosterol (referred to in the paper as 25HC3S) binds to and inhibits the activity of DNA methyltransferases (DNMTs) DNMT-1, 3a and 3b, epigenetic regulating enzymes that add methyl groups to DNA (a process called DNA methylation) and have been shown to be elevated in AH patients. As such, by inhibiting DNMT activity, larsucosterol inhibits DNA methylation, thereby regulating the expression of genes that modulate crucial cellular activities, including those associated with cell death, stress response, and lipid biosynthesis. These modulations may lead to improved cell survival, and reduced lipid accumulation and inflammation, as has been observed in various in vivo animal models and in results from our completed clinical trials in AH and NASH.

In addition to our Epigenetic Regulator Program, we developed a novel and proprietary post-surgical pain product called POSIMIR that utilizes our innovative SABER platform technology to enable continuous sustained delivery of bupivacaine, a non-opioid local analgesic, over 3 days in adults. Since our current focus is with our Epigenetic Regulator Program, we pursued a licensing strategy with POSIMIR. In December 2021, we entered a license agreement with Innocoll Pharmaceuticals Limited, pursuant to which the Company granted to Innocoll an exclusive, royalty-bearing, sublicensable right and license to develop, manufacture and commercialize POSIMIR in the United States. Under the agreement, DURECT will earn low to mid double-digit royalties from net sales of POSIMIR and is eligible to receive up to an additional $132 million in milestone payments.

NOTE: POSIMIR® is a trademark of Innocoll Pharmaceuticals, Ltd. in the U.S. and a trademark of DURECT Corporation outside of the U.S. SABER®, CLOUD™, ORADUR™ and ALZET ® are trademarks of DURECT Corporation. Other trademarks referred to belong to their respective owners. Full prescribing information for POSIMIR, including BOXED WARNING and Medication Guide can be found at www.posimir.com. Full prescribing information for PERSERIS, including BOXED WARNING and Medication Guide can be found at www.perseris.com.

As a result of the assignment of certain patent rights, DURECT also receives single digit sales-based earn-out payments from U.S. net sales of Indivior's PERSERIS (risperidone) drug for schizophrenia and single-digit royalties from net sales of Orient Pharma's Methydur Sustained Release Capsules (Methydur) for the treatment of attention deficit hyperactivity disorder (ADHD) in Taiwan. We also manufacture and sell ALZET osmotic pumps used in laboratory research and have several early-stage development programs with corporate collaborators on terms which typically call for our collaborator to fund all or a substantial portion of future development costs and then pay us milestone payments based on specific development or commercial achievements plus royalties on product sales.

Epigenetic Regulator Program and New Chemical Entities

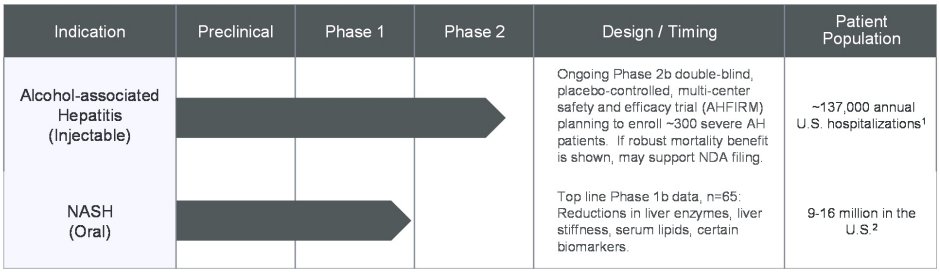
Epigenetic regulation influences the expression of genes through the silencing or initiation of gene activity without modifying the DNA sequence. For instance, methylation of cytosine nucleotides in promoter regions of DNA, facilitated by DNA methyltransferases (DNMTs), will generally result in downregulation of gene expression, while demethylation generally results in upregulation. DNA methylation/demethylation can thus regulate the expression of relevant genes, especially clusters of master genes that further modulate crucial cellular activities.

DURECT's Epigenetic 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 knowledge base supporting this program is a result of more than 30 years of lipid research by Shunlin Ren, M.D., Ph.D., Professor of Internal Medicine at the VCU Medical Center. The lead compound from this program, larsucosterol, is an endogenous sulfated oxysterol, which acts as an epigenetic regulator. Under a license with VCU, we hold the exclusive royalty-bearing worldwide right to develop and commercialize larsucosterol and related molecules discovered in the program.

The biological activity of larsucosterol has been demonstrated in over a dozen different animal disease models involving three animal species. Some of these models represent acute organ injuries (e.g., endotoxin shock, acute oxidative stress, ischemic-reperfusion injury in the kidney and brain) and several represent chronic metabolic disorders involving hepatic lipid accumulation and dysfunction (e.g., NASH and NAFLD).

Our major product research and development efforts for larsucosterol are described in the following table:

Summary of Larsucosterol (DUR-928) Clinical Trials



(1) US Department of Health and Human Services' Healthcare Cost and Utilization Project reports https://hcupnet.ahrq.gov (2) Estes C, et al. Hepatology, 2018;67:123-133.

In pharmacokinetic (PK) and toxicology studies conducted in mice, hamsters, rats, rabbits, dogs, minipigs and monkeys, larsucosterol has been found to be tolerable and safe by all routes of administration tested to date. These results support the use of larsucosterol in completed and ongoing human safety, PK, proof-of-concept, and efficacy trials. The chronic toxicity of larsucosterol was further

assessed in a 6-month oral study in rats and in a 9-month oral study in dogs. These studies were completed successfully and support long duration human clinical trials of larsucosterol.

Acute Organ Injury Program with Injectable larsucosterol

Market Opportunity. Alcohol-associated hepatitis (also called alcoholic hepatitis or AH), an acute form of alcohol-associated liver disease (ALD), is associated with long-term heavy intake of alcohol and often occurs after a recent period of increased alcohol consumption. AH is typically characterized by recent onset jaundice and hepatic failure. AH is associated with approximately 137,000 US hospitalizations per year. An analysis of 77 studies published between 1971 and 2016, which included data from a total of 8,184 patients, showed the overall mortality from AH was 26% at 28 days, 29% at 90 days and 44% at 180 days. A subsequent global study published in December 2021, which included 85 tertiary centers in 11 countries across 3 continents, prospectively enrolled 2,581 AH patients with a median MELD score of 23.5, reported mortality at 28 and 90 days of 20% and 30.9% respectively. There are no FDA approved therapies for AH and stopping alcohol consumption is not sufficient for recovery in many moderate and severe patients. Treatments to reduce liver inflammation, such as corticosteroids, have not demonstrated a benefit in survival at 90 days or 1 year, and have demonstrated an increased risk of infection. In addition, less than 50% of AH patients are eligible for corticosteroids. The cost related to treating hospitalized AH patients and their length of hospital stay were reported at AASLD's The Liver Meeting 2021:

Each hospitalization episode with AH diagnosis for patients who:	Average length of stay	Total healthcare cost per hospitalization episode
Died during the hospitalization	9 days	$151,500
Were discharged	6 days	$56,000
Marlowe, et. Al., AASLD 2021 Poster No. 381#		

The rate of AH patients undergoing liver transplants has more than doubled since the first COVID-19 shelter in-place orders in early 2020. The procedure costs over $875,000 and patients require lifelong immunosuppressive therapy to prevent organ rejection.

Clinical Program. In 2019, we completed a Phase 2a clinical trial evaluating intravenously infused larsucosterol in patients with moderate and severe AH. This was an open label, dose escalation (30, 90 and 150 mg), multi-center U.S. study, originally designed to be conducted in two sequential parts. Part A included patients with moderate AH and Part B included patients with severe AH. Severity of AH was determined by the Model of End-Stage Liver Disease (MELD) scores, a common scoring system to assess the severity and prognosis of AH patients; moderate was defined as MELD 11-20 and severe as MELD 21-30.

In this Phase 2a trial, dose escalation was permitted following review of safety and pharmacokinetic (PK) results of the prior dose level by a Dose Escalation Committee. The target number of patients for the study was 4 per dose group. Final enrollment included 19 patients with moderate and severe AH, who were administered larsucosterol intravenously at three different doses. Eight patients (four moderate and four severe) were dosed at 30mg, seven patients (three moderate and four severe) were dosed at 90mg and four patients (all severe) were dosed at 150mg. After being discharged on day two, one patient did not return for the scheduled day seven and day 28 follow-up visits; therefore Lille, bilirubin and MELD data reported below are based on 18 patients. The objectives of this study included assessment of safety, PK and pharmacodynamic (PD) signals, including liver biochemistry, biomarkers, and prognostic scores, including the Lille score, following larsucosterol treatment.

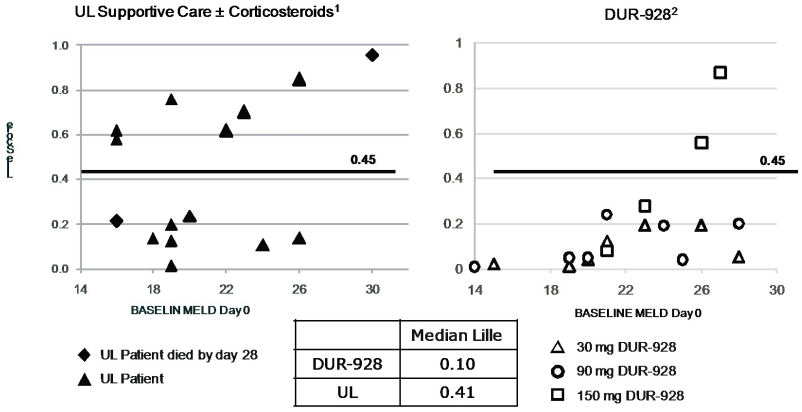
In November 2019, the results from this Phase 2a clinical trial of larsucosterol in alcoholic hepatitis (AH) were presented as a late-breaking oral presentation at The Liver Meeting®. The study results were also selected for inclusion in the 'Best of The Liver Meeting' summary slide presentation in the alcohol-related liver disease category.

All 19 patients treated with larsucosterol in this trial survived the 28-day follow-up period and there were no drug-related serious adverse events. Using an alternative measure of AH severity to MELD, Maddrey's Discrimination Function (DF), 15 of the 19 patients had DF scores of 32 or greater, indicating that they had severe AH. Patients treated with larsucosterol had a statistically significant reduction from baseline in bilirubin at day 7 and 28 and MELD at day 28. Lille scores, described below, were also statistically significantly lower than those from a well-matched group of patients in a contemporary trial as well as several published historical controls. 74% of all larsucosterol treated patients and 67% of those with severe AH were discharged from the hospital within four days of receiving a single dose of larsucosterol.

Lille

Lille scores are used in clinical practice to help determine the prognosis and response of AH patients after seven days of treatment. The lower the Lille score, the better the prognosis. Patients with a Lille score below 0.45 have a six-month survival rate of 85% compared to those with Lille scores above 0.45, who have only a 25% six-month survival rate. The chart below shows the Lille scores for individual AH patients treated with larsucosterol plotted as a function of their baseline MELD scores. In our study, the median Lille score for patients treated with larsucosterol was 0.10. The median Lille score among a cohort of 15 patients treated with standard of care at the University of Louisville (UL) was 0.41 (shown as historical control).

The chart below shows individual patient Lille scores plotted as a function of their baseline MELD scores.



	Median Lille
DUR-928	0.10
UL	0.41

1) *Our advisor, Dr. Craig McClain from the University of Louisville (UL), shared anonymized data from his study, in which 15 AH patients with initial MELD scores ranging from 15-30 received either supportive care alone (n=8 moderate AH patients) or supportive care with corticosteroids (n=7 severe AH patients). Two of the UL control patients died by day 28.*
2) *One patient in the* larsucosterol *(DUR-928) group did not return for the day 7 or 28 visit. All 19 patients, including this one, treated with* larsucosterol *in this trial survived the 28-day follow-up period.*
3) *Lille scores in the* larsucosterol *group were significantly lower than that of the UL patients (p=0.01; Wilcoxon's Rank Sum Test).*

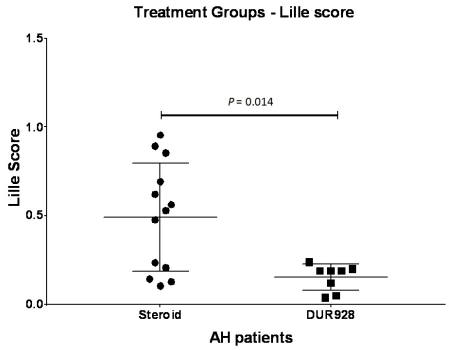
As shown below, 100% of patients in the 30 mg and 90 mg larsucosterol dosing groups were treatment responders based on their Lille scores. 89% of the overall larsucosterol patient population were treatment responders based on Lille. Patients with severe AH, as defined by Maddrey's Discriminant Function (DF) ≥32 or MELD 21-30, and baseline serum bilirubin above 8 mg/dL, had similarly high response rates to larsucosterol treatment.

AH Patient Category		**n[1]**	**Responders (Lille<0.45)**	**Lille Median (Quartile)**
All Patients[2]		18	89%	0.10 (0.04, 0.20)
30 or 90 mg larsucosterol [3]		14	100%	0.05 (0.04, 0.19)
DF≥32 (SAH)[2, 4]		15	87%	0.19 (0.05, 0.22)
30 or 90 mg larsucosterol [3]		11	100%	0.12 (0.05, 0.19)
MELD 21-30[2]		12	83%	0.19 (0.11, 0.25)
30 or 90 mg larsucosterol [3]		8	100%	0.19 (0.10, 0.19)
Baseline bilirubin >8mg/dl[2]		11	82%	0.10 (0.05, 0.20)
30 or 90 mg larsucosterol [3]		8	100%	0.10 (0.05, 0.19)

1) *One patient did not return for Day 7 and 28 visits.*
2) *Including patients receiving 30, 90 and 150 mg of* larsucosterol*.*
3) *Excluding patients receiving 150 mg of* larsucosterol*.*
4) *Maddrey's Discriminant Function (MDF or DF) is calculated using the patient's prothrombin time and serum bilirubin level. DF was introduced in 1978 as a predictor of significant mortality risk for AH patients. A DF≥32 identified AH patients with a 30-day mortality rate of ≥50%.*

The Lille scores of patients treated with larsucosterol in this trial were also significantly lower than several selected published historical studies *(Hepatology 2007, 45:1348-1354; Gut 2011, 60:255-260)*, in which patients had similar baseline bilirubin, albumin, creatinine, prothrombin time and DF scores, and were treated with standard of care with or without corticosteroids. Of course, due to the historical nature of these studies, such comparisons should be taken cautiously.

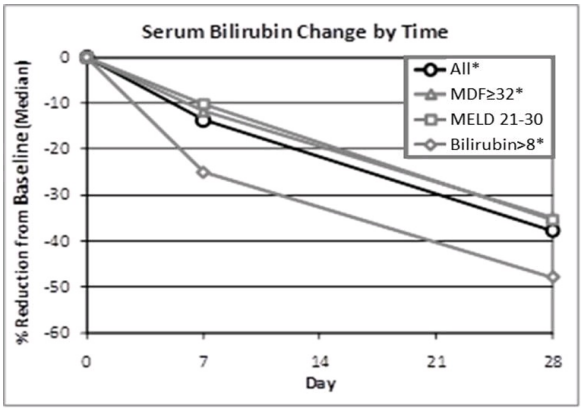
A sub-group analysis was conducted to compare severe AH patients in the 30 mg and 90 mg dosing groups (n=8) with well-matched severe AH patients (n=13) who received corticosteroids for 28 days in a contemporaneous study at the University of Louisville (UL). Patients shown below in the UL steroid group had a mean baseline MELD of 24.46 and mean baseline Maddrey's DF score of 62.98. The 8 patients in the larsucosterol group had baseline mean MELD of 24.50 and mean baseline Maddrey's DF score of 61.25. All patients treated with larsucosterol survived the 28-day follow up period, while 3 of the 13 patients (23%) in the UL steroid group died within the first 28 days.



The steroid group in the above graph includes the 7 severe AH patients treated with steroids from the UL group shown in the MELD vs Lille graph above plus an additional 6 severe AH patients subsequently treated in the UL study.

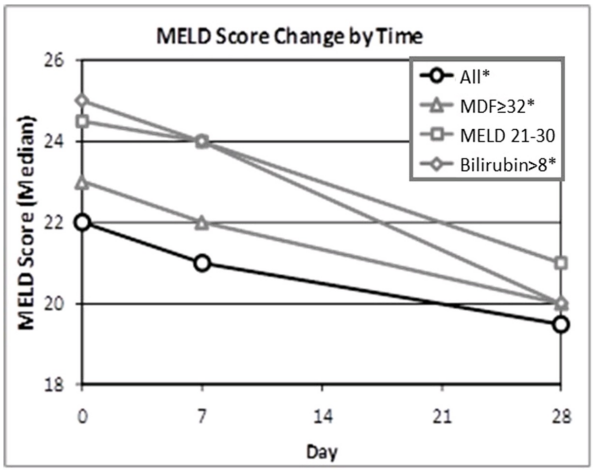
Bilirubin

Bilirubin is formed by the breakdown of red blood cells in the body. The level of total bilirubin in the blood is an indication of how the liver is functioning. High bilirubin levels usually signify liver dysfunction and disease. In this trial, patients treated with larsucosterol had a significant early reduction from baseline in bilirubin by day 7. Patients with more elevated bilirubin at baseline (serum bilirubin >8 mg/dL) had a median reduction from baseline of 25% by day 7 and 48% by day 28.



**p<0.05 compared to baseline (Wilcoxon's Signed Rank Test)*

MELD is another common scoring system used to assess the severity and prognosis of AH patients. Patients with MELD scores of 11-20 are classified as having moderate AH and patients with MELD scores of 21-30 are classified as having severe AH. As with Lille scores, the lower the MELD score, the better the prognosis for the AH patient. In this study (shown in the chart below), the median reduction from baseline in MELD among all larsucosterol treated patients was >2 points and among those with baseline bilirubin levels >8 mg/dL was 5 points by day 28.



**p<0.05 compared to baseline (Wilcoxon's Signed Rank Test)*
MELD is calculated based on (a) bilirubin, (b) serum creatinine (sCr), and (c) International Normalized Ratio (INR), which is a measure of prothrombin time.

Safety and Pharmacokinetics

In the Phase 2a study of larsucosterol in AH, larsucosterol was well tolerated at all doses tested. There were no drug-related serious adverse events and only three adverse events designated as possibly or probably related to larsucosterol: one occurrence of moderate generalized pruritus, one mild rash and one grade two alkaline phosphatase elevation. There were no discontinuations, early withdrawals or termination of study drug or study participation due to adverse events. All patients treated with larsucosterol survived through the 28-day follow-up period. Drug exposures were dose proportional and were not affected by the severity of the disease.

In December 2020, we announced that the FDA had 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.

In January 2021, we announced the dosing of the first patient in our Phase 2b study in subjects with AH to evaluate saFety and effIcacy of larsucosterol treatMent (AHFIRM). AHFIRM is a randomized, double-blind, placebo-controlled, international, multi-center Phase 2b study to evaluate the safety and efficacy of larsucosterol in approximately 300 patients with severe AH. The study is comprised of three arms targeting approximately 100 patients each: (1) Placebo plus standard of care (SOC, which may include the use of methylprednisolone, a corticosteroid, at the discretion of the treating physician); (2) larsucosterol (30 mg); and (3) larsucosterol (90 mg). All patients in the trial receive supportive care. Patients receive an intravenous (IV) dose of larsucosterol or placebo (sterile water) on day 1 and a second

IV dose on day 4 if they are still hospitalized. The primary outcome measure will be the 90-day survival rate for patients treated with larsucosterol compared to those treated with placebo plus SOC. Secondary endpoints include 28-day survival, the rate of adverse events, Lille and MELD (prognostic scores), and time in the intensive care unit. We are targeting more than 60 clinical trial sites across the United States, U.K., E.U. and Australia.

Phase 1 trials of larsucosterol administered through injection have supported the development of larsucosterol in AH. The initial Phase 1 trial in healthy subjects was a single-site, randomized, double-blinded, placebo-controlled, single-ascending-dose study that evaluated the safety, tolerability and PK of intramuscular (IM) injected larsucosterol. The 24-subject study (16 healthy volunteers on the drug and 8 on placebo) of four escalating dose levels resulted in dose proportional systemic exposure of larsucosterol. Larsucosterol was well-tolerated at all dose levels, with no serious treatment-related adverse events reported. We also conducted a multiple-dose study involving 10 healthy subjects, in which participants received IM-injected larsucosterol for 5 consecutive days (8 subjects on the drug, 2 on placebo) using the next to highest dose from the single dose study. No serious treatment related adverse events were reported, no subjects withdrew from the study, no accumulation in plasma concentrations were observed with repeat dosing, and the pain scores and injection site reactions were minimal. We also conducted a single-ascending dose intravenous (IV) infusion study with 16 healthy subjects and observed no treatment-related serious adverse events. The systemic exposure following IV infusion was dose proportional.

A Phase 1 drug-drug interaction study conducted in healthy subjects demonstrated that neither orally administered nor intravenously injected larsucosterol at doses tested affected the safety and PK of midazolam, a drug metabolized by CYP3A4, which is one of the important enzymes associated with clinically relevant drug-drug interactions.

We have also conducted a Phase 1b study with injected larsucosterol in patients with impaired kidney function (stage 3 and 4 chronic kidney disease (CKD)) and matched control subjects (MCS), matched by age, body mass and gender with normal kidney function. This study was a single-site, open-label, single-ascending-dose study in two successive cohorts (first a low dose of 30 mg and then a high dose of 120 mg) evaluating safety and PK of intramuscular injected larsucosterol. The low dose cohort consisted of 6 patients with CKD and 3 MCS; the high dose cohort consisted of 5 CKD patients and 3 MCS. In this trial, larsucosterol was well tolerated among all subjects and the PK parameters between the kidney function impaired patients and the MCS were comparable.

Chronic Liver Disease Program with Orally Administered Larsucosterol

Market Opportunity. Non-alcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease in both children and adults. It is estimated that NAFLD affects approximately 30% to 40% of adults and 10% of children in the United States. Non-alcoholic steatohepatitis (NASH), a more severe and progressive form of NAFLD, is one of the most common chronic liver diseases worldwide, with an estimated prevalence of 3-5% globally. No drug is currently approved for treatment of NAFLD or NASH. In addition to these liver diseases, there are a number of orphan liver diseases for which we may seek to develop larsucosterol.

Clinical Program. In 2020, we completed a Phase 1b randomized, multi-center, and open-label clinical study in the United States to evaluate safety, PK and signals of biological activity of larsucosterol in NASH patients with stage 1-3 fibrosis. Larsucosterol (at doses of 50 mg QD, 150 mg QD and 300 mg BID) was administered orally for 28 days with 20 patients or more per dose group for a total of 65 patients in the trial. Key endpoints included safety and PK, and clinical chemistry/efficacy signals, such as liver enzymes (ALT, AST and GGT), serum lipids (e.g., triglycerides), biomarkers (e.g., CK-18s, inflammatory cytokines), and insulin resistance (i.e., HOMA-IR), as well as liver fat content and liver stiffness by imaging (e.g., MRI-PDFF and FibroScan®).

Both the 50 mg and 600 mg dose groups showed a statistically significant median reduction at day 28 from baseline of serum alanine aminotransferase (ALT) levels at -16% and -17%, respectively. The 600 mg dose group also showed statistically significant median reductions at day 28 from baseline of serum aspartate aminotransferase (AST) (-18%) and gamma-glutamyl transferase (GGT) (-8%), and the 50 mg dose group had a statistically significant reduction at day 28 from baseline in liver stiffness as measured by Fibroscan (-10%).

Patients in the 50 mg or 150 mg dose groups also had statistically significant median reduction at day 28 from baseline of serum triglycerides (-13% in the 50 mg group) or LDL-C (-11% in the 150mg group). Patients with elevated baseline triglycerides (≥200 mg/dL; n=16) across all dose groups had a median reduction at day 28 from baseline of -24% ($p < 0.01$). Furthermore, patients in the 50 mg and 150 mg groups had 22% and 18% median reductions (not statistically significant) of HOMA-IR from baseline respectively after 4 weeks of daily oral dosing of larsucosterol. The 600 mg group did not show a change in HOMA-IR.

At day 28, 43% of patients in all three dose groups showed ≥ 10% liver fat reduction from baseline as measured by magnetic resonance imaging - proton density fat fraction (MRI-PDFF). In this subgroup, there was a significant reduction from baseline in median liver fat content (-18%, -19%, and -23%, in the 50 mg, 150 mg and 600 mg groups respectively). The reduction of liver fat content was accompanied by a significant median reduction from baseline of serum ALT (-21%, -19%, and -32%, in the 50 mg, 150 mg and 600 mg groups respectively), as well as both CK-18, M30 and M65 in the 50 mg and 600 mg groups.

Larsucosterol was well tolerated at all three doses evaluated. There were no serious adverse events reported during the study, and no discontinuations, early withdrawals or termination of study drug or study participation due to adverse events. PK parameters after repeat dosing were comparable to those after a single dose (from a prior study), indicating no accumulation of the drug after repeat dosing. We are working with a number of disease experts to determine next steps for larsucosterol in NASH.

We have completed multiple Phase I trials in healthy subjects with orally administered larsucosterol. These included single-ascending-dose and multiple-ascending-dose studies as well as a food effect study. In all of these studies larsucosterol was well-tolerated at all dose levels, with no serious treatment-related adverse events reported. Dose related increases in plasma concentrations were observed and no accumulation in plasma concentrations or food effects were observed with repeat dosing.

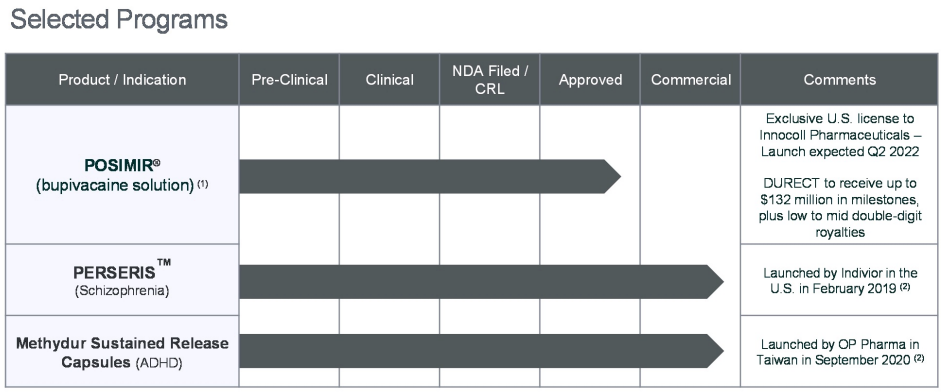
We also conducted a Phase 1b trial in cirrhotic and non-cirrhotic NASH patients and matched control subjects (MCS) (matched by age, body mass index and gender with normal liver function) utilizing orally administered larsucosterol. This was an open-label, single-ascending-dose safety and PK study conducted in Australia in two successive dose cohorts (first a low dose of 50 mg and then a high dose of 200 mg). Both cohorts consisted of 10 NASH patients and 6 MCS. Data from this study was presented at the International Liver Congress™ 2017 organized by the European Association for the Study of the Liver (EASL) in Amsterdam in April 2017. All patients and MCS in this study tolerated larsucosterol well. One patient (with a prior history of arrhythmia and an ongoing viral infection) in the high dose cohort experienced a serious adverse event (shortness of breath), which occurred without unusual biochemical changes and resolved without intervention but was considered possibly treatment related by the physician due to its temporal association with dosing. In both low and high dose cohorts, the PK parameters were comparable between the NASH patients and the MCS. In addition, the systemic exposure following the low and high doses of larsucosterol was dose dependent.

While this study was not designed to assess efficacy, we observed statistically significant reductions from baseline of several biomarkers after both doses of larsucosterol. A single oral dose of larsucosterol significantly reduced the levels of both full-length (M65) and cleaved (M30) cytokeratin-18 (CK-18), bilirubin, hsCRP, and IL-18 in these subjects. The mean reduction of full-length CK-18 (a generalized cell death marker) at the measured time point of greatest effect (12 hours after dosing) was 33% in the low dose cohort and 41% in the high dose cohort. The mean decrease of cleaved CK-18 (a cell apoptosis marker) at the measured time point of greatest effect (12 hours after dosing) was 37% in the low dose cohort and 47% in the high dose cohort. The mean reduction of total bilirubin (a liver function marker) at the measured time point of greatest effect (12 hours after dosing) was 27% in the low dose cohort and 31% in the high dose cohort. The mean decrease of high sensitivity C-Reactive Protein (hsCRP) (a marker of inflammation) at the measured time point of greatest effect (24 hours after dosing) was 8% in the low dose cohort and 13% in the high dose cohort. The mean decrease of IL-18 (an inflammatory mediator) at the measured time point of greatest effect (8 hours after dosing) was 4% in the low dose cohort and 8% in the high dose cohort.

We have also conducted a Phase 1b open-label, multi-center U.S. study to evaluate the safety, tolerability, and pharmacokinetics (PK) of larsucosterol in subjects with moderate (Child-Pugh B scores, n=10) and severe (Child-Pugh C scores, n=7) hepatic function impairment (HI), and matched control subjects (MCS, n=10) with normal hepatic function. Each subject received a single oral dose of 200 mg larsucosterol. Results from this study were presented at the International Liver Conference 2021 (EASL). Larsucosterol was safe and well-tolerated by all moderate and severe HI subjects with no adverse events and no dose-limiting toxicity reported throughout the study. As expected, clearance of larsucosterol was decreased in HI subjects compared to MCS with normal hepatic function, resulting in a 4-10-fold higher drug exposure (Cmax and AUC) in HI subjects. Additionally, a single oral dose of 200 mg of larsucosterol in subjects with HI resulted in statistically significant median reductions from baseline of the apoptosis biomarker M30 (cCK-18) at 12 hours post-dose.

Collectively, the biological signals observed in NASH and HI patients plus results from our animal and cell culture studies suggest potential therapeutic activity of larsucosterol for patients with liver diseases. However, additional studies are required to evaluate the safety and efficacy of larsucosterol, and there is no assurance that these biomarker, clinical chemistry and liver imaging effects will be associated with clinically relevant benefits, or that larsucosterol will demonstrate safety or efficacy in treating liver diseases in our ongoing or future trials.

Approved and Commercial Pharmaceutical Products



1. Full Prescribing Information, including the Boxed Warning, is available at www.posimir.com

2. DURECT to receive earn-outs or royalties based on net sales of PERSERIS and Methydur. PERSERIS prescribing information, including BOXED WARNING and Medication Guide visit www.perseris.com.

POSIMIR® (bupivacaine solution)

POSIMIR (bupivacaine solution) for infiltration use is a novel and proprietary product that combines the strength of 660 mg of bupivacaine base with the innovative SABER® platform technology, enabling continuous sustained delivery of a non-opioid local analgesic over 3 days in adults, which we believe coincides with the time period of the greatest need for post-surgical pain control in most patients. POSIMIR contains more bupivacaine than any other approved single-dose sustained-release bupivacaine product. At the end of surgery, POSIMIR is administered into the subacromial space under direct arthroscopic visualization, where it continuously releases bupivacaine for 72 hours or more.

In February 2021, the U.S. Food and Drug Administration (FDA) approved POSIMIR for infiltration use in adults for administration into the subacromial space under direct arthroscopic visualization to produce post-surgical analgesia for up to 72 hours following arthroscopic subacromial decompression.

In December 2021, we entered into a license agreement (the "Innocoll Agreement") with Innocoll. Pursuant to the Innocoll Agreement, we granted to Innocoll an exclusive, royalty-bearing, sublicensable right and license to develop, manufacture and commercialize POSIMIR in the United States. The License Agreement provides for the assignment of our supply agreement with a contract manufacturing organization to Innocoll and also provides Innocoll with the right, within the United States, to expand the approved indications of POSIMIR. We retain, outside the United States, all of the global rights to POSIMIR. Innocoll agreed to pay us an initial non-refundable, upfront fee of $4.0 million as well as a fee in the amount of $1.3 million primarily to cover the manufacturing supplies and excipients and certain equipment transferred to Innocoll pursuant to the terms of the License Agreement, and certain recently incurred DURECT expenses the parties negotiated for Innocoll to reimburse. In the fourth quarter of 2021, we recognized $4.1 million as collaborative research and development and other revenue, $1.1 million as product revenue, and a reduction of $0.1 million in net equipment. At December 31, 2021, we included $5.3 million due from Innocoll in accounts receivable on our balance sheet; these funds were received in January 2022. We will also receive $2.0 million upon the first commercial sale of POSIMIR in the United States. We are eligible to receive additional milestone payments of up to $130.0 million in the aggregate, depending on the achievement of certain regulatory, commercial, and intellectual property milestones with respect to POSIMIR. In addition, upon commercialization, we will receive tiered low to mid-double-digit royalty payments of net sales of POSIMIR in the United States. Pursuant to the terms of the License Agreement, except as otherwise expressly provided in the License Agreement, Innocoll is responsible for expenses relating to the manufacturing, development and commercialization of POSIMIR in the United States. Innocoll has stated that they expect to launch POSIMIR in the second quarter of 2022, subject to commercial supply timelines.

PERSERIS™ (risperidone)

In September 2017, we entered into an agreement with Indivior, under which we assigned to Indivior certain patents that may provide further intellectual property protection for PERSERIS, Indivior's extended-release injectable suspension for the treatment of schizophrenia in adults. In consideration for such assignment, Indivior made non-refundable upfront and milestone payments to DURECT totaling $17.5 million. Additionally, under the terms of the agreement with Indivior, DURECT receives quarterly earn-out payments that are based on a single digit percentage of U.S. net sales of PERSERIS into 2026. Indivior commercially launched PERSERIS in the U.S. in February 2019.

ORADUR™-ADHD Program

We developed a proprietary drug product for the treatment of ADHD called Methydur in collaboration with Orient Pharma (OP), a diversified multinational pharmaceutical, healthcare and consumer products company with headquarters in Taiwan. We have licensed worldwide Methydur rights to OP and they launched Methydur commercially in Taiwan in September 2020. OP may seek commercialization partners in other countries throughout the world, including China and the U.S. We receive a single digit royalty on sales of Methydur by OP or its commercialization partners as well as potential milestones and sub-license fees.

Drug Delivery Technologies and Programs

Our drug delivery technologies are designed to deliver the right drug to the right place, in the right amount and at the right time to treat a variety of chronic, acute and episodic diseases and conditions. We aim to improve therapy for a given disease or patient population by controlling the rate and duration of drug administration. In addition, if advantageous for the therapy, our technologies can target the delivery of the drug to its intended site of action.

Our technologies are suitable for providing long-term drug therapy because they can often store highly concentrated, stabilized drugs in a small volume and protect the drug from degradation by the body. This, in combination with the ability to continuously deliver desired doses of a drug, can extend the therapeutic value of a wide variety of drugs, including, in some cases, those which would otherwise be ineffective, too unstable, too potent or cause adverse side effects. In some cases, delivering the drug directly to the intended site of action can improve efficacy while minimizing unwanted side effects elsewhere in the body, which may limit the long-term use of many drugs. Our technologies may thus provide better therapy for chronic diseases or conditions, or for certain acute conditions where longer drug dosing is required or advantageous, by replacing multiple injection therapy or oral dosing, improving drug efficacy, reducing side effects and ensuring dosing compliance. Our technology may thereby improve patients' quality of life by eliminating more repetitive treatments, reducing dependence on caregivers and allowing patients to lead more independent lives.

We currently focus our drug delivery technology efforts around our SABER and CLOUD Bioerodible Injectable Depot Systems. SABER uses a high viscosity base component, such as sucrose acetate isobutyrate (SAIB), to provide controlled release of a drug. When the high viscosity SAIB is formulated with drug, biocompatible excipients and other additives, the resulting formulation is easily injectable with standard syringes and needles. After injection of a SABER formulation, the excipients diffuse away over time, leaving a viscous depot which provides controlled sustained release of drug. CLOUD is a class of bioerodible injectable depot technology which generally does not contain SAIB but includes various other release rate modifying excipients and/or bioerodible polymers to achieve the delivery of drugs for periods of days to months from a single injection.

The SABER technology is the basis of POSIMIR (described above). The SABER technology is also utilized in our ophthalmic program with Santen Pharmaceutical Co., Ltd. (Santen), as well as in feasibility programs.

DURECT Strategy

Our objective is to develop multiple pharmaceutical products that address significant unmet medical needs and improve patients' quality of life. To achieve this objective, our strategy includes the following key elements:

Focus on Areas with the Potential for Significant Value Creation. We view patients, physicians, the healthcare system, payers, and strategic partners, as all being important stakeholders in our company. We believe that developing the products in our pipeline, which may address significant unmet medical needs and may create value for our stakeholders, also has the potential to create value for our shareholders.

Apply our Drug Development Expertise to New Chemical Entities Derived from our Epigenetic Regulator Program. We have assembled a core team of employees with considerable experience in drug development, and it is our intent to leverage their capabilities by developing pharmaceuticals derived from our Epigenetic Regulator Program. We believe that these new chemical entities may have utility in acute organ injuries such as AH and for several metabolic diseases such as NASH. We believe that these product candidates may be of interest to other pharmaceutical companies and that it may be possible to license the rights to certain products, formulations, indications or territories from this program while retaining the rights to other product candidates, formulations, indications or territories for either our own development and commercialization or for licensing at a later stage of development. The sale of our LACTEL product line to Evonik in the fourth quarter of 2020 has streamlined the company and sharpened our focus on developing larsucosterol, the lead product candidate in our Epigenetic Regulator Program.

Focus on Certain Acute Indications and Chronic Debilitating Medical Conditions. Many of the diseases and disorders that present great challenges to medicine include acute organ injury, metabolic disorders, and other acute and chronic conditions. Our current efforts focus on exploiting our Epigenetic Regulator Program through which we have identified new chemical entities, including larsucosterol, our lead compound, that may have utility in conditions such as acute organ injuries, including AH and chronic metabolic/lipid disorders, including NASH.

Diversify Risk by Pursuing Multiple Programs in Development. In order to reduce the risks inherent in pharmaceutical product development, we have diversified our product pipeline such that we are pursuing multiple indications with our lead epigenetic regulator, larsucosterol, and we have several early-stage programs being developed in collaboration with partners. Between our own programs and those where we have collaborated, we have multiple programs with the potential to generate significant value. We believe that having multiple indications and programs in development helps mitigate the negative consequences to us of any setbacks or delays in any one of our indications or programs.

Enable Product Development Through Strategic Agreements. We believe that entering into selective strategic collaborations and other arrangements with respect to our product development programs and technology can enhance the success of our product development and commercialization, leverage and exploit the value of our intellectual property portfolio, mitigate our risk and enable us to better manage our operating costs. Additionally, such collaborations and arrangements enable us to leverage investment by third parties and reduce our net cash burn, while retaining significant economic rights.

Build Our Own Commercial Organization. In the future, we may elect to build our own commercial, sales and marketing capability in order to capture more of the economic value of certain products that we may develop. If we choose to enter into third-party collaborations to commercialize our pharmaceutical product candidates, we may in the future enter into these alliances under circumstances that allow us to participate in the sales and marketing of these products.

Strategic Agreements

We have entered into the following strategic collaboration and other key agreements:

Innocoll Pharmaceuticals Limited. In December 2021, we entered into the Innocoll Agreement, pursuant to which, we granted to Innocoll an exclusive, royalty-bearing, sublicensable right and license to

develop, manufacture and commercialize POSIMIR in the United States with respect to all uses and applications in humans. The License Agreement provides for the assignment of our supply agreement with a contract manufacturing organization to Innocoll and also provides Innocoll with the right, within the United States, to expand the approved indications of POSIMIR. We retain, outside the United States, all of the global rights to POSIMIR. Innocoll agreed to pay us an initial non-refundable, upfront fee of $4.0 million as well as a fee in the amount of $1.3 million primarily to cover the manufacturing supplies and excipients and certain equipment transferred to Innocoll pursuant to the terms of the License Agreement, and certain recently incurred DURECT expenses the parties negotiated for Innocoll to reimburse. In the fourth quarter of 2021, we recognized $4.1 million as collaborative research and development and other revenue, $1.1 million as product revenue, and a reduction of $0.1 million in net equipment. At December 31, 2021, we included $5.3 million due from Innocoll in accounts receivable on our balance sheet; these funds were received in January 2022. We will also receive $2.0 million upon the first commercial sale of POSIMIR in the United States. We are eligible to receive additional milestone payments of up to $130.0 million in the aggregate, depending on the achievement of certain regulatory, commercial, and intellectual property milestones with respect to POSIMIR. In addition, upon commercialization, we will receive tiered low to mid-double-digit royalty payments of net sales of POSIMIR in the United States. Pursuant to the terms of the License Agreement, except as otherwise expressly provided in the License Agreement, Innocoll is responsible for expenses relating to the manufacturing, development and commercialization of POSIMIR in the United States. The License Agreement includes customary representations and warranties on behalf of us and Innocoll, including representations as to the licensed intellectual property, regulatory matters and compliance with applicable laws. The License Agreement also provides for certain mutual indemnities for breaches of representations, warranties and covenants.

Virginia Commonwealth University Intellectual Property Foundation. We have entered into an exclusive in-license and research and development agreement with the Virginia Commonwealth University Intellectual Property Foundation regarding certain new chemical entities under development through our Epigenetic Regulator Program, including larsucosterol. Under this licensing arrangement, we have agreed to undertake certain efforts to bring licensed products to market, pay for prosecution of related patents and report on progress to VCU. In addition, we are obligated to pay low single-digit percentage patent royalties on net sales of licensed products, subject to annual minimum payments and additional milestone payments. This license includes rights to nine patent families. We may terminate this agreement at any time by written notice, and VCU may terminate this agreement by written notice if there is an uncured material breach.

Indivior UK Ltd. In September 2017, we entered into an agreement with Indivior, under which we assigned to Indivior certain patents that may provide further intellectual property protection for PERSERIS, Indivior's extended-release injectable suspension for the treatment of schizophrenia in adults. In consideration for such assignment, Indivior made non-refundable upfront and milestone payments to DURECT totaling $17.5 million. Additionally, under the terms of the agreement with Indivior, DURECT receives quarterly earn-out payments that are based on a single digit percentage of U.S. net sales of PERSERIS into 2026. Indivior commercially launched PERSERIS in the U.S. in February 2019. We also receive a non-exclusive right under the assigned patents to develop and commercialize certain risperidone-containing products and products that do not contain risperidone or buprenorphine. The agreement contains customary representations, warranties and indemnities of the parties.

Santen Pharmaceutical Co., Ltd. In December 2014, we and Santen entered into a definitive agreement (the "Santen Agreement"), pursuant to which, we granted Santen an exclusive worldwide license to our proprietary SABER formulation platform and other intellectual property to develop and commercialize a sustained release product utilizing our SABER technology to deliver an ophthalmology drug. Santen controls and funds the development and commercialization program, and the parties have established a joint management committee to oversee, review and coordinate the development activities of the parties under the Agreement.

In connection with the license agreement, Santen paid us a non-refundable upfront fee of $2.0 million in cash and agreed to make contingent cash payments to us of up to $76.0 million upon the achievement of certain milestones, of which $13.0 million are development-based milestones (none of which has been achieved as of December 31, 2021), and $63.0 million are commercialization-based

milestones including milestones requiring the achievement of certain product sales targets (none of which has been achieved as of December 31, 2021). Santen also pays for certain of our costs incurred in the development of the licensed product. If the product is commercialized, we 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. Santen may terminate the Agreement without cause at any time upon prior written notice, and either party may terminate the Agreement upon certain circumstances including a material uncured breach. As of December 31, 2021, the cumulative aggregate payments received by us under this agreement were $3.3 million. Since 2018, the parties have been working together on a limited set of research and development activities funded by Santen.

Commercial Product Lines

ALZET

The ALZET product line consists of miniature, implantable osmotic pumps and accessories used for research in mice, rats and other laboratory animals. These pumps are neither approved nor intended for human use. ALZET pumps continuously deliver drugs, hormones and other test agents at controlled rates from one day to six weeks without the need for external connections, frequent handling or repeated dosing. In laboratory research, these infusion pumps can be used for systemic administration when implanted under the skin or in the body. They can be attached to a catheter for intravenous, intracerebral, or intra-arterial infusion or for targeted delivery, where the effects of a drug or test agent are localized in a particular tissue or organ. The wide use and applications of the ALZET product line is evidenced by the more than 20,000 scientific references that now exist.

LACTEL® Absorbable Polymers

On December 31, 2020, we closed an Asset Purchase Agreement with Evonik Corporation (Evonik), pursuant to which Evonik purchased certain assets related to our LACTEL Absorbable Polymers product line. Under the terms of the Asset Purchase Agreement, Evonik paid us approximately $15.1 million and also agreed to assume certain liabilities with respect to the transferred assets and assembled workforce.

Marketing and Sales

Historically, we have established strategic distribution and marketing alliances for our product candidates to leverage the established sales organizations that certain pharmaceutical companies have in markets we are targeting. In the future, we may elect to build our own commercial, sales and marketing capability in order to capture more of the economic value of certain products that we may develop. If we choose to enter into third-party collaborations to commercialize our pharmaceutical product candidates, we may in the future enter into these alliances under circumstances that allow us to participate in the sales and marketing of these products. We will continue to pursue strategic alliances and collaborators from time to time consistent with our strategy to leverage the established sales organizations of third-party collaborators.

We market and sell our ALZET product line through a direct sales force in the U.S. and through a network of distributors outside of the U.S.

Suppliers

We purchase the larsucosterol drug substance from a third-party manufacturer and larsucosterol clinical trial materials from another third-party manufacturer. As needed, we purchase sucrose acetate isobutyrate, a raw material for our ORADUR and SABER-based pharmaceutical systems, including Methydur, POSIMIR, and SucroMate, from Eastman Chemical Company. We expect that we will continue to be able to obtain sufficient supply of these raw materials to meet our needs for the foreseeable future. We do not have in place long term supply agreements with respect to all of the components of any of our pharmaceutical product candidates, however, and are subject to the risk that we may not be able to procure all required components in adequate quantities with acceptable quality, within acceptable time frames or at reasonable cost.

Customers

Our product revenues principally are derived from sales of the ALZET product line to academic and pharmaceutical industry researchers, and from the sale of certain key excipients that are included in POSIMIR, Methydur Sustained Release Capsules, SucroMate and other products. Until such time that we are able to bring our pharmaceutical product candidates to market, if at all, we expect these to be our

principal sources of product revenue. We also receive revenue from collaborative research and development arrangements with our third-party collaborators. In 2021, Innocoll accounted for 37% of our total revenue. In 2020, Gilead accounted for 76% of our total revenues pursuant to an agreement that has been terminated.

Manufacturing

The process for manufacturing our pharmaceutical product candidates is technically complex, requires special skills, and must be performed in qualified facilities. We have entered into development and commercial manufacturing agreements with third parties for the manufacture of larsucosterol and POSIMIR (now assigned to Innocoll). In addition, we have a small multi-discipline manufacturing facility in California that we have used to manufacture research and clinical supplies of several of our pharmaceutical product candidates under GMP, including larsucosterol dosage forms and POSIMIR. In the future, we may develop additional manufacturing capabilities for our pharmaceutical product candidates and components to meet our demands and those of our third-party collaborators by contracting with third party manufacturers and by potentially constructing additional manufacturing space at our current facilities in California. We manufacture our ALZET product line and certain key components for POSIMIR and Methydur at one of our California facilities**.**

Patents and Proprietary Rights

Our success depends in part on our ability to obtain patents, to protect trade secrets, to operate without infringing upon the proprietary rights of others and to prevent others from infringing on our proprietary rights. Our policy is to seek to protect our proprietary position by, among other methods, filing U.S. and foreign patent applications related to our proprietary molecules and technology, inventions and improvements that are important to the development of our business. As of March 3, 2022, we owned or exclusively in-licensed over 25 unexpired issued U.S. patents and over 135 unexpired issued foreign patents (which include granted European patent rights that have been validated in various EU member states). In addition, we have over 30 pending U.S. patent applications and over 145 foreign applications pending in Europe, Australia, Japan, Canada and other countries.

The patent status of our most advanced drug candidates is as follows:

Our Epigenetic Regulator Program includes ten in-licensed patent families and eleven patent families solely owned by us. Five patent families each include at least one granted patent that could provide protection until at least 2026, 2032, 2033, 2034, and 2035, respectively. The other patent families include pending patent applications, which if granted, could result in patents providing protecting until at least 2037 to 2042. Patent terms are potentially subject to terminal disclaimers as well as patent term adjustments and extensions. Of the twenty-one patent families covering larsucosterol and/or other molecules in the Epigenetic Regulator Program, two were only filed in the United States, and the other eleven have been filed or likely will be filed both in the U.S. and internationally. Since larsucosterol is an endogenous molecule, patent claims directed to larsucosterol compositions of matter may be more difficult to maintain or enforce in the United States under Myriad Genetics and other recent court decisions. One of the U.S. patents issued before Myriad Genetics, and seven of the larsucosterol U.S. patents issued after Myriad Genetics. The granted claims in the U.S. include both composition of matter and method of treatment claims. There can be no assurance that the pending patent applications will be granted. Further, there can be no assurance that VCU will not attempt to terminate their license to us, which termination could result in the loss of our rights to these patent families.

In the United States, POSIMIR is covered by four patent families. Two patent families include granted patents that could provide protection until 2025 and 2026, respectively. The other two patent families include pending patent applications, which if granted, could result in patents expiring in 2041 and 2042, respectively. In Europe, POSIMIR is covered by two granted patents with one that could expire in 2025 and one that could expire in 2026. The families that could provide protection until at least 2041 and 2042, respectively, will likely be filed in Europe.

Proprietary rights relating to our planned and potential products will be protected from unauthorized use by third parties only to the extent that they are covered by valid and enforceable patents or are effectively maintained as trade secrets. Patents owned by or licensed to us may not afford protection

against competitors, and our pending patent applications now or hereafter filed by or licensed to us may not result in patents being issued. In addition, the laws of certain foreign countries may not protect our intellectual property rights to the same extent as do the laws of the U.S.

The patent positions of biopharmaceutical companies involve complex legal and factual questions and, therefore, their enforceability cannot be predicted with certainty. Our patents or patent applications, or those licensed to us, if issued, may be challenged, invalidated or circumvented, and the rights granted thereunder may not provide proprietary protection or competitive advantages to us against competitors with similar technology. Furthermore, our competitors may independently develop similar technologies or duplicate any technology developed by us. Because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that, before any of our products can be commercialized, any related patent may expire or remain in existence for only a short period following commercialization, thus reducing any advantage of the patent, which could adversely affect our ability to protect future product development and, consequently, our operating results and financial position.

Because patent applications in the U.S. are typically maintained in secrecy for at least 18 months after filing and since publication of discoveries in the scientific or patent literature often lag behind actual discoveries, we cannot be certain that we were the first to make inventions or file for protection of inventions set forth in our patents or patent applications.

Our planned or potential products may be covered by third-party patents or other intellectual property rights, in which case we would need to obtain a license to continue developing or marketing these products. Any required licenses may not be available to us on acceptable terms, if at all. If we do not obtain any required licenses, we could encounter delays in product introductions while we attempt to design around these patents, or could find that the development, manufacture or sale of products requiring such licenses is foreclosed. Litigation may be necessary to defend against or assert such claims of infringement, to enforce patents issued to us, to protect trade secrets or know-how owned by us, or to determine the scope and validity of the proprietary rights of others. In addition, interference, derivation, post-grant oppositions, and similar proceedings may be necessary to determine rights to inventions in our patents and patent applications. Litigation or similar proceedings could result in substantial costs to and diversion of effort by us and could have a material adverse effect on our business, financial condition and results of operations. These efforts by us may not be successful.

We may rely, in certain circumstances, on trade secrets to protect our technology. However, trade secrets are difficult to protect. We seek to protect our proprietary technology and processes, in part, by confidentiality agreements with our employees and certain contractors. There can be no assurance that these agreements will not be breached, that we will have adequate remedies for any breach, or that our trade secrets will not otherwise become known or be independently discovered by competitors. To the extent that our employees, consultants or contractors use intellectual property owned by others in their work for us, disputes may also arise as to the rights in related or resulting know-how and inventions.

Government Regulation

The Food and Drug Administration. The FDA and comparable regulatory agencies in state and local jurisdictions and in foreign countries impose substantial requirements upon the development, manufacture and marketing of pharmaceutical products. These agencies and other federal, state and local entities regulate research and development activities and the testing, manufacture, quality control, safety, effectiveness, labeling, storage, distribution, record keeping, approval, advertising and promotion of our products. We believe that our products in development will be regulated as drugs by the FDA rather than as biologics or devices.

The process required by the FDA under the new drug provisions of the Federal Food, Drug and Cosmetics Act (the Act) before our products in development may be marketed in the U.S. generally involves the following:

- preclinical laboratory and animal tests;
- submission of an Investigational New Drug (IND) application which must become effective before clinical trials may begin;

- adequate and well-controlled human clinical trials to establish the safety and efficacy of the proposed pharmaceutical products candidates in their intended uses; and
- FDA approval of a new drug application.

Section 505 of the Act describes three types of new drug applications: (1) an application that contains full reports of investigations of safety and effectiveness (section 505(b)(1)); (2) an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2)); and (3) an application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics and intended use, among other things, to a previously approved product (section 505(j)). We expect that our drug candidates deriving from our Epigenetic Regulator Program will be evaluated for approval after submission of a new drug application under section 505(b)(1).

The testing and approval process require substantial time, effort, and financial resources, and we cannot be certain that any approval will be granted on a timely basis, if at all. Even though several of our pharmaceutical products candidates utilize active drug ingredients that are commercially marketed in the United States in other dosage forms, we need to establish safety and effectiveness of those active ingredients in the formulation and dosage forms that we are developing.

Preclinical tests include laboratory evaluation of the product, its chemistry, formulation and stability, as well as animal studies to assess the potential safety and efficacy of the pharmaceutical product candidate. We then submit the results of the preclinical tests, together with manufacturing information and analytical data, to the FDA as part of an IND, which must become effective before we may begin human clinical trials. Each subsequent new clinical protocol must also be submitted to the FDA under the IND. An IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions about the conduct of the trials as outlined in the IND and imposes a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin. Our submission of an IND may not result in FDA authorization to commence clinical trials. Further, an independent Institutional Review Board at each medical center proposing to conduct the clinical trials must review and approve any clinical study as well as the related informed consent forms and authorization forms that permit us to use individually identifiable health information of study participants.

Human clinical trials are typically conducted in three sequential phases which may overlap:

- Phase 1: The drug is initially introduced into healthy human subjects or patients and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion.
- Phase 2: Involves clinical trials in a limited patient population to identify possible adverse effects and safety risks, to determine the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.
- Phase 3: When Phase 2 clinical trials demonstrate that a dosage range of the product is effective and has an acceptable safety profile, Phase 3 clinical trials are undertaken to further evaluate dosage, clinical efficacy and to further test for safety in an expanded patient population, at multiple, geographically dispersed clinical study sites.

In the case of products for severe diseases, such as chronic pain, or life-threatening diseases such as cancer, the initial human testing is often conducted in patients with disease rather than in healthy volunteers. Since these patients already have the target disease or condition, these studies may provide initial evidence of efficacy traditionally obtained in Phase 2 trials, and thus these trials are frequently referred to as Phase 1/2 clinical trials or Phase 1b trials. We cannot be certain that we will successfully complete Phase 1, Phase 2 or Phase 3 clinical trials of our pharmaceutical products in development within any specific time period, if at all. Furthermore, the FDA or the Institutional Review Board or the sponsor may suspend clinical trials at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk. During the clinical development of products, sponsors frequently meet and consult with the FDA in order to ensure that the design of their studies will likely

provide data both sufficient and relevant for later regulatory review; however, no assurance of approvability can be given by the FDA.

The results of product development, preclinical studies and clinical studies are submitted to the FDA as part of a new drug application, or NDA, for approval of the marketing and commercial shipment of the product. Submission of an NDA may require the payment of a substantial user fee to the FDA, and although the agency has defined user fee goals for the time in which to respond to sponsor applications, there can be no assurance that the FDA will act in any particular timeframe. The FDA may deny a new drug application if the applicable regulatory criteria are not satisfied or may require additional clinical trials be conducted. Even if such data is submitted, the FDA may ultimately decide that the new drug application does not satisfy the criteria for approval. Once issued, the FDA may withdraw product approval if compliance with regulatory standards is not maintained or if safety problems occur after the product reaches the market. Requirements for additional Phase 4 studies (post approval marketing studies) to confirm safety and effectiveness in a broader commercial use population may be imposed as a condition of marketing approval. In addition, the FDA requires surveillance programs to monitor approved products which have been commercialized, and the agency has the power to require changes in labeling or to prevent further marketing of a product based on the results of these post-marketing programs. Any comparative claims comparing a product to other dosage forms or competitive products typically need to be supported by two adequate and well-controlled head-to-head clinical trials.

Satisfaction of FDA requirements or similar requirements of state, local and foreign regulatory agencies typically takes several years and the actual time required may vary substantially, based upon the type, complexity and novelty of the pharmaceutical product. Government regulation may delay or prevent marketing of potential products for a considerable period of time and impose costly procedures upon our activities. We cannot be certain that the FDA or any other regulatory agency will grant approval for any of our pharmaceutical products under development on a timely basis, if at all. Success in preclinical or early-stage clinical trials does not assure success in later stage clinical trials. Data obtained from preclinical and clinical activities is not always conclusive and may be susceptible to varying interpretations which could delay, limit or prevent regulatory approval. Evolving safety concerns can result in the imposition of new requirements for expensive and time-consuming tests, such as for QT interval cardiotoxicity testing. Even if a product receives regulatory approval, the approval may be significantly limited to specific indications. Further, even after regulatory approval is obtained, any problems associated with a product may result in restrictions on the product or even complete withdrawal of the product from the market. Any pharmaceutical products that we may develop and obtain approval for would also be subject to adverse findings of the active drug ingredients being marketed in different dosage forms and formulations. Delays in obtaining, or failures to obtain regulatory approvals would have a material adverse effect on our business. Marketing our pharmaceutical products abroad will require similar regulatory approvals and is subject to similar risks. In addition, we cannot predict what adverse governmental regulations may arise from future U.S. or foreign governmental action.

There are several FDA programs intended to help facilitate the development of new drugs that meet certain criteria. Specifically, new drugs are eligible for Fast Track designation if they are intended to treat a serious or life- threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug may request the FDA to designate the drug as a Fast Track product at any time during the clinical development of the product. Under a Fast Track designation, the FDA may consider for review sections of the marketing application on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application.

A product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review to facilitate the review.

A product that is being studied for safety and effectiveness in treating serious or life-threatening illnesses and provides meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that it may be approved on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. In addition, the FDA currently requires pre-approval of promotional materials as a condition for accelerated approval, which could adversely impact the timing of the commercial launch of the product.

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in or shorten the duration of the regulatory review and approval process. If a product that has orphan drug designation subsequently receives FDA approval for the disease for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same disease, except in limited circumstances, for seven years. These circumstances are an inability to supply the drug in sufficient quantities or a situation in which a new formulation of the drug has shown superior safety or efficacy or a major contribution to patient care. This exclusivity, however, could also block the approval of our products for seven years if a competitor obtains earlier approval of the same drug for the same indication.

A product may also be eligible for receipt of a Breakthrough Therapy designation. The Breakthrough Therapy designation is intended to expedite the FDA’s review of a potential new drug for serious or life-threatening diseases where “preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.” The designation of a drug as a Breakthrough Therapy provides the same benefits as are available under the Fast Track program, as well as intensive FDA guidance on the product’s development program. Fast Track designation, priority review, accelerated approval and Breakthrough Therapy designation do not change the standards for approval, but they may expedite the development or approval process.

Any pharmaceutical products manufactured or distributed by us pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including record-keeping requirements and reporting of adverse experiences with the product or the active pharmaceutical ingredient or other components of the product. The FDA may also require post-approval clinical or non-clinical trials. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and state agencies for compliance with good manufacturing practices, which impose procedural and documentation requirements upon us and our third-party manufacturers. We cannot be certain that we or our present or future suppliers will be able to comply with the GMP regulations and other FDA regulatory requirements.

The Federal Food, Drug, and Cosmetic Act strictly regulates drug product marketing, prohibits manufacturers from marketing drug products for off-label use and regulates the distribution of drug samples. The FDA has actively enforced regulations prohibiting the marketing of products for unapproved uses, and federal and state authorities are also actively litigating against sponsors who promote their drugs for unapproved uses under various fraud and abuse and false claims act statutes. We and our products are also subject to a variety of state laws and regulations in those states or localities where our products are or will be marketed. Any applicable state or local regulations may hinder our ability to market our products in those states or localities. We are also subject to numerous federal, state and local laws relating to such matters as safe working conditions, manufacturing practices, environmental protection, fire hazard control, and disposal of hazardous or potentially hazardous substances. We may incur significant costs to comply with such laws and regulations now or in the future.

The FDA's policies may change and additional government regulations may be enacted which could prevent or delay regulatory approval of our product candidates. Moreover, increased attention to the containment of health care costs in the U.S. and in foreign markets could result in new government regulations that could have a material adverse effect on our business. We cannot predict the likelihood, nature or extent of adverse governmental regulation that might arise from future legislative or administrative action, either in the U.S. or abroad. *The Drug Enforcement Administration.* The Drug Enforcement Administration (DEA) regulates chemical compounds as Schedule I, II, III, IV or V substances, with Schedule I substances considered to present the highest risk of substance abuse and Schedule V substances the lowest risk. Certain active ingredients in ORADUR-Methylphenidate are listed by the DEA as Schedule II under the Controlled Substances Act of 1970. Consequently, their manufacture, research, shipment, storage, sale and use are subject to a high degree of oversight and regulation. For example, all Schedule II drug prescriptions must be signed by a physician, physically presented to a pharmacist and may not be refilled without a new prescription. Furthermore, the amount of Schedule II substances we can obtain for clinical trials and commercial distribution is limited by the DEA and our quota may not be sufficient to complete clinical trials or meet commercial demand. There is a risk that DEA regulations may interfere with the supply of the drugs used in our clinical trials, and, in the future, our ability to produce and distribute our products in the volume needed to meet commercial demand, which could negatively impact us and our collaborators.

Other Healthcare Laws. In addition to FDA and DEA restrictions on the marketing of pharmaceutical products, other foreign, federal and state healthcare regulatory laws restrict business practices in the pharmaceutical industry. These laws include, but are not limited to, federal and state anti-kickback, false claims, data privacy and security, and physician payment and drug pricing transparency laws.

The U.S. federal Anti-Kickback Statute prohibits, among other things, any person or entity from knowingly and willfully offering, paying, soliciting, receiving or providing any remuneration, directly or indirectly, overtly or covertly, to induce or in return for purchasing, leasing, ordering, or arranging for or recommending the purchase, lease, or order of any good, facility, item or service reimbursable, in whole or in part, under Medicare, Medicaid or other federal healthcare programs. The term "remuneration" has been broadly interpreted to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical and medical device manufacturers on the one hand and prescribers, purchasers, formulary managers and beneficiaries on the other hand. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not meet the requirements of a statutory or regulatory exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the U.S. federal Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all its facts and circumstances. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated. In addition, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. Moreover, a claim including items or services resulting from a violation of the U.S. federal Anti-Kickback Statute

constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. The majority of states also have anti-kickback laws, which establish similar prohibitions and, in some cases, may apply to items or services reimbursed by any third-party payor, including commercial insurers.

In addition, there has been a recent trend of increased federal and state regulation of payments made to physicians and certain other healthcare providers. The Affordable Care Act imposed, among other things, new annual reporting requirements through the Physician Payments Sunshine Act for covered manufacturers for certain payments and "transfers of value" provided to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit timely, accurately and completely the required information for all payments, transfers of value and ownership or investment interests may result in civil monetary penalties. Covered manufacturers must submit reports by the 90th day of each subsequent calendar year and the reported information is publicly made available on a searchable website. In addition, certain states require implementation of compliance programs and compliance with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, impose restrictions on marketing practices and/or require the tracking and reporting of marketing expenditures and pricing information as well as gifts, compensation and other remuneration or items of value provided to physicians and other healthcare professionals and entities. Finally, the Physician Self-Referral (Stark) Law prohibits physicians from referring Medicare or Medicaid patients to providers of "designated health services" with whom the physician or a member of the physician's immediate family has an ownership interest or compensation arrangement, unless a statutory or regulatory exception applies.

Competition

We may face competition from other companies in numerous industries including pharmaceuticals, medical devices and drug delivery.

Competition for larsucosterol, if approved, will depend on the specific indication(s) for which larsucosterol is approved. 89Bio, AbbVie, Afimmune, Akaza Bioscience, Akero Therapeutics, Ascletis, AstraZeneca, Axcella Health, Bristol Myers Squibb, Cirius Therapeutics, CytoDyn, Dr. Falk Pharma, Eli Lilly, Enanta, ENYO Pharma, Evive Biotech, Galectin, Galmed, Genentech, Genfit, Gilead, Hanmi, HighTide Biopharma, Intercept, Inventiva Pharma, Ionis Pharmaceuticals, Isotechnika, Kowa, LifeMax, Lipidio, Lipocine, Madrigal, MediciNova, MedImmune, Mitsubishi Tanabe, NGM Biopharmaceuticals, Nimbus, NorthSea Therapeutics, Novartis, Novo Nordisk, Pfizer, PharmaKing, Poxel, Promethera Biosciences, Seal Rock Therapeutics, Surrozen, Terns Pharmaceutical, Thera Technologies, Viking Therapeutics, and others have development plans for products to treat NAFLD/NASH, AH or other liver diseases. Our current and potential competitors may succeed in obtaining patent protection or commercializing products before us. Many of these entities have significantly greater research and development capabilities than we do, as well as substantially more marketing, manufacturing, financial and managerial resources. These entities represent significant competition for us. Acquisitions of, or investments in, competing pharmaceutical or biotechnology companies by large corporations could increase such competitors' financial, marketing, manufacturing and other resources.

Competition for our ALZET product line primarily consists of customers choosing to utilize delivery methods for their research projects other than an osmotic pump. We also face competition for our ALZET product line from other companies including low-cost foreign competitors.

Any pharmaceutical products we develop will compete in highly competitive markets. Many of our potential competitors in these markets have greater development, financial, manufacturing, marketing, and sales resources than we do and we cannot be certain that they will not succeed in developing products or technologies which will render our technologies and products obsolete or noncompetitive. In addition, many of those potential competitors have significantly greater experience than we do in their respective fields.

Corporate History, Headquarters and Website Information

We were incorporated in Delaware in February 1998. Our principal executive offices are located at 10260 Bubb Road, Cupertino, California 95014. Our telephone number is (408) 777-1417, and our website address is www.durect.com. Information contained on our website is not a part of this Annual

Report on Form 10-K and the inclusion of our website address in this Annual Report on Form 10-K is an inactive textual reference only. We make our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to these reports available free of charge on our website as soon as reasonably practicable after we file these reports with the Securities and Exchange Commission (SEC). The SEC maintains an internet site that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. The SEC's website to access all of this information is www.sec.gov. Our Code of Ethics can be found on our website.

Human Capital

Our approach to human capital resource management starts with our mission to advance novel and potentially lifesaving investigational therapies derived from our Epigenetic Regulator Program. Our industry exists in a complex regulatory environment. The unique demands of our industry, together with the challenges of running an enterprise focused on the discovery, development, manufacture and commercialization of innovative medicines, require talent that is highly educated and/or has significant industry experience. Additionally, for certain key functions, we require specific scientific expertise to oversee and conduct R&D activities and the complex manufacturing requirements for biopharmaceutical products.

The biopharmaceutical industry is highly competitive and recruiting and retaining employees is critical to the continued success of our business. We are an equal opportunity employer and we are fundamentally committed to creating and maintaining a work environment in which employees are treated with respect and dignity. All human resources policies, practices and actions related to hiring, promotion, compensation, benefits and termination are administered in accordance with the principal of equal employment opportunity, meaning that they are made on the basis of individual skills, knowledge, abilities, job performance and other legitimate criteria and without regard to race, color, religion, sex, sexual orientation, gender expression or identity, ethnicity, national origin, ancestry, age, mental or physical disability, genetic information, any veteran status, any military status or application for military service, or membership in any other category protected under applicable law. By focusing on employee retention and engagement, we also improve our ability to support our clinical trials, our pipeline, our platform technologies, business and operations, and also protect the long-term interests of our stockholders. Our success also depends on our ability to attract, engage and retain a diverse group of employees.

Our base pay program aims to compensate management and staff members relative to the value of the contributions of their role, which takes into account the skills, knowledge and abilities required to perform each position, as well as the experience brought to the job. We also provide annual incentive programs to reward our management team and staff members in alignment with achievement of Company-wide goals that are established annually and designed to drive aspects of our strategic priorities that support and advance our strategy across our Company. Our management team and staff members are eligible for the grant of equity awards under our long-term incentive program that are designed to align the experience of these staff with that of our stockholders. All management team and staff members also participate in a regular performance measurement process that aligns pay to performance and through which they receive performance and development feedback.

Our benefit programs are also generally broad-based, promote health and overall well-being and emphasize saving for retirement. All management team and regular staff members are eligible to participate in the same core health and welfare and retirement savings plans. Other employee benefits include employee stock purchase plan, medical plans, dental plans, vacation and sick-pay plans, employee assistance programs, flexible spending accounts, life and accident insurance and short and long-term disability benefits.

Our Compensation Committee provides oversight of our compensation plans, policies and programs.

As of March 3, 2022, we had 79 employees, including 45 in research and development, 10 in manufacturing and 24 in selling, general and administrative. At least 36 of our employees have advanced

degrees of some sort (e.g., MD, PhD, DVM, JD, MBA). The Company strives for gender diversity and diversity beyond gender throughout the organization. Of our employees, 38% are male and 62% are female. From time to time, we also employ independent contractors to support our research, development and administrative organizations. None of our employees are represented by a collective bargaining unit, and we have never experienced a work stoppage. We consider our relations with our employees to be good.

Executive Officers of the Registrant

Our executive officers and their ages as of March 3, 2022 are as follows:

Name	Age	Position
James E. Brown, D.V.M.	65	President, Chief Executive Officer and Director
Michael H. Arenberg, J.D., M.B.A.	52	Chief Financial Officer
Norman L. Sussman, M.D.	69	Chief Medical Officer
Judy R. Joice	65	Senior Vice President, Operations and Corporate Quality Assurance

James E. Brown, D.V.M. co-founded DURECT in February 1998 and has served as our President, Chief Executive Officer and a Director since June 1998. He previously worked at ALZA Corporation as Vice President of Biopharmaceutical and Implant Research and Development from June 1995 to June 1998. Prior to that, Dr. Brown held various positions at Syntex Corporation, a pharmaceutical company, including Director of Business Development from May 1994 to May 1995, Director of Joint Ventures for Discovery Research from April 1992 to May 1995, and held a number of positions including Program Director for Syntex Research and Development from October 1985 to March 1992. Dr. Brown holds a B.A. from San Jose State University and a D.V.M. (Doctor of Veterinary Medicine) from the University of California, Davis where he also conducted post-graduate work in pharmacology and toxicology.

Michael H. Arenberg was appointed Chief Financial Officer effective October 2018. Mr. Arenberg has been with DURECT since 1999, most recently serving as Senior Vice President, Corporate and Business Development, where he negotiated and closed over 50 collaborations, including several important in-licensing transactions. Mr. Arenberg earned his undergraduate degree from the University of Colorado, his law degree from the University of Denver, his MBA from the Leavy School of Business at Santa Clara University.

Norman L. Sussman, M.D., FAASLD, joined DURECT as Chief Medical Officer in November 2020. He has extensive clinical experience and expertise in the field of liver disease and brings over 30 years of clinical research and development experience in academia and industry. Prior to joining DURECT he was an Associate Professor of Medicine and Surgery at Baylor College of Medicine and a faculty member of Baylor College of Medicine intermittently since 1985. During that time, he served as a Principal Investigator for research focused on the assessment and management of acute liver failure and artificial liver support. Dr. Sussman gained leadership experience in industry as the founder and Vice President of both Amphioxus Cell Technologies from 1995 to 2003 and Hepatix, Inc from 1993 to 1995. Most recently, he has also served in senior leadership roles as a member of the Baylor Faculty Senate and as Director of the telehealth program, Project ECHO®, at Baylor St. Luke’s Medical Center. Dr. Sussman received his MBBCh from the University of the Witwatersrand in Johannesburg, South Africa. He then completed his residency at St. Louis University Hospital and his post-doctoral fellowship at Washington University. He is Board Certified in Internal Medicine, Gastroenterology, and Transplant Hepatology. Dr. Sussman is also a Fellow of the American Association of the Study of Liver Disease, which is a designation that recognizes his superior level of professional achievement in the field of hepatology.

Judy R. Joice has served as our Senior Vice President, Operations and Corporate Quality Assurance since March 2014 and as our Vice President, Operations and Corporate Quality Assurance since April 2011. Previously, Ms. Joice served as our Vice President, Corporate Quality Assurance since July 2008 and as our Executive Director, Quality Assurance from July 2007 to July 2008. She has over 30 years' experience in the pharmaceutical industry with such companies as Nektar Therapeutics, Oread, Roche Pharmaceuticals, and Syntex Research. During her career, Ms. Joice has gained broad experience in CMC development activities including novel excipients, new chemical entities, devices, and combination products. She has developed, implemented and managed all aspects of company-wide quality systems and compliance functions, ranging from drug development through commercial manufacturing. Ms. Joice has a B.S. in Chemistry from California State University, Hayward.

Item 1A. Risk Factors.

In addition to the other information in this Form 10-K, a number of factors may affect our business and prospects. These factors include but are not limited to the following, which you should consider carefully in evaluating our business and prospects. If any of the following risks actually occur, our business, financial condition, results of operations and growth prospects may be materially and adversely affected.

Summary

- We are dependent on the success of larsucosterol (also called DUR-928) and the path to regulatory approval is uncertain; we cannot be certain that it will ever receive regulatory approval or be commercialized
- Fast Track Designation for larsucosterol in AH may not actually lead to faster FDA review or an approval
- Safety data and indications of activity from completed larsucosterol clinical trials may not predict safety, activity or efficacy in future trials
- Open-label trials of larsucosterol in NASH and AH have inherent limitations
- Ongoing and future clinical trials for larsucosterol may be delayed and may not demonstrate efficacy or safety
- We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates
- Key components of larsucosterol are provided by a limited number of suppliers, and supply shortages or loss of these suppliers could result in delays or interruptions in supply or increased costs
- The COVID-19 pandemic has impacted and may adversely impact our business for the foreseeable future, including posing challenges to conducting clinical trials
- We have a significant amount of debt. Compliance with repayment obligations and other covenants may be difficult; failure to fulfill our obligations may cause the repayment obligations to accelerate
- We will require and may have difficulty or be unsuccessful in raising needed capital in the future

- We do not control the commercialization of POSIMIR, PERSERIS or Methydur
- For certain of our product candidates, we depend on third-party collaborators, and we have limited or no control over their development, regulatory strategy or potential commercialization
- Cancellation of collaborations may adversely affect potential economic benefits
- If we do not enter into new collaboration agreements, our revenues and/or cash flows will be reduced relative to prior periods
- Our cash flows are likely to differ from our reported revenues
- Our business strategy includes entering into additional collaborative agreements to support development, clinical trials, manufacturing and commercialization of product candidates. We may not be able to successfully negotiate or enter into acceptable collaboration agreements
- Failure to comply with governmental regulations could materially harm our business
- We have a history of operating losses, expect to continue to have losses and may never achieve profitability; and we may not successfully manage our company through varying business cycles
- We may develop our own sales force and commercial group to market future products, but we have limited sales and marketing experience and may not be able to do so effectively
- Write-offs related to impairment of goodwill, long-lived assets, inventories and other non-cash charges may adversely impact profitability and cause cash flows to differ from reported revenues
- Global credit and financial market conditions could negatively impact the value of our investments
- We depend upon key personnel who may terminate their employment with us at any time, and we may not be able to attract and retain sufficient qualified personnel
- Cyber-attacks or other failures in telecommunications or information technology systems could result in information theft, data corruption and significant disruption of our business operations
- Our corporate headquarters, certain manufacturing facilities and personnel are located in a seismically active area near wildfire zones; our business also involves environmental risks and risks related to handling regulated substances
- As a non-accelerated filer, we are not required to comply with auditor attestation requirements of the Sarbanes-Oxley Act and, consequently, investors may find our common stock less attractive
- If we are unable to protect, maintain or enforce our IP rights or secure rights to third-party IP, we may lose valuable assets, lose market share or incur costly litigation or our third-party collaborators may choose to terminate their agreements with us, which may depend on our IP
- We may be sued by third parties claiming that our products or product candidates infringe on their IP rights, particularly because there is substantial uncertainty about the validity and breadth of biopharmaceutical patents
- Competitive products or technologies could impair our ability to establish, maintain or grow our business
- Our relationships with physicians, patients and third-party payers are subject to anti-kickback, fraud and abuse, privacy and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings
- We could be exposed to significant product liability claims and we are subject to healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages and reputational harm
- Healthcare reform measures could hinder or prevent our product candidates’ commercial success
- Market acceptance of our products or product candidates is uncertain, and failure to achieve market acceptance or adequate reimbursement from third-party payers will harm our future revenues and profitability
- Inability to train physicians to use our products may prevent market acceptance of our products
- Risks related to actions on trade by the U.S. and foreign governments, new accounting pronouncements and legislative actions could adversely affect the Company's results of operations and financial condition
- Our operating history makes evaluating our stock difficult, the price of our stock may be volatile
- Investors may experience substantial dilution of their investment
- Our ability to use net operating losses and other tax attributes is uncertain and may be limited

- We have broad discretion over the use of our cash and investments, which may not always yield a favorable return
- Our certificate of incorporation, bylaws and Delaware law could discourage an acquisition of us
- Having Delaware as the exclusive forum for substantially all disputes between us and our stockholders could limit our stockholders' ability to obtain a favorable judicial forum for disputes
- Our stock price currently does not meet the minimum bid price for continued listing on Nasdaq.

Risks Related To Our Business

We are dependent on the success of larsucosterol and the path to regulatory approval is uncertain; we cannot be certain that it will receive regulatory approval or be commercialized

Our business depends substantially on the successful development of larsucosterol, which has completed multiple clinical trials, including a Phase 1b clinical trial in NASH and a Phase 2a clinical trial in AH, and is currently enrolling patients for a Phase 2b clinical trial (AHFIRM) in patients with severe AH. Ongoing and future clinical trials will need to establish clinically and statistically significant proof of efficacy, and sufficient evidence of safety to support filing for regulatory approval and/or additional clinical trials and ultimately regulatory approval. Larsucosterol will require additional development, including completion of ongoing clinical trials and potentially additional clinical trials as well as potentially further preclinical studies, and other non-clinical parameters, to obtain regulatory clearances before it can be commercialized. Positive results obtained during early development do not necessarily mean later development will succeed or that regulatory clearances or approvals will be obtained. Our drug development efforts may not lead to commercial drugs, for several reasons such as if larsucosterol fails to be shown to be safe and effective or if we do not have adequate financial or other resources to advance larsucosterol through clinical development and the approval processes. We consider larsucosterol to be our lead and most important asset. If larsucosterol fails to demonstrate safety or efficacy at any time or during any phase of development, we would experience potentially significant delays in, or be required to abandon, development of larsucosterol, which would materially harm our business. Even if the Phase 2b AHFIRM trial successfully demonstrates a survival benefit over placebo, (1) additional clinical trial(s) may be required to support an NDA filing and ultimately to support approval by FDA and/or other regulatory bodies; and (2) accelerated regulatory pathways (such as an FDA priority review designation) may not be available.

We do not anticipate that larsucosterol will be eligible to receive regulatory approval from the FDA or comparable foreign authorities and begin commercialization for a number of years, if ever. Even if we ultimately receive regulatory approval for larsucosterol, we or our potential future partners, if any, may be unable to commercialize it successfully for a variety of reasons. These include, for example, the availability of alternative, potentially superior or less expensive treatments, lack of cost-effectiveness, the lack of favorable access and/or commercial pricing, the cost or technical challenges of manufacturing the product on a commercial scale and competition with other treatments. The success of larsucosterol may also be limited by the prevalence and severity of any adverse side effects, including mortality. If we fail to obtain regulatory approval and successfully commercialize larsucosterol, we may be unable to raise sufficient capital or generate sufficient revenues to attain or maintain profitability, and our financial condition and stock price may decline.

Fast Track designation of larsucosterol by the FDA may not actually lead to a faster development or regulatory review or approval

The FDA grants Fast Track designation to therapies that are considered capable of addressing unmet medical needs and possess the potential to treat serious or life-threatening disease conditions in order to facilitate its development and expedite the review procedure. Even though larsucosterol has received Fast Track designation for the treatment of AH, we may not experience a faster development process, review or approval compared to conventional FDA procedures, or receive FDA approval at all, in that indication or any other. A Fast Track designation does not change the standards for approval. The FDA may also withdraw Fast Track designation if it believes that the designation is no longer supported by data from our clinical development program.

Safety data and indications of activity from completed Phase 1 and 2 clinical trials of larsucosterol may not predict safety, activity or therapeutic efficacy in future trials

Although Phase 1 and Phase 2 clinical trials of larsucosterol have shown positive initial data in AH patients, including reductions in bilirubin and MELD scores from baseline and promising Lille scores, and demonstrated in NASH patients that larsucosterol may lead to the reduction from baseline in liver enzymes, liver stiffness and serum lipids as well as certain biomarkers, such initial results, indications of activity and biomarker changes as well as favorable tolerability may ultimately not be correlated with

treatment or improvement in the associated disease, and there is a risk that larsucosterol may not demonstrate therapeutic efficacy in larger placebo-controlled trials such as AHFIRM, despite encouraging initial data and improvements in biomarker levels in smaller, early trials. The failure of larsucosterol to show efficacy in one indication may negatively affect its perceived value in other indications, and the emergence of safety signals in ongoing or future clinical trials would significantly harm our business.

Open-label trials of larsucosterol in NASH and AH have inherent limitations

The most recently completed NASH and AH trials of larsucosterol were open-label trials with no control groups. Open label trials have inherent risk of bias given that the patients and physicians know that the patients received active study drug, which can lead to placebo effects. Trials without control groups have an inherent risk in that the comparisons used to determine the study drug's effect and side effect profile are based on comparisons with baseline (pre-treatment) levels (for blood chemistry and biomarker endpoints) and/or with historical controls, which may not have been conducted under similar enough conditions to make accurate comparisons and/or draw accurate conclusions from those comparisons. Additionally, larger placebo-controlled clinical trials are required to evaluate the safety and efficacy of larsucosterol to treat any indication, including AH and NASH. There can be no assurance that ongoing or future studies will demonstrate the safety or efficacy of larsucosterol in a statistically significant or clinically meaningful manner.

Ongoing and future clinical trials for larsucosterol in AH may be delayed and may not demonstrate efficacy or safety in the indications tested

The Phase 2b AHFIRM trial of larsucosterol in patients with AH is subject to potential delays resulting from the COVID-19 pandemic as well as timing of entering contracts with clinical sites and contract research organizations, obtaining institutional review board approvals and delays in other activities that need to be put in place prior to clinical trial initiation at each clinical trial site. Given uncertainty of COVID-19-related impacts on clinical trial sites in the U.S., U.K., E.U. and Australia, the timing of availability of top-line data from this trial cannot be predicted with certainty. There can be no assurance that the trial will enroll as anticipated if at all, and delays in enrollment could add to the costs and expenses of this trial and harm our business. There can also be no assurance that biological activity demonstrated in previous animal disease models or earlier clinical trials of larsucosterol will also be seen in ongoing trials or future clinical trials, or that any clinically relevant biological activity will be observed, or that enrollment rates will be favorable or that these additional trials will not identify safety issues. Failure of the AHFIRM trial to achieve desired results in its anticipated timeframe would negatively impact our business and ability to raise additional capital.

We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of larsucosterol or any other product candidate

We may experience delays in completing our preclinical studies and initiating or completing clinical trials, and we may experience numerous unfavorable events during, or as a result of, any future clinical trials that we could conduct that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:

- regulators or institutional review boards, or IRBs, or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at one or more prospective trial sites;
- we may experience delays in reaching, or fail to reach, agreement on acceptable terms with prospective trial sites and prospective contract research organizations, or CROs, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites. We may be forced to accept unfavorable contract provisions in such agreements based on country, territory or local laws or requirements of institutions or IRBs where important clinical investigators practice;
- clinical trials of our product candidates may produce negative or inconclusive results, clinical trial subjects receiving placebo or standard of care may experience better than expected outcomes, and we may decide, or regulators may require us, to conduct additional preclinical studies or clinical trials or we may decide to abandon product development programs;

- non-compliance by clinical trial sites or clinical investigators with the study protocol or applicable laws;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate, or participants may drop out of these clinical trials or fail to return for post-treatment follow-up at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all, or may deviate from the clinical trial protocol or drop out of the trial, which may require that we add new clinical trial sites or investigators;
- we may elect to, or regulators or IRBs or ethics committees may require us or our investigators to, suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of our product candidates may be greater than we anticipate;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate; and
- our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or IRBs or ethics committees to suspend or terminate the trials, or reports may arise from preclinical or clinical testing of other therapies that raise safety or efficacy concerns about our product candidates

We could encounter delays if a clinical trial is suspended or terminated by us, by the IRBs of the institutions at which such trials are being conducted, by the Data Safety Monitoring Board, or DSMB, for such trial or by the FDA or other regulatory authorities. Such authorities may impose such a suspension or termination or clinical hold due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities, safety issues or adverse side effects, failure to demonstrate a benefit from using a product, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. Many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates. Further, the FDA may disagree with our clinical trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials.

Our product development costs will also increase if we experience delays in testing or regulatory approvals. We do not know whether any of our future clinical trials will begin as planned, or whether any of our current or future clinical trials will need to be restructured or will be completed on schedule, if at all. Significant preclinical study or clinical trial delays, including those caused by the COVID-19 pandemic, also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations. Any delays in our ongoing or future preclinical or clinical development programs may harm our business, financial condition and prospects significantly.

Key components of larsucosterol are provided by a limited number of suppliers, and supply shortages or loss of these suppliers could result in delays or interruptions in supply or increased costs

While we have entered into contract manufacturing agreements with multiple vendors for larsucosterol, we currently have a third-party sole supplier for GMP supplies of larsucosterol. This third party is our sole source for the drug product required for development and commercialization of this drug candidate.

The reliance on a sole or limited number of suppliers could result in:

- an inability to obtain an adequate supply of larsucosterol;

- delays associated with finding and contracting with a new supplier (if we can find one capable of replacing the old supplier and negotiate commercially reasonable terms) and then transferring the know-how and technology required to perform the services to the new supplier; and
- reduced control over pricing, quality and delivery time.

There can be no assurance that we will receive sufficient quantities of larsucosterol to commence and conduct the non-clinical trials, clinical trials and CMC activities we are planning, and delays in supply could delay development of larsucosterol. In addition, certain of our third-party manufacturers and suppliers may be experiencing delays as a result of the COVID-19 pandemic or have otherwise encountered delays in providing their goods and services. As a result, we may not be able to manufacture our product candidates for our clinical trials and conduct other research and development operations and maintain current clinical and pre-clinical timelines. In addition, if additional third parties in our supply chain are adversely impacted by restrictions resulting from the pandemic, including staffing shortages, raw material shortages, production slowdowns and/or disruptions in delivery systems, our supply chain may be disrupted in other ways, further limiting our ability to manufacture our product candidates for our clinical trials and conduct our research and development operations.

We have supply agreements in place for certain components of our products and product candidates, but do not have in place long term supply agreements with respect to all of the components of any of our products or product candidates. Therefore, the supply of a particular component could be terminated without DURECT's consent at any time without penalty to the supplier. In addition, we may not be able to procure required components or drugs from third-party suppliers at a commercially reasonable quantity, quality, cost and timing. In addition, certain of our suppliers may be experiencing delays as a result of the COVID-19 pandemic or have otherwise encountered delays in providing their services. Any interruption in the supply of single source components (including active pharmaceutical ingredients, excipients, or components like vials, stoppers, filters and the like), products or product candidates, could cause us to seek alternative sources of supply or attempt to manufacture these items internally if feasible. Furthermore, in some cases, we are relying on our third-party collaborators to procure supply of necessary components. If the supply of any components for our products or product candidates is interrupted, components from alternative suppliers may not be available in sufficient volumes or at acceptable quality levels within required timeframes, if at all, to meet our needs or those of our third-party collaborators. This could delay our ability to obtain commercial product supplies or complete development and obtain approval for commercialization and marketing of our product candidates, causing us to lose sales, incur additional costs, delay new product introductions and could harm our reputation and make access to capital more difficult, expensive or impossible. The COVID-19 pandemic has affected and is likely to continue to affect the manufacturing and shipment of goods globally. Many countries have imposed or are imposing certain restrictions on the movement of people and goods and may continue to lift and reimpose such restrictions as needed. Any delay in production or delivery of the components and drug substances used in our products or product candidates for any reason, including due to an extended closure of our suppliers' plants as a result of efforts to limit the spread of COVID-19, could adversely impact our business and hinder our growth.

The COVID-19 pandemic has impacted and may adversely impact our business for the foreseeable future

The global COVID-19 pandemic has disrupted our operations and delayed our clinical trials. In particular, the COVID-19 pandemic delayed the initiation of our AHFIRM Phase 2b clinical trial to evaluate the safety and efficacy of larsucosterol in severe alcohol-associated hepatitis (AH) patients, and it has delayed and may in the future delay the pace of enrollment in this trial and other clinical trials. As a result of the COVID-19 pandemic, there have been and may continue to be longer lead times required for acquiring components and supplies used in manufacturing of larsucosterol, and there have been periods of reduced demand for our ALZET products, which are used in scientific and pre-clinical research. In addition, COVID-19 may have an adverse impact on the economies and financial markets of many countries, resulting in a severe and prolonged global economic downturn that could continue to affect demand for our ALZET product line and impact our operating results. The COVID-19 pandemic may also adversely impact our ability to raise additional capital to provide sufficient funding to continue our

product development efforts, including clinical trials. COVID-19 initially had an adverse impact on the capital markets and could again, which would make it more difficult for companies such as ours to access capital. The extent to which the pandemic impacts our operations will depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the duration and severity of the pandemic, the impact of new variants of the virus, and the actions that may be required to contain the COVID-19 virus or treat its impact. As a result of the COVID-19 pandemic, we may continue to experience disruptions that could severely impact our business, preclinical studies and clinical trials including:

- delays or difficulties in enrolling patients in our clinical trials;
- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- interruption of key clinical trial activities, such as clinical trial site data monitoring, due to limitations on travel imposed or recommended by federal, state or local governments, employers and others or interruption of clinical trial subject visits and study procedures, which may impact the integrity of subject data and clinical study endpoints, the ability to collect, ship and analyze biological samples from clinical trial patients due to concerns about potential contamination of samples and/or exposure of clinical staff to patients with COVID-19;
- interruption or delays in the operations of the FDA or other regulatory authorities, which may impact review and approval timelines;
- disruption or delays in manufacturing of clinical and commercial supplies due to issues experienced by our contract manufacturing organizations and/or shortages and delays in obtaining raw materials and supplies required in the manufacturing processes;
- interruption of or delays in receiving supplies of our products and product candidates from our contract manufacturing organizations due to staffing shortages, production slowdowns or stoppages, prioritization of pandemic-related activities over ours and disruptions in delivery systems;
- interruptions in preclinical studies due to restricted or limited operations at laboratory facilities;
- limitations on employee resources that would otherwise be focused on the conduct of our preclinical studies, clinical trials, and manufacturing activities including because of sickness of employees or their families or the desire of employees to avoid contact with groups of people; and
- material delays and complications with respect to our research and development programs.

We may not successfully manage our company through varying business cycles, including the COVID-19 pandemic

Our success will depend on properly sizing our company through growth and contraction cycles caused in part by changing business conditions, which places a significant strain on our management and on our administrative, operational and financial resources. For example, in connection with the COVID-19 pandemic, we required most of our personnel, including all of our administrative employees, to work remotely, restricted on-site staff to only those personnel who must perform activities that must be completed on-site, implemented social distancing on-site, and closed certain of our offices temporarily. Our increased reliance on personnel working from home may negatively impact

productivity, or disrupt, delay, or otherwise adversely impact our business. In addition, this could increase our cyber security risk, create data accessibility concerns, and make us more susceptible to communication disruptions, any of which could adversely impact our business operations or delay necessary interactions with the FDA, manufacturing sites, research or clinical trial sites. To manage through such cycles, we may expand or contract our facilities, our operational, financial and management systems and our personnel. If we were unable to manage growth and contractions effectively our business would be harmed.

The path to regulatory approval of larsucosterol is uncertain

Larsucosterol is in clinical development for the potential treatment of AH; NASH is also being explored. In AH and NASH, there are no currently approved drugs. We will have to interact with the FDA and other regulatory agencies regarding important aspects of the clinical development program, potentially including the size and design of clinical trials, the specific primary and secondary endpoints for the clinical trials, inclusion and exclusion criteria, stopping rules, duration of follow up, size of the safety databases, statistical analysis plans and other matters. This uncertainty may make it difficult to predict the timing or expense required to obtain regulatory approval for larsucosterol. We also may need to revise our clinical development plans after trials have commenced or been completed, which could add to the time and expense associated with the clinical development of larsucosterol. If we are unable to reach agreement with the FDA or other regulatory agencies regarding clinical development plans for larsucosterol, we may curtail or limit our development activities for this product candidate.

Delays or difficulties in the enrollment of subjects in clinical trials may increase our overall development expenses and delay clinical trial data and receipt of necessary regulatory approvals

Successful and timely completion of clinical trials will require that we enroll a sufficient number of subjects and/or patients within a reasonable period of time. Enrollment, a significant factor in the timing of clinical trials, is affected by many factors including the size and nature of the patient population, our ability to recruit clinical sites and the ability of clinical sites to successfully recruit subjects to participate in clinical trials. Initiation of and enrollment in many clinical trials has been and is being adversely affected by COVID-19, which has at times caused some institutions to stop enrolling patients, has created a large number of clinical trial proposals for potential clinical trial sites to review and consider, and has caused many individuals to avoid contact with hospitals or other healthcare providers. Additionally, some of the patients in our clinical trials, including AH patients, are hospitalized and concerns about exposure to COVID-19 limit clinical trial staff's access to patients, the frequency of interactions between patients and staff, the ability to obtain blood draws and other biological sample collection, and may limit the ability to ship samples to outside laboratories for analysis. In areas heavily impacted by COVID-19, there may be limited hospital staff available for clinical trial activities due to staff becoming infected or due to de-prioritization of clinical trial activities. Trials may be subject to delays as a result of patient enrollment taking longer than anticipated or patient withdrawal. We may not be able to initiate or continue clinical trials for larsucosterol if we are unable to sign and maintain sufficient clinical sites, locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or other regulatory authorities or if we are unable to collect and analyze biological samples required for trial endpoints. It is possible that the inclusion and exclusion criteria for patients to be enrolled in these trials or COVID-19-related issues may make the trials more difficult to conduct or may significantly extend the time required for enrollment and the cost of these trials.

We cannot predict how successful we will be at enrolling patients in our clinical trials. Enrollment is affected by many factors including:

- the eligibility criteria for the trial in question;
- the prevalence and incidence of the conditions being studied;
- COVID-19-related challenges with patient access, hospital prioritization, clinical trial staff availability, ability to collect, ship and analyze patients' biological samples, availability of personal protective equipment (PPE), swabs, reagents and other materials and supplies;
- the perceived risks and benefits of our product candidates;

- clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new drugs or therapeutic biologics that may be approved for the indications we are investigating;
- the efforts to facilitate timely enrollment in clinical trials;
- competition for clinical sites and patients from other clinical trials;
- the willingness of potential clinical trial patients to provide informed consent to participate in the trial;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- the proximity and availability of clinical trial sites for prospective patients.

Our inability to sign up and maintain sufficient clinical trial sites and/or enroll a sufficient number of patients for clinical trials would result in significant delays and could require us to abandon one or more clinical trials altogether. Enrollment delays in these clinical trials may result in increased development costs for our drug candidates or delays in regulatory filings and approvals, which would cause the value of our company to decline and limit our ability to obtain additional financing.

The FDA or other regulatory agencies may require more information or clinical studies for all of our product candidates, and our product candidates may never be approved

The failure to adequately demonstrate the safety and effectiveness of a pharmaceutical product candidate under development to the satisfaction of FDA and other regulatory agencies will result in delays to the regulatory approval or non-approvability of our product candidates, and could materially harm our business. Clinical trials may not demonstrate the sufficient levels of safety and efficacy necessary to obtain the requisite regulatory approvals for our product candidates, or may require such significant numbers of patients or additional costs to make it impractical to satisfy the regulatory agency's requirements, and thus our product candidates may not be approved for marketing. During the review process, the FDA or other regulatory agencies may request additional information regarding the efficacy or safety of our product candidates, and providing such additional information could require significant additional work and expense, and take a significant amount of time, resulting in a material delay of approval or the failure to obtain approval or lead the company to abandon the development of that product candidate. During the review process, the FDA, or other regulatory agencies, may also request more information regarding the chemistry, manufacturing or controls related to our product candidates, and answering such questions could require significant additional work and expense, and take a significant amount of time, resulting in a material delay of approval or the failure to obtain approval or abandonment of the product candidate. Additionally, even if our product candidates receive FDA or other regulatory agency approval, the regulatory agency may require that we conduct additional clinical or non-clinical studies after such approval, place limitations on the use of our products in applicable labels, require marketing under a REMS program, include commercially unattractive language in the approved product label, delay approval to market our products or limit the indicated use of our products, which may harm our business and results of operations.

We currently have a significant amount of debt. Compliance with repayment obligations and other covenants may be difficult, and failure by us to fulfill our obligations under the applicable loan agreements may cause the repayment obligations to accelerate

In July 2016, we entered into a Loan and Security Agreement (the Loan Agreement) with Oxford Finance LLC (Oxford Finance), pursuant to which Oxford Finance provided a $20 million secured single-draw term loan to us with an initial maturity date of August 1, 2020. The term loan was fully drawn at close and the proceeds may be used for working capital and general business requirements. The term loan repayment schedule provided initially for interest only payments for the first 18 months, followed by consecutive monthly payments of principal and interest in arrears starting on March 1, 2018 and continuing through the maturity date of August 1, 2020. Following five amendments, we make interest only payments under the amended Loan Agreement until June 1, 2023 and the final maturity date of the

loan is September 1, 2025. The Loan Agreement provides for a floating interest rate (7.95% initially and 7.95% as of December 31, 2021) based on an index rate plus a spread and an additional payment equal to 10% of the principal amount of the term loan, which is due when the term loan becomes due or upon the prepayment of the facility. Any increases in prevailing interest rates could increase our expenses under the Loan Agreement. If we elect to prepay the loan, there is also a prepayment fee between 0.75% and 2.5% of the principal amount of the term loan depending on the timing of prepayment. Our debt repayment obligations under the Loan Agreement, as amended, may prove a burden to the Company as they become due, particularly following the expiration of the interest-only period.

The Loan Agreement contains customary events of default, including, among other things, our failure to fulfill certain of our obligations under the Loan Agreement and the occurrence of a material adverse change in our business, operations or condition (financial or otherwise), a material impairment of the prospect of repayment of any portion of the loan, the failure to deliver an unqualified audit report and board approved financial projections within time periods set forth in the Loan Agreement, or a material impairment in the perfection or priority of lender's lien in the collateral or in the value of such collateral. In the event of default by us under the Loan Agreement, the lender would be entitled to exercise its remedies thereunder, including the right to accelerate the debt, upon which we may be required to repay all amounts then outstanding under the Loan Agreement, which could harm our business, operations and financial condition.

In addition, the term loan is secured by substantially all of our assets, except that the collateral does not include any equity interests in the Company, any intellectual property (including all licensing, collaboration and similar agreements relating thereto), and certain other excluded assets. The Loan Agreement contains customary representations, warranties and covenants by us, which covenants limit our ability to convey, sell, lease, transfer, assign or otherwise dispose of certain of our assets; engage in any business other than the businesses currently engaged in by us or reasonably related thereto; liquidate or dissolve; make certain management changes; undergo certain change of control events; create, incur, assume, or be liable with respect to certain indebtedness; grant certain liens; pay dividends and make certain other restricted payments; make certain investments; make payments on any subordinated debt; and enter into transactions with any of our affiliates outside of the ordinary course of business or permit our subsidiaries to do the same. Complying with these covenants may make it more difficult for us to successfully execute our business strategy.

We will require and may have difficulty or be unsuccessful in raising needed capital in the future

Our business currently does not generate sufficient revenues to meet our capital requirements and we do not expect that it will do so in the near future. We have expended and will continue to expend substantial funds to conduct the research, development, manufacturing and clinical testing of our product candidates, funding and establishing additional clinical- and commercial-scale manufacturing arrangements and facilities, and to provide for the pre-commercial and commercial activities associated with the marketing, sales and distribution of our products and product candidates. We will require additional funds for these purposes. Additional funds may not be available on acceptable terms, if at all, and such availability will depend on a number of factors, some of which are outside of our control, including general capital markets conditions and investors' view of our prospects and valuation. If adequate funds are unavailable from operations or additional sources of financing, we may have to delay, reduce the scope of or eliminate one or more of the above-mentioned activities which would materially harm our business, financial condition and results of operations.

We believe that our cash, cash equivalents and investments and anticipated revenues will be adequate to satisfy our capital needs for at least the next 12 months from December 31, 2021. However, our independent auditors may not agree with this assessment, and our actual capital requirements will depend on many factors, including:

- continued progress and cost of our research and development programs;
- progress with preclinical studies and clinical trials;
- the time and costs involved in obtaining regulatory approvals, if any;
- costs involved in establishing manufacturing capabilities for pre-clinical, non-clinical, clinical and commercial quantities of our products and product candidates;
- success in entering into collaboration agreements and achieving milestones under such agreements;
- the continuation of our collaborative agreements that provide financial funding for certain of our activities;
- regulatory actions with respect to our and our collaborators' products and product candidates;
- costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing intellectual property rights;
- costs of developing sales, marketing and distribution channels and our ability and that of our collaborators to sell our products, products we have a financial interest in and eventually, product candidates;
- competing technological and market developments;
- market acceptance of our products, products we have a financial interest in and, eventually, product candidates;
- any failure to comply with the covenants in our debt instruments that results in acceleration of repayment obligations;
- impacts of the COVID-19 pandemic;
- costs for recruiting and retaining employees and consultants; and
- unexpected legal, accounting and other costs and liabilities related to our business.

We may consume available resources more rapidly than currently anticipated, resulting in the need for additional funding. We may seek to raise additional funds through equity or debt financings, convertible debt financings, collaborative arrangements with corporate collaborators or other sources, which, in each case, may be dilutive to existing stockholders and may cause the price of our common stock to decline. In addition, in the event that additional funds are obtained through arrangements with collaborators or other sources, we may have to relinquish rights to some of our technologies, products or product candidates that we would otherwise seek to develop or commercialize ourselves. If adequate funds are not available, we may be required to significantly reduce or refocus our product development efforts and other activities, resulting in delays in generating future revenue.

We do not control the commercialization of POSIMIR, PERSERIS or Methydur

We rely on Innocoll for the commercialization of POSIMIR. The current approved labeling for POSIMIR is limited, and Innocoll is responsible for completing post-marketing non-clinical studies and any additional studies required by FDA, and negative results from these studies could adversely affect commercialization of POSIMIR. Innocoll is also responsible for manufacturing POSIMIR. If Innocoll does not successfully launch and then grow POSIIMIR sales, the royalty payments we receive under our agreement with them will be limited and we may not receive any milestone payments from them. We rely on Indivior for the commercialization of PERSERIS. There can be no assurance that PERSERIS sales will maintain current levels or grow materially. If Indivior does not successfully grow PERSERIS sales, future earn-out payments we receive under our agreement with them will be limited. We rely on Orient Pharma for the commercialization of Methydur. If Orient Pharma does not successfully grow Methydur sales, the royalty payments we receive under our agreement with them will be limited. The sales of each of these products may be negatively impacted by the COVID-19 pandemic.

For certain of our product candidates, we depend to a large extent on third-party collaborators, and we have limited or no control over the development, sales, distribution and disclosure for those product candidates

Our performance for certain of our product candidates depends to a large extent on the ability of our third-party collaborators to successfully develop and obtain regulatory approvals. We have entered into agreements with Innocoll, Indivior, Santen and Orient Pharma under which we granted such third parties the right to develop, apply for regulatory approval for, market, promote or distribute certain products or product candidates, subject to payments to us in the form of product royalties, earn-out and other payments. We have limited or no control over the expertise or resources that any collaborator may devote to the development, clinical trial strategy, regulatory approval, marketing or sale of these product candidates, or the timing of their activities. Any of our present or future collaborators may not perform their obligations as expected. These collaborators may breach or terminate their agreement with us or otherwise fail to conduct their collaborative activities successfully and in a timely manner. Enforcing any of these agreements in the event of a breach by the other party could require the expenditure of significant resources and consume a significant amount of management time and attention. Our collaborators may also conduct their activities in a manner that is different from the manner we would recommend or would have chosen, had we been developing such product candidates ourselves. Further, our collaborators may elect not to develop or commercialize product candidates arising out of our collaborative arrangements or not devote sufficient resources to the development, clinical trials, regulatory approval, manufacture, marketing or sale of these product candidates. If any of these events occur, we may not recognize revenue from the commercialization of our product candidates based on such collaborations. In addition, these third parties may have similar or competitive products to the ones which are the subject of their collaborations with us, or relationships with our competitors, which may reduce their interest in developing or selling our products or product candidates. We may not be able to control public disclosures made by some of our third-party collaborators, which could negatively impact our stock price.

Cancellation of collaborations regarding our product candidates may adversely affect potential economic benefits

Third-party collaboration agreements typically allow the third party to terminate the agreement (or a specific program within an agreement) at will by providing notice. Termination can result from failure of the collaboration to achieve anticipated milestones, from changes in strategy of the other party or for other reasons. In these cases, the product rights revert to us or certain rights of the partner to use our proprietary technology are terminated. If there have been payments under such agreements that are being recognized over time, termination of such agreements (or programs) can lead to a near-term increase in our reported revenues resulting from the immediate recognition of the balance of such payments. Termination deprives us of potential future economic benefits under such agreements, and may make it more difficult, unattractive or impossible to enter into agreements with other third parties for use of the assets and/or technologies that were subject to the terminated agreement. For example, termination of our agreements with Innocoll, Santen or Orient Pharma could have negative effects on the Company.

If we do not enter into new collaboration agreements, our revenues and/or cash flows will be reduced relative to prior periods

Our revenues have been based to a significant extent on collaborative arrangements with third parties, pursuant to which we receive payments based on our performance of research and development activities set forth in these agreements. For example, approximately 58% of our total revenues in 2019 were derived from our collaboration agreement with Gilead. In June 2020, Gilead notified us that they were terminating this collaboration, resulting in accelerated recognition of $22.7 million in deferred revenue related to a nonrefundable upfront license fee and a milestone payment totaling $35.0 million that had previously been received. In addition, we have seen periodic fluctuations in revenues associated with our other collaboration agreements, which reflect the current development stage of the product candidates subject to those agreements, and our collaborator's needs for our services. Long-term growth of our collaboration revenues requires us to enter into new collaboration agreements, and there can be no assurance that we will do so. Even if we enter into new collaboration agreements, we may not be able to fulfill our obligations or attain milestones set forth in any specific agreement, which could cause our revenues and/or cash flows to fluctuate or be less than anticipated and may expose us to liability for contractual breach. In addition, these agreements may require us to devote significant time and resources to communicating with and managing our relationships with such collaborators and resolving possible issues of contractual interpretation which may detract from time our management would otherwise devote to managing our operations. Such agreements are generally complex and contain provisions that could give rise to legal disputes, including potential disputes concerning ownership of intellectual property. Such disputes can delay or prevent the development of potential new product candidates, or can lead to lengthy, expensive litigation or arbitration. In general, our collaboration agreements, may be terminated by the other party at will or upon specified conditions including, for example, if we fail to satisfy specified performance milestones or if we breach the terms of the agreement. Acquisitions of our collaborators or strategic changes or re-organizations or re-prioritizations of our collaborators can lead to turnover of program staff, a review of development programs and strategies by the acquirer, and other events that can disrupt a program, resulting in program delays or discontinuations.

If we do not enter into new collaboration agreements, our anticipated revenues and/or cash flows will be reduced relative to periods of increased R&D revenues, such as occurred in 2020.

Our cash flows are likely to differ from our reported revenues

Our revenues will likely differ from our cash flows from revenue-generating activities. Upfront payments received upon execution of collaborative agreements may be recorded as deferred revenue, in which case they are generally recognized over the period of our performance obligations with the third-party collaborator pursuant to the applicable agreement. The period of performance obligations may also be revised on a prospective basis. As of December 31, 2021, we had $910,000 of deferred revenue which will be recognized in future periods and may cause our reported revenues to be greater than cash flows from our ongoing revenue-generating activities. Assumptions related to revenue recognition of deferred revenue are reviewed in each accounting period and changes are recorded in the current period. In certain circumstances, changes in assumptions related to the timing and amount of work required to complete a performance obligation tied to deferred revenue can result in negative revenue for an accounting period or the accelerated recognition of non-cash revenue.

Our business strategy includes the entry into additional collaborative agreements. We may not be able to enter into additional collaborative agreements or may not be able to negotiate commercially acceptable terms for these agreements

Our current business strategy includes the entry into additional collaborative agreements for the development and commercialization of our products and product candidates, including, but not limited to larsucosterol and others. The negotiation and consummation of these types of agreements typically involve simultaneous discussions with multiple potential collaborators and require significant time and resources from our officers, business development, legal, and research and development staff. In addition, in attracting the attention of pharmaceutical and biotechnology company collaborators, we compete with numerous other third parties with product opportunities as well as the collaborators' own internal product opportunities. We may not be able to consummate additional collaborative agreements, or we may not be

able to negotiate commercially attractive terms for these agreements. If we do not consummate additional collaborative agreements, we may have to consume money more rapidly on our product development efforts, defer development activities or forgo the exploitation of certain opportunities, abandon development of certain product candidates or indications for certain product candidates, any of which could have a material adverse effect on our business.

Failure to comply with ongoing governmental regulations for our products or product candidates could materially harm our business

Developing, manufacturing, marketing or promoting a drug is subject to very strict regulations and controls. Furthermore, clearance or approval may entail ongoing requirements for post-marketing studies or surveillance. The manufacture and marketing of drugs are subject to continuing FDA and foreign regulatory review and requirements that we update our regulatory filings. Later discovery of previously unknown problems with a product, manufacturer or facility, or our failure to update regulatory files, may result in restrictions, including withdrawal of the product from the market. Any of the following or other similar events, if they were to occur, could delay or preclude us from further developing, marketing or realizing full commercial value of our products or product candidates, which in turn would materially harm our business, financial condition and results of operations:

- failure to obtain or maintain requisite governmental approvals;
- failure to meet GMP, GLP and/or other governmental requirements for drug development;
- failure to obtain approvals for commercially valuable intended uses of our products and product candidates; or
- FDA required product withdrawals, clinical holds or warnings arising from identification of serious adverse side effects in our products and product candidates.

Manufacturers of drugs must comply with the applicable FDA good manufacturing practice (GMP) regulations, which include production design controls, testing, quality control and quality assurance requirements as well as the corresponding maintenance of records and documentation. Compliance with current GMP regulations is difficult and costly. Manufacturing facilities are subject to ongoing periodic inspection by the FDA and corresponding state and in some cases, foreign agencies, including unannounced inspections, and must be licensed before they can be used for the commercial manufacture of our products and product candidates. We and/or our present or future suppliers and distributors may be unable to comply with the applicable GMP regulations and other FDA and/or foreign regulatory requirements. If we, our third-party collaborators or our respective suppliers do not achieve compliance for our products or product candidates we or they manufacture, the FDA or foreign equivalents may refuse or withdraw marketing clearance or approvals, put our or our partner’s clinical trial on hold, withdraw or reject an investigational new drug (IND) application or require product recall, which may cause interruptions or delays in the development, manufacture and sale of our products and product candidates.

We have a history of operating losses, expect to continue to have losses in the future and may never achieve or maintain profitability

We have incurred significant operating losses since our inception in 1998 and, as of December 31, 2021, had an accumulated deficit of approximately $526.0 million. We expect to continue to incur significant operating losses over the next several years as we continue to incur significant costs for research and development, clinical trials, manufacturing, sales, and general and administrative functions. Our ability to achieve profitability depends upon our ability, alone or with others, to successfully complete the development of our proposed product candidates, obtain the required regulatory clearances, manufacture and market our proposed product candidates and successfully commercialize our approved products. Development of pharmaceutical product candidates is costly and requires significant investment. In addition, we may choose to license from third parties either rights to particular drugs or other appropriate technology and/or intellectual property rights for use in our products and product candidates. The license fees as well as the operating costs of using or developing these technologies or rights would increase the costs of our products and product candidates as well as our operating costs generally.

To date, we have not generated significant revenue from royalties, earn-out payments, milestone payments or the commercial sale of our products or product candidates and do not expect to do so in the near future. Our current revenues are from the ALZET product line, from certain excipient sales, from earn-out payments from Indivior related to sales of PERSERIS, from royalty payments from Orient Pharma related to sales of Methydur in Taiwan, and from payments under collaborative research and development agreements with third parties. We do not expect our product revenues to increase significantly in the near future, and we do not expect that collaborative research and development revenues will exceed our operating expenses in the near future. We do not anticipate meaningful revenues to derive from the commercialization and marketing of our products and product candidates in the near future, do not expect to receive meaningful royalties from POSIMIR until the product has been successfully launched and achieves meaningful sales (if ever) and therefore do not expect to generate sufficient revenues to cover expenses or achieve profitability in the near future.

Changes in tax law could adversely affect our business and financial condition

The rules dealing with U.S. federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the IRS and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. For example, on March 11, 2021, President Biden signed into law the "American Rescue Plan Act", which included extenders to the refundable employee retention credit under the Coronavirus Aid, Relief, and Economic Security (CARES) Act and limitations to executive compensation effective for tax years beginning after 2026. Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations.

We may develop our own sales force and commercial group to market future products but we have limited sales and marketing experience with respect to pharmaceuticals and may not be able to do so effectively

We have a small sales and marketing group focused on our ALZET product line. We may choose to develop our own sales force and commercial group to market larsucosterol, if approved, or other products that we may develop in the future. Developing a sales force and commercial group would require substantial expenditures and the hiring of qualified personnel. We have limited sales and marketing experience, and may not be able to effectively recruit, train or retain sales and marketing personnel. If we are not able to put in place an appropriate sales force and commercial group for our products in development and provide that commercial team with sufficient financial and other resources, we may not be able to effectively launch or commercialize these or any other products. We may not be able to effectively sell our products and product candidates, if approved, and our failure to do so could limit or materially harm our business.

We and our third-party collaborators may not sell our product candidates effectively

We and our third-party collaborators (including Innocoll, Indivior and OP Pharma) compete with many other companies that currently have extensive and well-funded marketing and sales operations. Our marketing and sales efforts and those of our third-party collaborators may be unable to compete successfully against these other companies. We and our third-party collaborators, where applicable, may be unable to establish a sufficient sales and marketing organization on a timely basis, if at all. We and our third-party collaborators, where applicable, may be unable to engage qualified distributors. Even if engaged, these collaborators and distributors may:

- fail to adequately market our products or product candidates;
- fail to satisfy financial or contractual obligations to us;
- cease operations, terminate our collaboration or re-allocate resources away from our products or product candidates with little or no notice to us;
- offer, design, manufacture or promote competing product lines;

- fail to maintain adequate inventory and thereby restrict use of our products or product candidates; or
- build up inventory in excess of demand thereby limiting future purchases of our products of product candidates resulting in significant quarter-to-quarter variability in our sales.

The failure of us or our third-party collaborators to effectively develop, gain regulatory approval for, sell, manufacture and market our products and product candidates will hurt our business, prospects, financial results and may impact our access to capital.

We rely heavily on third parties to support development, clinical testing and manufacturing of our products and product candidates

We rely on third-party contract research organizations, consultants, service providers and suppliers to provide critical services to support development, clinical testing, and manufacturing of our products and product candidates. For example, we currently depend on third-party vendors to manage and monitor most of our clinical trials. We rely on third-parties to manufacture or perform manufacturing steps relating to our products, product candidates and components. We anticipate that we will continue to rely on these and other third-party contractors to support development, clinical testing, and manufacturing of our products and product candidates. These third parties may not execute their responsibilities and tasks competently in compliance with their contractual obligations to us, applicable laws and regulations or in a timely or cost-effective fashion. Failure of these contractors to provide the required services in a competent or timely manner or on reasonable commercial terms could materially delay the development and approval of our product candidates or commercialization of our products, increase our expenses and materially harm our business, financial condition, results of operations and access to capital.

Write-offs related to the impairment of our goodwill, long-lived assets, inventories and other non-cash charges, as well as stock-based compensation expenses may adversely impact or delay our profitability

We may incur significant non-cash charges related to impairment write-downs of our long-lived assets, including goodwill. We are required to perform periodic impairment reviews of our goodwill at least annually. The carrying value of goodwill on our balance sheet was $6.2 million at December 31, 2021. To the extent these reviews conclude that the expected future cash flows generated from our business activities are not sufficient to recover the cost of our long-lived assets, we will be required to measure and record an impairment charge to write-down these assets to their realizable values. We completed our last review during the fourth quarter of 2021 and determined that goodwill was not impaired as of December 31, 2021. However, there can be no assurance that upon completion of subsequent reviews a material impairment charge will not be recorded. If future periodic reviews determine that our assets are impaired and a write-down is required, it will adversely impact or delay our profitability.

Inventories, in part, include certain excipients that are sold to customers and included in products and product candidates in development. These inventories are capitalized based on management’s judgment of probable sale prior to their expiration date which in turn is primarily based on management’s internal estimates. The valuation of inventory requires us to estimate the value of inventory that may become expired prior to use. We may be required to expense previously capitalized inventory costs upon a change in our judgment, due to, among other potential factors, a denial or delay of approval of a product by the necessary regulatory bodies, changes in product development timelines, or other information that suggests that the inventory will not be saleable.

Global credit and financial market conditions could negatively impact the value of our current portfolio of cash equivalents, short-term investments or long-term investments and our ability to meet our financing objectives

Our cash and cash equivalents are maintained in highly liquid investments with remaining maturities of 90 days or less at the time of purchase. Our short-term investments consist primarily of readily marketable debt securities with original maturities of greater than 90 days from the date of purchase but remaining maturities of less than one year from the balance sheet date. Our long-term investments consist primarily of readily marketable debt securities with maturities of one year or beyond from the balance

sheet date. While, as of the date of this filing, we are not aware of any downgrades, material losses, or other significant deterioration in the fair value of our cash equivalents, short-term investments or long-term investments since December 31, 2021, no assurance can be given that deterioration in conditions of the global credit and financial markets would not negatively impact our current portfolio of cash equivalents, short-term investments or long-term investments or our ability to meet our financing objectives.

We depend upon key personnel who may terminate their employment with us at any time. We may need to hire additional qualified personnel and may not be able to do so on a timely basis, if at all

Our success will depend to a significant degree upon the continued services of key management, technical and scientific personnel. In addition, our success will depend on our ability to attract and retain other highly skilled personnel, particularly as we develop and expand our Epigenetic Regulator Program. Competition for qualified personnel is intense, and the process of hiring and integrating such qualified personnel is often lengthy. The market for qualified personnel in the San Francisco Bay Area is very competitive and we may be unable to recruit such personnel on a timely basis, if at all. Our management and other employees may voluntarily terminate their employment with us at any time. Current job market dynamics, where the number of workers who quit their job in a single month in 2021 has broken multiple all-time U.S. records (referred to as the "Great Resignation"), further increases the challenge of employee retention. The loss of the services of key personnel, or the inability to attract and retain additional qualified personnel, could result in delays to product development or approval, loss of sales and diversion of management resources as well as difficulties or inability to raise sufficient capital to fund the Company’s operations.

Our business involves environmental risks and risks related to handling regulated substances

In connection with our research and development activities and our manufacture of materials, products and product candidates, we are subject to federal, state and local laws, rules, regulations and policies governing the use, generation, manufacture, storage, air emission, effluent discharge, handling and disposal of certain materials, biological specimens and wastes. Although we believe that we have complied with the applicable laws, regulations and policies in all material respects and have not been required to correct any material noncompliance, we may be required to incur significant costs to comply with environmental and health and safety regulations in the future. Our research and development involves the use, generation and disposal of hazardous materials, including but not limited to certain hazardous chemicals, solvents, agents and biohazardous materials. Although we believe that our safety procedures for storing, handling and disposing of such materials comply with the standards prescribed by state and federal regulations, we cannot completely eliminate the risk of accidental contamination or injury from these materials. We currently contract with third parties to dispose of these substances generated by us, and we rely on these third parties to properly dispose of these substances in compliance with applicable laws and regulations. If these third parties do not properly dispose of these substances in compliance with applicable laws and regulations, we may be subject to legal action by governmental agencies or private parties for improper disposal of these substances. The costs of defending such actions and the potential liability resulting from such actions are often very large. In the event we are subject to such legal action or we otherwise fail to comply with applicable laws and regulations governing the use, generation and disposal of hazardous materials and chemicals, we could be held liable for any damages that result, and any such liability could exceed our resources.

Cyber-attacks or other failures in telecommunications or information technology systems could result in information theft, data corruption and significant disruption of our business operations

We utilize information technology, systems and networks to process, transmit and store electronic information in connection with our business activities. As use of digital technologies has increased, cyber incidents, including deliberate attacks and attempts to gain unauthorized access to computer systems and networks, have increased in frequency and sophistication. These threats pose a risk to the security of our systems and networks and the confidentiality, availability and integrity of our data, and may cause a disruption in our operations, harm our reputation, cause us to pay to retrieve our data if it becomes infected or otherwise subject to ransomware, and increase our stock trading risk. There can be no assurance that we will be successful in preventing cyber-attacks or successfully mitigating their effects.

Similarly, there can be no assurance that our third-party collaborators, distributors and other contractors and consultants will be successful in protecting our clinical and other data that is stored on their systems. Any cyber-attack or destruction or loss of data could have a material adverse effect on our business and prospects. In addition, we may suffer reputational harm or face litigation or adverse regulatory action as a result of cyber-attacks or other data security breaches and may incur significant additional expense to implement further data protection measures.

Our corporate headquarters, certain manufacturing facilities and personnel are located in a geographical area that is seismically active and near wildfire zones

Our corporate headquarters, certain manufacturing facilities and personnel are located in a geographical area that is known to be seismically active and prone to earthquakes, as well as wildfires and related power outages or power shortages. Should such a natural disaster or power outage or power shortage occur, our ability to conduct our business could be severely restricted, and our business and assets, including the results of our research, development and manufacturing efforts, could be harmed or destroyed.

As a non-accelerated filer, we are not required to comply with the auditor attestation requirements of the Sarbanes-Oxley Act and, consequently, some investors may find our common stock less attractive

We are a non-accelerated filer as defined by Rule 12b-2 of the Exchange Act, and as such, are not required to provide an auditor attestation of management's assessment of internal control over financial reporting, which is generally required for SEC reporting companies under Section 404(b) of the Sarbanes-Oxley Act. Therefore, our internal controls over financial reporting will not receive the level of review provided by the process relating to the auditor attestation included in annual reports of issuers that are subject to the auditor attestation requirements. Because we are not required to have our auditors provide an attestation of our management's assessment of internal control over financial reporting, a material weakness in internal control may remain undetected for a longer period. In addition, if investors may find our common stock less attractive because we are not required to comply with the auditor attestation requirements. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and the trading price for our common stock as well as our ability to raise capital may be negatively affected.

Risks Related to Our Intellectual Property

If we are unable to adequately protect, maintain or enforce our intellectual property rights or secure rights to third-party patents, we may lose valuable assets, experience reduced market share or incur costly litigation to protect our rights or our third-party collaborators may choose to terminate their agreements with us

Our ability to commercially exploit our products will depend significantly on our ability to obtain and maintain patents, maintain trade secret protection and operate without infringing the proprietary rights of others.

As of March 3, 2022, we owned or exclusively in-licensed over 25 unexpired issued U.S. patents and over 135 unexpired issued foreign patents (which include granted European patent rights that have been validated in various EU member states). In addition, we have over 30 pending U.S. patent applications and over 145 foreign applications pending in Europe, Australia, Japan, Canada and other countries.

There can be no assurance that the pending patent applications will be granted. Further, there can be no assurance that VCU will not attempt to terminate their license to us, which termination could result in the loss of our rights to certain of these patent families.

The patent positions of pharmaceutical companies, including ours, are uncertain and involve complex legal and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued. Consequently, our patent applications or those that are licensed to us may not issue into patents, and any issued patents may not provide protection against competitive technologies or may be held invalid if challenged. Our competitors may also independently develop products similar to ours or design around or otherwise circumvent patents issued to us or licensed by us. In addition, the laws of some foreign countries may not protect our proprietary rights to the same extent as U.S. law, if at all.

We also rely upon trade secrets, technical know-how and continuing technological innovation to develop and maintain our competitive position. We require our employees, consultants, advisors and collaborators to execute confidentiality and assignment-of-inventions agreements with us. These agreements typically provide that all materials and confidential information developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances, and that all inventions arising out of the individual's relationship with us will be our exclusive property. These agreements may be breached, and in some instances, we may not have an appropriate remedy available for breach of the agreements. Furthermore, our competitors may independently develop substantially equivalent proprietary information and techniques, reverse engineer our information and techniques, or otherwise gain access to our proprietary technology.

We may be unable to meaningfully protect our rights in trade secrets, technical know-how and other non-patented technology. We may have to resort to litigation or arbitration to protect our intellectual property rights, or to determine their scope, validity or enforceability. In addition, interference, derivation, post-grant oppositions, and similar proceedings may be necessary to determine rights to inventions in our patents and patent applications. Enforcing or defending our proprietary rights is expensive, could cause diversion of our resources and may be unsuccessful. Any failure to enforce or protect our rights could cause us to lose the ability to exclude others from using our technology to develop or sell competing products. In addition, in some circumstances our collaborators have the first right to enforce our patents against third party infringers, and such collaborators may not enforce such claims adequately or successfully or in the manner that we would do ourselves.

Our collaboration agreements may depend on our intellectual property

We are party to collaborative agreements with Innocoll, Orient Pharma and Santen among others. Our third-party collaborators have entered into these agreements based on the exclusivity that our intellectual property rights confer on the products being developed. The loss or diminution of our intellectual property rights could result in a decision by our third-party collaborators to terminate their agreements with us. In addition, these agreements are generally complex and contain provisions that could give rise to legal disputes, including potential disputes concerning ownership of intellectual property and data under collaborations. Such disputes can lead to lengthy, expensive litigation or arbitration requiring us to devote management time and resources to such disputes which we would otherwise spend on our business.

We may be sued by third parties claiming that our products or product candidates infringe on their intellectual property rights, particularly because there is substantial uncertainty about the validity and breadth of biopharmaceutical patents

We or our collaborators may be exposed to future litigation by third parties based on claims that our products, product candidates or activities infringe the intellectual property rights of others or that we or our collaborators have misappropriated the trade secrets of others. This risk is exacerbated by the fact that the validity and breadth of claims covered in medical technology, pharmaceutical and biotechnology patents and the breadth and scope of trade secret protection involve complex legal and factual questions for which important legal principles are unresolved. Any litigation or claims against us or our collaborators, whether or not valid, could result in substantial costs, could place a significant strain on our financial resources and could harm our reputation and business prospects. We also may not have sufficient funds to litigate, particularly against parties with substantially greater resources. In addition, pursuant to our collaborative agreements, we have provided our collaborators with the right, under

specified circumstances, to defend against any claims of infringement of the third-party intellectual property rights, and such collaborators may not defend against such claims adequately or successfully or in the manner that we would do ourselves. Intellectual property litigation or claims could force us or our collaborators to do one or more of the following, any of which could harm our business or financial results:

- cease selling, incorporating or using any of our products or product candidates that incorporate the challenged intellectual property;
- obtain a license from the holder of the infringed intellectual property right, which license may be costly or may not be available on reasonable terms, if at all; or
- redesign our products or product candidates, which would be costly and time-consuming and may not be successful.

Risks Related To Our Industry

The markets for our pharmaceutical products, product candidates and for our ALZET product line are rapidly changing and competitive, and new products or technologies developed by others could impair our ability to establish, maintain or grow our business and remain competitive

The pharmaceutical industry is subject to rapid and substantial technological change. Developments by others may render our products, product candidates under development or technologies noncompetitive or obsolete, or we may be unable to keep pace with technological developments or other market factors. Technological competition in the industry from pharmaceutical and biotechnology companies, universities, governmental entities and others diversifying into the field is intense and is expected to increase.

We may face competition from other companies in numerous industries including pharmaceuticals, biotechnology, medical devices and drug delivery. Competition for larsucosterol, if approved, will depend on the specific indication(s) for which larsucosterol is approved. 89Bio, AbbVie, Afimmune, Akaza Bioscience, Akero Therapeutics, Ascletis, AstraZeneca, Axcella Health, Bristol Myers Squibb, Cirius Therapeutics, CytoDyn, Dr. Falk Pharma, Eli Lilly, Enanta, ENYO Pharma, Evive Biotech, Galectin, Galmed, Genentech, Genfit, Gilead, Hanmi, HighTide Biopharma, Intercept, Inventiva Pharma, Ionis Pharmaceuticals, Isotechnika, Kowa, LifeMax, Lipidio, Lipocine, Madrigal, MediciNova, MedImmune, Mitsubishi Tanabe, NGM Biopharmaceuticals, Nimbus, NorthSea Therapeutics, Novartis, Novo Nordisk, Pfizer, PharmaKing, Poxel, Promethera Biosciences, Seal Rock Therapeutics, Surrozen, Terns Pharmaceutical, Thera Technologies, Viking Therapeutics, and others have development plans for products to treat NAFLD/NASH, AH or other liver diseases.

Competition for our ALZET product line primarily consists of customers choosing to utilize delivery methods for their research projects other than an osmotic pump. We also face competition for our ALZET product line from other companies including low cost foreign competitors.

We are engaged in the development of novel therapeutic technologies. Our resources are limited and we may experience technical challenges inherent in such novel technologies. Competitors have developed or are in the process of developing technologies that are, or in the future may be, the basis for competitive products. Some of these products may have an entirely different approach or means of accomplishing similar therapeutic effects than our products and product candidates. Our competitors may develop products that are safer, more effective or less costly than our products and product candidates and, therefore, present a serious competitive threat to our product candidates and product offerings.

The widespread acceptance of therapies that are alternatives to ours may limit market acceptance of our products and product candidates if commercialized. Post-operative pain is currently being treated by oral medication, transdermal drug delivery systems, such as drug patches, long-acting and short-acting injectable products and implantable drug delivery devices which will be competitive with our products and product candidates. Many of these treatments are widely accepted in the medical community and have a long history of use. The established use of these competitive products may limit the potential for our products and product candidates to receive widespread acceptance if and when commercialized.

Our relationships with physicians, patients and third-party payers are subject to applicable anti-kickback, fraud and abuse, privacy and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings

Healthcare providers, physicians and third-party payers will play a primary role in the recommendation and prescription of POSIMIR and any additional product candidates for which we obtain marketing approval. Our future arrangements with third-party payers and customers may expose us and our partners to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we and our partners may market, sell and distribute our products. As a pharmaceutical company, even though we do not and may not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payers, federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. These regulations include:

- the Federal Healthcare Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid, and which will constrain our marketing practices and the marketing practices of our licensees, educational programs, pricing policies, and relationships with healthcare providers or other entities;
- the federal physician self-referral prohibition, commonly known as the Stark Law, which prohibits physicians from referring Medicare or Medicaid patients to providers of "designated health services" with whom the physician or a member of the physician's immediate family has an ownership interest or compensation arrangement, unless a statutory or regulatory exception applies;
- federal false claims laws that prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other government reimbursement programs that are false or fraudulent, and which may expose entities that provide coding and billing advice to customers to potential criminal and civil penalties, including through civil whistleblower or qui tam actions, and including as a result of claims presented in violation of the Federal Healthcare Anti-Kickback Statute, the Stark Law or other healthcare-related laws, including laws enforced by the FDA;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also created federal criminal laws that prohibit knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statements in connection with the delivery of or payment for healthcare benefits, items or services, and which as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- federal physician sunshine requirements under the Affordable Care Act, which requires manufacturers of drugs, devices, biologics and medical supplies to report annually to HHS

information related to payments and other transfers of value to physicians, other healthcare providers, and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members and applicable group purchasing organizations;

- the Federal Food, Drug, and Cosmetic Act, which, among other things, strictly regulates drug product marketing, prohibits manufacturers from marketing drug products for off-label use and regulates the distribution of drug samples;
- state and foreign law equivalents of each of the above federal laws, such as anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payers, including private insurers, state laws requiring pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and which may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures, many of which differ from each other in significant ways and often are not preempted by federal laws such as HIPAA, thus complicating compliance efforts; and
- HIPPA and other state and foreign laws governing the privacy and security of health information or other personal information, such as the European Union General Data Protection Regulation, or GDPR, (EU 2016/679), which require limitations regarding access and use of certain personal and health information.

Efforts to ensure that our business arrangements with third parties comply with applicable healthcare and privacy laws and regulations do and will in the future involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare or privacy laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any physicians or other healthcare providers or entities with whom we expect to do business are found to not be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Healthcare reform measures could hinder or prevent our product candidates' commercial success

In the United States and some non-U.S. jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes to the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities, affect our ability to profitably sell any product or product candidates for which we obtain marketing and otherwise affect our future revenue and profitability and the future revenue and profitability of our collaborators or potential collaborators.

For example, in March 2010, the Affordable Care Act was enacted in the United States to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. The law appears likely to continue the downward pressure on the pricing of medical items and services, especially under the Medicare program, and increased the industry's regulatory burdens and operating costs.

The previous U.S. presidential administration signed two Executive Orders designed to delay the implementation of certain provisions of the Affordable Care Act or otherwise circumvent some of the requirements for health insurance mandated by the Affordable Care Act. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the Affordable Care Act. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the Affordable Care Act have been signed into law. The Tax Cuts and Jobs Act of 2017 includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." As legislative and regulatory developments are ongoing, we cannot predict the ultimate content, timing or effect of healthcare reform legislation or the impact of potential legislation on our business.

In addition, other legislative changes have been proposed and adopted since the Affordable Care Act was enacted. These changes include reductions to Medicare payments to providers of up to 2% per fiscal year that will remain in effect through 2027; the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. More recently, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for pharmaceutical products. For example, the marketing, pricing and sale of the Company's products are subject to regulation, investigations and legal actions including under the Medicaid Drug Rebate Program under the Affordable Care Act, which has increased the statutory minimum rebates a manufacturer must pay under the program as well as a new methodology by which rebates are owed for drugs that are inhaled, infused, instilled, implanted or injected. We are also subject to federal and state false claims acts, as well as federal and state antitrust and consumer protection laws. Increased scrutiny of health care industry business practices in recent years by government agencies and state attorneys general in the U.S., and any resulting investigations and prosecutions, carry risk of significant civil and criminal penalties including, but not limited to, debarment from participation in such government healthcare programs.

Individual states in the United States have also become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical product and medical device pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. For example, in October 2017, California passed a new law, effective in January 2019, which requires transparency from biopharmaceutical companies regarding price increases for prescription drugs. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and medical devices to purchase and which suppliers will be included in their prescription drug and other healthcare programs.

We expect that the Affordable Care Act, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria, new payment methodologies and in additional downward pressure on the price that we receive for any approved or cleared product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we or our partners are slow or unable to adapt to new requirements or policies, or if we or our partners are not able to maintain regulatory compliance, our products and product candidates may lose any regulatory approval that may have been obtained, which would reduce the likelihood that we may achieve or sustain profitability, or be able to enter attractive collaboration agreements, which would adversely affect our business.

We could be exposed to significant product liability claims which could be time consuming and costly to defend, divert management attention and adversely impact our ability to obtain and maintain insurance coverage

The testing, clinical development, manufacture, marketing and sale of our products and product candidates involve an inherent risk that product liability claims will be asserted against us. Although we are insured against such risks up to an annual aggregate limit in connection with clinical trials and commercial sales of our products and product candidates, our present product liability insurance may be

inadequate and may not fully cover the costs of any claim(s) or any ultimate damages we might be required to pay. Product liability claims or other claims related to our products and product candidates, regardless of their outcome, could require us to spend significant time and money in litigation or to pay significant damages. Any successful product liability claim may prevent us from obtaining adequate product liability insurance in the future on commercially desirable or reasonable terms. In addition, product liability coverage may cease to be available in sufficient amounts or at an acceptable cost. An inability to obtain sufficient insurance coverage at an acceptable cost or otherwise to protect against potential product liability claims could prevent or inhibit the commercialization of our products or product candidates if and when approved. A product liability claim could also significantly harm our reputation and delay or prevent market acceptance of our products and product candidates.

Acceptance of our products and product candidates in the marketplace is uncertain, and failure to achieve market acceptance will delay our ability to generate or grow revenues

Our future financial performance will depend upon the successful introduction and customer acceptance of our products or products we have licensed to others, including larsucosterol, if approved, POSIMIR, if commercially launched, and including Indivior's PERSERIS and Orient Pharma's Methydur. Even if approved for marketing, these products and product candidates may not achieve market acceptance. The degree of market acceptance will depend upon a number of factors, including:

- the degree of unmet need in the market for the approved indication(s);
- the receipt of regulatory clearance of marketing claims for the uses that we are developing;
- the approved product labeling;
- pricing, reimbursement and formulary access;
- the degree of resources applied to promotion and other commercial activities;
- the establishment and demonstration in the medical community of the safety and clinical efficacy of our products and their potential advantages over existing therapies; and
- pricing, access and reimbursement policies of government and third-party payors such as insurance companies, health maintenance organizations, hospital formularies and other health plan administrators.

Physicians, patients, payers or the medical community in general may be unwilling to accept, utilize or recommend any of the products we have developed. If these products do not achieve widespread market acceptance, we will not achieve meaningful revenues.

If users of our products are unable to obtain adequate reimbursement from third-party payers, obtain access to our product(s), or if new restrictive legislation is adopted, market acceptance of our products may be limited and we may not achieve meaningful revenues or profitability

The continuing efforts of government and insurance companies, health maintenance organizations and other payers of healthcare costs to contain or reduce costs of health care may affect our future revenues and profitability, and the future revenues and profitability of our potential customers, suppliers and third-party collaborators and the availability of capital. For example, in certain foreign markets, pricing, access and/or profitability of prescription pharmaceuticals is subject to government control. In the United States, recent federal and state government initiatives have been directed at lowering the total cost of health care, and the U.S. Congress and state legislatures will likely continue to focus on health care reform, the cost of prescription pharmaceuticals and on the reform of the Medicare and Medicaid systems. While we cannot predict whether any such legislative or regulatory proposals will be adopted, the announcement or adoption of such proposals could materially harm our business, financial condition and results of operations.

The successful commercialization of our current and future products will depend in part on the extent to which appropriate reimbursement levels for the cost of our products and related treatment are obtained from governmental authorities, private health insurers and other organizations, such as HMOs. Third-party payers often limit access, payments and/or reimbursement for medical products and services. Also, the trend toward managed health care in the United States and the concurrent growth of organizations such as HMOs, which could control or significantly influence the purchase of health care services and products, as well as legislative proposals to reform health care or reduce government

insurance programs, may limit access, reimbursement or payment for our products. The cost containment measures that health care payers and providers are instituting and the effect of any health care reform could materially harm our ability to operate profitably and access capital.

If we or our third-party collaborators are unable to train physicians to use our products and product candidates to treat patients' diseases or medical conditions, we may not achieve market acceptance of our products

Broad use of certain of our products, such as POSIMIR, will require extensive training of numerous physicians on their proper and safe use. The time required to train physicians could delay introduction of our products and adversely affect market acceptance of our products. We or third parties selling our products may be unable to rapidly train physicians in numbers sufficient to generate adequate demand for our products. Any delay in training would materially delay the demand for our products and harm our business and financial results. In addition, we or our partners may expend significant funds towards such training before any orders are placed for our products, which would increase our expenses and harm our financial results.

Potential new accounting pronouncements and legislative actions are likely to impact our future financial position or results of operations

Future changes in financial accounting standards may cause adverse, unexpected fluctuations in the timing of the recognition of revenues or expenses and may affect our financial position or results of operations. New pronouncements and varying interpretations of pronouncements have occurred with frequency and may occur in the future and we may make changes in our accounting policies in the future. Compliance with changing regulation of corporate governance and public disclosure may result in additional expenses. Changing laws, regulations and standards relating to corporate governance and public disclosure, including the Sarbanes-Oxley Act of 2002, new SEC regulations, state and local laws and regulations, PCAOB pronouncements and Nasdaq rules, are creating uncertainty for companies such as ours and insurance, accounting and auditing costs are high as a result of this uncertainty and other factors. Compliance with evolving corporate governance and public disclosure standards may result in increased general and administrative expenses and a diversion of management time and attention from value-creating activities to compliance activities.

Risks related to actions on trade by the U.S. and foreign governments could adversely affect the Company's results of operations and financial condition

The U.S. government under the previous administration indicated its intent to adopt a new approach to trade policy and in some cases to renegotiate, or potentially terminate, certain existing bilateral or multilateral trade agreements. It also initiated the imposition of tariffs on certain foreign products. Changes in U.S. trade policy have resulted in, and could continue to result in, one or more U.S. trading partners adopting responsive trade policy making it more difficult or costly for us to export our products to those countries. These measures could also result in increased costs for goods imported into the United States. This in turn could require us to increase prices to our customers which may reduce demand, or, if we are unable to increase prices, result in lowering our margin on products sold.

There is also a concern that the imposition of additional tariffs by the United States could result in the adoption of additional tariffs by other countries. A potential resulting trade war could have a significant adverse effect on world trade and the world economy. We cannot predict future trade policy or the terms of any renegotiated trade agreements and their impact on our business. The adoption and expansion of trade restrictions, the occurrence of a trade war, or other governmental action related to tariffs or trade agreements or policies has the potential to adversely impact demand for our products, our costs, our customers, our suppliers, and the U.S. economy, which in turn could adversely impact our business, financial condition, access to capital and results of operations.

Risks Related To Our Common Stock

Our operating history makes evaluating our stock difficult

Our quarterly and annual results of operations have historically fluctuated and we expect will continue to fluctuate for the foreseeable future. We believe that period-to-period comparisons of our

operating results should not be relied upon as predictive of future performance. Our prospects must be considered in light of the risks, expenses and difficulties encountered by companies with a limited number of approved pharmaceutical products, particularly companies in new and rapidly evolving markets such as pharmaceuticals and biotechnology. To address these risks, we must, among other things, obtain regulatory approval for and commercialize our product candidates, which may not occur. We may not be successful in addressing these risks and difficulties. We expect to require additional funds to complete the development of larsucosterol or our other product candidates, and to fund operating losses to be incurred in the next several years.

Investors may experience substantial dilution of their investment

In order to raise capital and for other purposes, we may in the future offer and issue additional shares of our common stock or other securities convertible into or exchangeable for our common stock, and the price per share at which we sell additional shares of our common stock or other securities convertible into or exchangeable for our common stock in future transactions may be higher or lower than the price per share at which investors in our common stock bought their shares. In July 2021, we filed a shelf registration statement ("the 2021 Registration Statement") to sell up to $250 million of securities from time to time in one or more public offerings, including up to $75.0 million of shares of common stock through an at the market sales agreement with Cantor Fitzgerald (the "2021 Sales Agreement"). When the 2021 Registration Statement was declared effective in August 2021, the 2021 Sales Agreement replaced a prior similar 2015 Sales Agreement with Cantor Fitzgerald. Any sales in the public market of our common stock, under our 2021 Sales Agreement, in offerings under our shelf registration statement or otherwise, could adversely affect prevailing market prices for our common stock. Through several financings between 2019 and March 3, 2022, and through our 2015 Sales Agreement and 2018 Sales Agreement with Cantor Fitzgerald during this period, we have raised an aggregate of $79.4 million. As of March 3, 2022, we had up to $250.0 million of our securities available for sale under the 2021 Registration Statement, of which $75.0 million of our common stock are available pursuant to the 2021 Sales Agreement. In addition, as of December 31, 2021, 25,362,025 shares of our common stock were issuable upon exercise of stock options outstanding under our stock option plans at a weighted average exercise price of $1.39 per share, 6,793,921 additional shares of common stock were reserved for potential future issuance under our stock option plan, and an aggregate of 383,412 shares of common stock were reserved for potential future issuance under our 2000 Employee Stock Purchase Plan. Investors will incur dilution from the sale of any additional shares or upon the issuance of any shares pursuant to such plans, or upon exercise of any outstanding options.

Our stock price has in the past and may in the future not meet the minimum bid price for continued listing on Nasdaq. Our ability to continue operations or to publicly or privately sell equity securities and the liquidity of our common stock could be adversely affected if we are delisted from Nasdaq

In several instances in the past, including as recently as February 2022, we received written notification from Nasdaq informing us that because the closing bid price of our common stock was below $1.00 for 30 consecutive trading days, our shares no longer complied with the minimum closing bid price requirement for continued listing on Nasdaq under Nasdaq Marketplace Rules. Each time, we were given a period of 180 days from the date of the notification and in one case an extra 180-day period to regain compliance with Nasdaq's listing requirements by having the closing bid price of our common stock listed on Nasdaq be at least $1.00 for at least 10 consecutive trading days.

While we have regained compliance within the applicable time periods in the past, if our shares again no longer comply with the minimum closing bid price requirement for continued listing on the Nasdaq Capital Market under Nasdaq Marketplace Rule 5550(a)(2) and we do not regain compliance within the applicable 180-day time period, Nasdaq will notify us that our securities will be subject to delisting. One strategy to regain compliance in such circumstances would be to implement a reverse stock split. The Company could appeal Nasdaq's determination to delist its securities to a Hearings Panel. During any appeal process, shares of our common stock would continue to trade on the Nasdaq Capital Market.

There can be no assurance that we will maintain compliance with the requirements for listing our common stock on the Nasdaq Capital Market. Delisting from Nasdaq would constitute an event of default

under our loan facility with Oxford, entitling Oxford to accelerate our obligations under such facility, among other actions. Under such circumstances, we could be required to renegotiate the repayment terms of our loan facility, on terms which would not be as favorable to the Company as our current terms, or we could be required to take other actions, such as discontinuing some or all of our operations, selling assets, or other action. Delisting could also adversely affect our ability to raise additional capital through the public or private sale of equity securities, would significantly affect the ability of investors to trade our securities and would negatively affect the value and liquidity of our common stock. Delisting could also have other negative results, including the potential loss of confidence by employees, the loss of institutional investor interest and fewer business development opportunities.

Our ability to use net operating losses and certain other tax attributes is uncertain and may be limited

Our ability to use our federal and state net operating losses to offset potential future taxable income and related income taxes that would otherwise be due is dependent upon our generation of future taxable income before the expiration dates of the net operating losses, and we cannot predict with certainty when, or whether, we will generate sufficient taxable income to use any or all of our net operating losses. In addition, utilization of net operating losses to offset potential future taxable income and related income taxes that would otherwise be due is subject to annual limitations under the “ownership change” provisions of Sections 382 and 383 of the Internal Revenue Code of 1986, as amended (Internal Revenue Code) and similar state provisions, which may result in the expiration of net operating losses before future utilization. In general, under the Code, if a corporation undergoes an “ownership change,” generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation’s ability to use its pre-change net operating losses and other pre-change tax attributes (such as research and development credit carryforwards) to offset its post-change taxable income or taxes may be limited. Our equity offerings and other changes in our stock ownership, some of which are outside of our control, may have resulted or could in the future result in an ownership change. If an ownership change limitation were to apply, utilization of our net operating losses and tax credit carryforwards could be limited in future periods and a portion of the carryforwards could expire before being available to reduce future income tax liabilities.

The price of our common stock may be volatile

The stock markets in general, and the markets for pharmaceutical stocks in particular, have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. These broad market fluctuations may adversely affect the trading price of our common stock.

Price declines in our common stock could result from general market and economic conditions and a variety of other factors, including:

- adverse results (including adverse events or failure to demonstrate safety or efficacy) or delays in our clinical and non-clinical trials of larsucosterol or other product candidates;
- announcements of FDA non-approval of our product candidates, approvals with narrow indications, commercially limiting labels, clinical holds or delays in the FDA or other foreign regulatory agency review process;
- adverse actions taken by regulatory agencies or law enforcement agencies with respect to our products and product candidates, clinical trials, manufacturing processes, accounting practices or sales and marketing activities, or those of our third-party collaborators;
- announcements of technological innovations, patents, product approvals, sales performance or new products by our competitors;
- failure of third-party collaborators to continue development or successful commercialization of the respective products and product candidates they are developing or commercializing;
- failure by our commercial licensee (Innocoll) to successfully launch POSIMIR within a reasonable time, if at all, manufacture and store adequate supplies, and/or to achieve sales expectations and successfully commercialize POSIMIR;
- regulatory, judicial and patent developments in the United States and foreign countries;

- any lawsuit or arbitration involving us or our products and product candidates including intellectual property infringement or product liability suits;
- announcements concerning our competitors, or the biotechnology or pharmaceutical industries in general;
- developments concerning our strategic alliances or acquisitions or termination of such alliances;
- actual or anticipated variations in our operating results;
- changes in recommendations by securities analysts, misstatements or mischaracterizations in analyst reports or dropping or lack of analyst coverage;
- negative press coverage or online or social media misinformation about the Company or its partners or their respective products or personnel;
- deviations in our operating results from the estimates of analysts;
- sales of our common stock by our executive officers or directors or sales of substantial amounts of common stock by us or others;
- potential failure to meet continuing listing standards from The Nasdaq Capital Market;
- loss or disruption of facilities due to natural disasters;
- acceleration of our debt obligations due to a determination by our lender that a material adverse change has occurred;
- changes in accounting principles; or
- loss of any of our key scientific or management personnel.

The market price of our common stock may fluctuate significantly in response to factors which are beyond our control. The stock market in general has periodically experienced extreme price and volume fluctuations. For example, the outbreak of the COVID-19 coronavirus and its new variants, pronouncements by the Federal Reserve, oil price volatility and other factors have caused broad stock market and industry fluctuations. In addition, the market prices of securities of technology and pharmaceutical companies have also been extremely volatile, and have experienced fluctuations that often have been unrelated or disproportionate to the operating performance of these companies. These broad market fluctuations could result in extreme fluctuations in the price of our common stock, which could cause a decline in the value of our common stock.

In the past, following periods of volatility in the market price of a particular company’s securities, litigation has often been brought against that company. If litigation of this type is brought against us, it could be extremely expensive, particularly if we were to lose the lawsuit and have to pay damages, and divert management’s attention and our company’s resources.

We have broad discretion over the use of our cash and investments, and their investment may not always yield a favorable return

Our management has broad discretion over how our cash and investments are made and used. We may from time to time invest in ways with which our stockholders may not agree and that do not yield favorable returns.

Our certificate of incorporation, our bylaws and Delaware law contain provisions that could discourage another company from acquiring us

Provisions of Delaware law, our certificate of incorporation and bylaws may discourage, delay or prevent a merger or acquisition that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions include:

- authorizing the issuance of “blank check” preferred stock without any need for action by stockholders;
- providing for a classified board of directors with staggered terms;
- requiring supermajority stockholder voting to effect certain amendments to our certificate of incorporation and bylaws;
- eliminating the ability of stockholders to call special meetings of stockholders;
- prohibiting stockholder action by written consent; and
- establishing advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted on by stockholders at stockholder meetings.

Our bylaws provide that the Court of Chancery of the State of Delaware is the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders’ ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees

Our bylaws provide that the Court of Chancery of the State of Delaware is the exclusive forum for any derivative action or proceeding brought on behalf of the Company, any action asserting a claim of breach of a fiduciary duty owed by any director, officer or other employee of the Company, any action asserting a claim arising pursuant to any provision of the General Corporation Law of Delaware or our Certificate of Incorporation or bylaws or any action asserting a claim governed by the internal affairs doctrine. The choice of forum provision may limit a stockholder’s ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees.

Alternatively, if a court were to find the choice of forum provision contained in our certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business and financial condition.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

The following chart indicates the facilities that we lease, the location and size of each such facility and their designated use.

Location	Approximate Square Feet	Operation	Expiration
Cupertino, CA	30,149 sq. ft.	Office, Laboratory and Manufacturing	Lease expires 2024 (with an option to renew for an additional five years)
Cupertino, CA	20,100 sq. ft.	Office and Laboratory	Lease expires 2024 (with an option to renew for an additional five years)
Vacaville, CA	24,634 sq. ft.	Manufacturing	Lease expires 2023 (with an option to renew for an additional five years)

We believe that our existing facilities are adequate to meet our current and foreseeable requirements or that suitable additional or substitute space will be available as needed.

Item 3. Legal Proceedings.

We are not a party to any material legal proceedings.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

Item 5. Market for Registrant’s Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities.

Our common stock is traded on the Nasdaq Capital Market under the symbol “DRRX”.

As of March 3, 2022, there were approximately 96 holders of record of the common stock. This does not include the number of persons whose stock is in nominee or “street name” accounts through brokers.

Dividend Policy

We have never paid cash dividends on our common stock. We currently intend to retain any future earnings to fund the development and growth of our business. Therefore, we do not currently anticipate paying any cash dividends in the foreseeable future.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

Item 6. [Reserved]

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations.

This Management's Discussion and Analysis of Financial Condition and Results of Operations as of December 31, 2021 and 2020 should be read in conjunction with our Financial Statements, including the Notes thereto, and "Risk Factors" section included elsewhere in this Form 10-K. This Form 10-K contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, and Section 27A of the Securities Act of 1933, as amended. When used in this report or elsewhere by management from time to time, the words "believe," "anticipate," "intend," "plan," "estimate," "expect," "potential," "possibility," and similar expressions are forward-looking statements. Such forward-looking statements contained herein are based on current expectations.

Forward-looking statements made in this report include, for example, statements about:

- the clinical trial plans and timelines for larsucosterol (also known as DUR-928);
- potential uses and benefits of larsucosterol to treat alcohol-associated hepatitis (also called alcoholic hepatitis or AH), non-alcoholic steatohepatitis (NASH), or other conditions;
- the results and timing of clinical trials, the ability to enroll patients in clinical trials in a timely and cost-effective manner;
- the likelihood of future clinical trial results of larsucosterol being positive and/or similar to results from previous trials, the possible commencement of future clinical trials, enrollment rates and timing of announcements of the results from our clinical trials;
- the possibility of filing for marketing approval for larsucosterol for the treatment of AH if the AHFIRM trial is successful and the likelihood of FDA or other regulatory bodies granting such marketing approval;
- our intention to seek, and ability to enter into and maintain strategic alliances and collaborations;
- the potential benefits and uses of our products, product candidates and technologies, including larsucosterol, POSIMIR, and our SABER and CLOUD technologies;
- the potential milestone and royalty payments we may receive from Innocoll related to POSIMIR, earn-out payments we may receive from Indivior related to the commercialization of PERSERIS, and milestone, sub-license fees and royalty payments we may receive from Santen or Orient Pharma;
- the progress of our third-party collaborations, including estimated milestones;
- responsibilities of our third-party collaborators, including the responsibility to make cost reimbursement, milestone, royalty and other payments to us, and our expectations regarding our collaborators' plans with respect to our products and product candidates and continued development and commercialization of our products and product candidates;
- our responsibilities to our third-party collaborators, including our responsibilities to conduct research and development, clinical trials and/or manufacture excipients, products or product candidates;
- market opportunities for product candidates in our product development pipeline;
- potential regulatory filings for or approval of larsucosterol; the progress and results of our research and development programs and our evaluation of additional development programs;
- requirements for us to purchase pre-clinical, clinical trial and commercial supplies of product candidates and/or products, as well as raw materials or active pharmaceutical ingredients from third parties, and the ability of third parties to provide us with our requirements for such supplies and raw materials;
- conditions for obtaining regulatory approval of our product candidates;
- submission and timing of applications for regulatory approval and timing of responses to our regulatory submissions;
- the impact of FDA, EMA and other government regulation on our business;
- our ability to obtain, assert and protect patents and other intellectual property rights, including intellectual property licensed to our collaborators, as well as avoiding the intellectual property rights of others;

- products and companies that will compete with our products and the product candidates we develop and/or license to third-party collaborators;
- the possibility we may commercialize our own products and build up our commercial, sales and marketing capabilities and other required infrastructure;
- the possibility that we may develop additional manufacturing capabilities;
- our employees, including the number of employees and the continued services of key management, technical and scientific personnel;
- our future performance, including our anticipation that we will not derive meaningful revenues from our products and product candidates in development for at least the next twelve months, potential for future inventory write-offs and our expectations regarding our ability to achieve profitability;
- sufficiency of our cash resources, anticipated capital requirements and capital expenditures, our ability to comply with covenants of our term loan, and our need or desire for additional financing, including potential sales under our shelf registration statement;
- our expectations regarding research and development expenses, and selling, general and administrative expenses;
- the composition of future revenues; and
- accounting policies and estimates.

Forward-looking statements are not guarantees of future performance and involve risks and uncertainties. Actual events or results may differ materially from those discussed in the forward-looking statements as a result of various factors. For a more detailed discussion of such forward looking statements and the potential risks and uncertainties that may impact upon their accuracy, see the "Risk Factors" section and "Overview" section of this Management's Discussion and Analysis of Financial Condition and Results of Operations. These forward-looking statements reflect our view only as of the date of this report. We undertake no obligations to update any forward-looking statements. You should also carefully consider the factors set forth in other reports or documents that we file from time to time with the Securities and Exchange Commission.

This discussion and analysis generally addresses 2021 and 2020 items and year-over-year comparisons between 2021 and 2020. Discussions of 2019 items and year-over-year comparisons between 2020 and 2019 that are not included in this Annual Report on Form 10-K can be found in "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations" in our Annual Report on Form 10-K for the fiscal year ended December 31, 2020, filed with the SEC on March 5, 2021.

Overview

We are a biopharmaceutical company advancing novel and potentially lifesaving investigational therapies derived from our Epigenetic Regulator Program. Larsucosterol (also known as DUR-928), a new chemical entity in clinical development, is the lead candidate in our Epigenetic Regulator Program. An endogenous, orally bioavailable small molecule, larsucosterol has been shown in both *in vitro* and *in vivo* studies to play an important regulatory role in lipid metabolism, stress and inflammatory responses, and cell death and survival. Alcohol-associated hepatitis (AH) is a life-threatening acute liver condition with no approved therapeutics and a 28-day and 90-day historical mortality rate of 20%-26% and 29%-31%, respectively. 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 called 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. If the AHFIRM trial is successful, it may support an NDA filing and we may decide to develop our own commercial, sales and marketing organization. We have also investigated larsucosterol in patients with nonalcoholic steatohepatitis (NASH) and are considering further development for this indication. In March 2021, a peer-reviewed research paper describing the binding sites and proposed mechanism of

action of larsucosterol was published in The Journal of Lipid Research. The publication shows that larsucosterol (referred to in the paper as 25HC3S) binds to and inhibits the activity of DNA methyltransferases (DNMTs) DNMT-1, 3a and 3b, epigenetic regulating enzymes that add methyl groups to DNA (a process called DNA methylation) and have been shown to be elevated in AH patients. As such, by inhibiting DNMT activity, larsucosterol inhibits DNA methylation, thereby regulating the expression of genes that modulate crucial cellular activities, including those associated with cell death, stress response, and lipid biosynthesis. These modulations may lead to improved cell survival, and reduced lipid accumulation and inflammation, as has been observed in various in vivo animal models and in results from our completed clinical trials in AH and NASH.

In addition to our Epigenetic Regulator Program, we developed a novel and proprietary post-surgical pain product called POSIMIR that utilizes our innovative SABER platform technology to enable continuous sustained delivery of bupivacaine, a non-opioid local analgesic, over 3 days in adults. In December 2021, we entered a license agreement with Innocoll Pharmaceuticals Limited, pursuant to which the Company granted to Innocoll an exclusive, royalty-bearing, sublicensable right and license to develop, manufacture and commercialize POSIMIR in the United States. Under the agreement, DURECT will earn low to mid double-digit royalties from net sales of POSIMIR and is eligible to receive up to an additional $132 million in milestone payments.

As a result of the assignment of certain patent rights, DURECT also receives single digit sales-based earn-out payments from U.S. net sales of Indivior's PERSERIS (risperidone) drug for schizophrenia and single-digit royalties from net sales of Orient Pharma's Methydur Sustained Release Capsules (Methydur) for the treatment of attention deficit hyperactivity disorder (ADHD) in Taiwan. We also manufacture and sell ALZET osmotic pumps used in laboratory research and have several early-stage development programs with corporate collaborators on terms which typically call for our collaborator to fund all or a substantial portion of future development costs and then pay us milestone payments based on specific development or commercial achievements plus royalties on product sales.

Collaborative Research and Development and Other Revenues

Collaborative research and development and other revenues consist of three broad categories: (a) the recognition of upfront license payments over the period of our continuing involvement with the third party, (b) the reimbursement of qualified research expenses by third parties and (c) milestone payments in connection with our collaborative agreements. During the last three years, we generated collaborative research and development revenues from collaborative agreements with Innocoll, Gilead, Santen and others.

Product Revenues

We also currently generate product revenue from the sale of two product lines:

- ALZET® osmotic pumps which are used for animal research; and
- certain key excipients that are included in Methydur and one excipient that is included in POSIMIR and in a marketed animal health product.

In December 2020, we completed the sale of our LACTEL Absorbable Polymers product line to Evonik Corporation. Under the terms of the Asset Purchase Agreement, Evonik paid us approximately $15.1 million, and also agreed to assume certain liabilities with respect to the transferred assets and assembled workforce. The LACTEL product line is reflected as a discontinued operation in our statements of operations and comprehensive loss for the year ended December 31, 2020. Our financial information discussed in the Management's Discussion and Analysis of Financial Condition and Results of Operations excludes the impact of the LACTEL product line.

Because we consider our core business to be developing and commercializing pharmaceuticals, we do not intend to significantly increase our investments in or efforts to sell or market any of our existing product lines. However, we expect that we will continue to make efforts to increase our revenues related to collaborative research and development by extending and expanding our current collaborations as well as entering into additional research and development agreements with third-party collaborators to develop product candidates based on our drug delivery technologies.

Operating Results

Since our inception in 1998, we have generally had a history of operating losses. At December 31, 2021, we had an accumulated deficit of $526.0 million. Our net losses were $36.3 million and $582,000, and for the years ended December 31, 2021 and 2020, respectively. These losses have resulted primarily from costs incurred to research and develop our product candidates and to a lesser extent, from selling, general and administrative costs associated with our operations and product sales. We expect our research and development expenses to increase in 2022 compared to 2021 as we continue to incur research and development expenses related to larsucosterol. We expect our selling, general and administrative expenses to increase in 2022 compared to 2021. Over the next twelve months, we anticipate a limited increase in revenues primarily from the launch of POSIMIR by our licensee, Innocoll. However, we expect to incur continuing losses and negative cash flows from operations for the foreseeable future.

Critical Accounting Estimates

The preparation of financial statements in conformity with generally accepted accounting principles requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the dates of the financial statements and the reported amounts of revenues and expenses during the reporting periods. The most significant estimates and assumptions relate to revenue recognition, contract research liabilities, and stock-based compensation. Actual amounts could differ significantly from these estimates.

Revenue Recognition

Product Revenues, Net

We manufacture and sell ALZET osmotic pumps used in laboratory research, and manufacture and sell certain excipients for use as raw materials in certain products, including POSIMIR, an animal health product and Methydur.

Revenues from product sales are recognized when the customer obtains control of our product, which occurs at a point in time, typically upon shipment to the customer. We expense incremental costs of obtaining a contract as and when incurred if the expected amortization period of the asset that we would have recognized is one year or less.

Trade Discounts and Allowances: We provide certain customers with discounts that are explicitly stated in our contracts and are recorded as a reduction of revenues in the period the related product revenues are recognized.

Product Returns: Consistent with industry practice, we generally offer customers a limited right of return for products that have been purchased from us. We estimate the amount of our product sales that may be returned by our customers and record this estimate as a reduction of revenues in the period the related product revenues is recognized. We currently estimate product return liabilities using our own historical sales information. We expect product returns to be minimal.

Collaborative Research and Development Revenues

We enter into license agreements under which we license certain rights to our product candidates to third parties. The terms of these arrangements typically include payment to us of one or more of the following: non-refundable, up-front license fees; reimbursement of development costs incurred by us under approved work plans; development, regulatory, intellectual property and commercial milestone payments; payments for manufacturing supply services we provide ourselves or through our contract manufacturers; sales-based milestones and royalties on net sales of licensed products. Each of these payments results in collaborative research and development revenues, except for revenues from royalties or earn-out payments on net sales of licensed products, which are classified as other revenues.

In determining the appropriate amount of revenue to be recognized as we fulfill our obligations under each of our agreements, we perform the following steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance

obligations, including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) we satisfy each performance obligation. As part of the accounting for these arrangements containing multiple performance obligations, we must develop assumptions that require judgment to determine the stand-alone selling price for each performance obligation identified in the contract. We use key assumptions to determine the stand-alone selling price, which may include forecasted revenues, development timelines, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success. We expect to recognize revenue for the variable consideration currently being constrained when it is probable that a significant revenue reversal will not occur.

Licenses of intellectual property: If the license to our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenues from non-refundable, up-front fees allocated to the license when the license is transferred to the customer and the customer is able to use and benefit from the license. For licenses that are bundled with other promises, we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, up-front fees. We evaluate the measure of progress each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

Milestone Payments: At the inception of each arrangement that includes development milestone payments, we evaluate whether the milestones are considered probable of being reached and estimate the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the control of us or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. The transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis, for which we recognize revenue as or when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, we re-evaluate the probability of achievement of such development milestones and any related constraint, and if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect collaborative research and development revenues and net income (loss) in the period of adjustment.

Manufacturing Supply Services: Arrangements that include a promise for future supply of raw materials or drug product for either clinical development or commercial supply at the customer’s discretion are generally considered options. We assess if these options provide a material right to the customer and if so, they are accounted for as separate performance obligations. If we are entitled to additional payments when the customer exercises these options, any additional payments are recorded in collaborative research and development revenues when the customer obtains control of the goods, which is upon delivery.

Royalties and Earn-outs: For arrangements that include sales-based royalties or earn-outs, including milestone payments based on first commercial sale or the level of sales, and the license is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty or earn-out has been allocated has been satisfied (or partially satisfied). To date, we have not recognized material royalty revenue resulting from our collaborative arrangements or material earn-out revenues from any of our patent purchase agreements.

Research and development revenue related to services performed under the collaborative arrangements with the Company's third-party collaborators is recognized as the related research and development services are performed. These research payments received under each respective agreement are not refundable and are generally based on reimbursement of qualified expenses, as defined in the agreements. Research and development expenses under the collaborative research and development agreements generally approximate or exceed the revenue recognized under such agreements over the term of the respective agreements. Deferred revenue may result when the Company does not expend the required level of effort during a specific period in comparison to funds received under the respective agreement.

The Company receives payments from its customers based on development cost schedules established in each contract. Up-front payments are recorded as deferred revenue upon receipt or when due, and may require deferral of revenue recognition to a future period until the Company performs its obligations under these arrangements. Amounts are recorded as accounts receivable when the Company's right to consideration is unconditional. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the customer and the transfer of the promised goods or services to the customer will be one year or less.

Prepaid and Accrued Contract Research Expenses

We incur significant costs associated with third party consultants and organizations for pre-clinical studies, clinical trials, contract manufacturing, validation, testing, regulatory advice and other research and development-related services. We are required to estimate periodically the cost of services rendered but unbilled based on management's estimates of project status. If these good faith estimates are inaccurate, actual expenses incurred could materially differ from our estimates.

Stock-Based Compensation

Employee stock-based compensation is estimated at the date of grant based on the employee stock award's fair value using the Black-Scholes option-pricing model and is recognized as expense ratably over the requisite period.

We estimate the volatility of our common stock at the date of grant based on the historical volatility of our common stock. We base the risk-free rate that we use in the Black-Scholes option valuation model on the implied yield in effect at the time of option grant on U.S. Treasury zero-coupon issues with equivalent remaining terms. We have never paid any cash dividends on our common stock and we do not anticipate paying any cash dividends in the foreseeable future. Consequently, we use an expected dividend yield of zero in the Black-Scholes option valuation model. Upon the adoption of ASU 2016-09, we account for forfeitures as they occur and record stock-based compensation expense only for those awards that vest. We amortize the fair value of options granted on a straight-line basis. All options are amortized over the requisite service periods of the awards, which are generally the vesting periods. We may elect to use different assumptions under the Black-Scholes option valuation model in the future, which could materially affect our net income or loss and net income or loss per share.

Results of Operations

Comparison of years ended December 31, 2021 and 2020

Collaborative research and development and other revenues

We recognize revenues from collaborative research and development activities and service contracts. Collaborative research and development and other revenue primarily represents reimbursement

of qualified expenses related to collaborative agreements with various third parties to research, develop and commercialize potential products using our drug delivery technologies, and revenue from the recognition of upfront fees and milestone payments in connection with our collaborative or license agreements.

We expect our collaborative research and development and other revenues to fluctuate in future periods pending our efforts to enter into potential new collaborations, our existing third-party collaborators' commitment to and progress in the research and development programs, and any royalty or earn-out revenue recognized from collaborators or counterparties. The collaborative research and development and other revenues associated with our major collaborators or counterparties are as follows (in thousands):

	Year ended December 31,	
	2021	2020
Collaborator/Counterparty		
Innocoll (1)	$ 4,100	$ —
Gilead (2)	—	22,879
Other (3)	2,231	1,062
Total collaborative research and development and other revenue	$ 6,331	$ 23,941

(1) We signed a license agreement with Innocoll on December 21, 2021, pursuant to which Innocoll agreed to pay a nonrefundable upfront license fee of $4.0 million and $1.3 million primarily for the sale of manufacturing supplies and excipients. In December 2021, we recognized $4.1 million as collaborative research and development and other revenue and $1.1 million in product revenue upon the transfer of control of the license and the manufacturing supplies excipients, and equipment to Innocoll, we recognized $4.1 million as collaborative research and development and other revenue, $1.1 million as product revenue, and a reduction of $0.1 million in net equipment (see Note 2 Strategic Agreements - Agreement with Innocoll in the financial statements).

(2) We signed a license agreement with Gilead on July 19, 2019. Amounts related to recognition of upfront fees and milestone payments were zero and $22.7 million for the twelve months ended December 31, 2021 and 2020, respectively. We received a nonrefundable upfront license fee and a milestone payment totaling $35.0 million in 2019 which was being recognized as revenue as our obligation was being satisfied using the cost-to-cost input method (see Note 2 Strategic Agreements - Agreement with Gilead Sciences, Inc. in the financial statements). In June 2020, we received notice that Gilead was terminating the License Agreement and a related R&D agreement between Gilead and us. As a result, we recognized all our remaining deferred revenue as there were no remaining substantive performance obligations to be provided to Gilead by the Company as of the date when the termination notice was received. Amounts recognized as revenue during the twelve months ended December 31, 2020 also included our reimbursable collaborative research and development services performed under our agreement with Gilead.

(3) Includes: (a) amounts related to earn-out revenue from Indivior UK Limited (Indivior) with respect to PERSERIS net sales; (b) feasibility programs; (c) research and development activities funded by Santen Pharmaceutical Co. Ltd. (Santen) and (d) royalty revenue from OP Pharma with respect to Methydur net sales. Since 2018, we have been working with Santen on a limited set of research and development activities funded by Santen.

The decrease in collaborative research and development revenues in 2021 compared with 2020 was primarily due to lower revenue recognized from our agreement with Gilead, partially offset by higher revenue recognized from our agreements with Innocoll, Indivior, Santen and feasibility agreements with other companies.

Innocoll agreed to pay us a $4.0 million upfront fee and a payment of $1.3 million primarily for the sale of manufacturing supplies and excipients in connection with the license agreement signed in

December 2021. Through December 31, 2021, $5.2 million had been recognized as revenue as there were no remaining substantive performance obligations to be provided to Innocoll by the Company.

We received a $25.0 million upfront fee in connection with the license agreement signed with Gilead in July 2019 and in October 2019 we also received a $10 million milestone payment from Gilead. Through December 31, 2020, all of these amounts had been recognized as revenue as there were no remaining substantive performance obligations to be provided to Gilead by the Company as of the date when the termination notice was received.

We received a $2.0 million upfront fee in connection with the license agreement signed with Santen in December 2014. The $2.0 million upfront fee was being recognized as collaborative research and development revenue over the term of our continuing involvement with Santen. At December 31, 2021, $1.2 million of the $2.0 million upfront fee had been recognized as revenue.

As of March 3, 2022, we had potential milestones of up to $208.0 million that we may receive in the future under our collaborative arrangements, of which $23.0 million are development-based milestones, $10.0 million are patent-based milestones and $175.0 million are sales-based milestones. Within the category of development-based milestones, $2.0 million are related to early-stage clinical testing (defined as Phase 1 or 2 activities), $3.0 million are related to late-stage clinical testing (defined as Phase 3 activities), $3.0 million are related to regulatory filings and $15.0 million are related to regulatory approvals. No milestone payments were received between December 31, 2021 and March 3, 2022, and we do not anticipate receiving any of these milestone revenues other than $2.0 million of a sales-based milestone triggered by first commercial sale of POSIMIR by Innocoll within the next twelve months, if at all.

Product revenues

In December 2020, we completed the sale of our LACTEL Absorbable Polymers product line to Evonik Corporation. Revenue from the LACTEL product line, related cost of product revenues, associated research and development, and selling, general and administrative has been reclassified to discontinued operations for all periods presented.

A portion of our revenues is derived from product sales, which include our ALZET osmotic pump product line, and certain excipients that are included in POSIMIR, Methydur and in a marketed animal health product. Net product revenues were $7.6 million and $6.2 million in 2021 and 2020, respectively.

The increase in product revenues in 2021 was primarily attributable to higher revenue from our ALZET osmotic pump product line as a result of higher units sold compared to 2020 and higher product revenue related to manufacturing supplies and excipients that are included in POSIMIR from the Innocoll license agreement entered in December 2021.

Cost of product revenues

Cost of product revenues was $2.0 million and $1.4 million in 2021 and 2020, respectively. Cost of product revenues includes the cost of product revenue from our ALZET product line, and certain excipients that are included in POSIMIR, Methydur and a marketed animal health product.

The increase in cost of product revenues in 2021 was primarily attributable to higher cost of goods sold related to certain excipients and materials that are included in POSIMIR from the Innocoll license agreement entered in December 2021, partially offset by lower cost of goods sold related to our ALZET product line arising from lower manufacturing costs in 2021 compared to 2020.

Stock-based compensation expense related to cost of product revenues was $19,000 and $13,000, in 2021 and 2020, respectively.

As of December 31, 2021 and 2020, we had 10 and 9 manufacturing employees, respectively.

Research and development. Research and development expenses are primarily comprised of salaries, benefits, stock-based compensation and other compensation cost associated with research and development personnel, overhead and facility costs, preclinical and non-clinical development costs, clinical trial and related clinical manufacturing costs, contract services, and other outside costs. Research and development expenses were $31.8 million and $27.7 million in 2021 and 2020, respectively. Stock-based compensation expense recognized related to research and development personnel was $1.2 million,

and $981,000 in 2021 and 2020, respectively. We expect our research and development expenses to increase in 2022 compared to 2021 as we continue to incur research and development expenses related to larsucosterol.

Research and development expenses increased by $4.1 million in 2021 compared to 2020. The increase in 2021 was primarily attributable to higher research and development costs associated with larsucosterol, POSIMIR, depot injectable and other research programs, partially offset by lower research and development costs associated with the Gilead program compared to 2020, as more fully discussed below.

Research and development expenses associated with our major development programs after the removal of the effects of our sale of the LACTEL product line were as follows (in thousands):

	Year Ended December 31,	
	2021	2020
Larsucosterol	$ 25,074	$ 21,319
POSIMIR	4,249	3,656
Gilead program (1)	65	1,011
Depot injectable programs	1,388	862
Other	1,070	861
Total research and development expenses	$ 31,846	$ 27,709

(1) See Note 2 Strategic Agreements in the financial statements for more details about our agreements with Gilead.

Larsucosterol

Our research and development expenses for larsucosterol increased to $25.1 million in 2021 from $21.3 million in 2020, primarily due to higher clinical trial related expenses and higher contract manufacturing expenses for this drug candidate compared with 2020.

We continue to assess the impact of the COVID-19 outbreak on our business, including our larsucosterol Phase 2b trial in alcohol-associated hepatitis; COVID-19 may affect our ability to initiate and/or complete recruitment and data analysis for our clinical trials, including larsucosterol trials, in our planned timeframe.

POSIMIR

Our research and development expenses for POSIMIR increased to $4.2 million in 2021 from $3.7 million in 2020, primarily due to higher consulting expenses and higher contract manufacturing expenses for POSIMIR.

It is possible that the COVID-19 pandemic will adversely impact the timing of potential commercialization of POSIMIR which is now controlled by Innocoll.

Gilead Program

Our research and development expenses for the Gilead program decreased to $65,000 in 2021 from $1.0 million in 2020, primarily due to lower employee-related costs and outside costs devoted to the program compared with 2020. In June 2020, Gilead provided notice that it was terminating the Gilead Agreement and a related R&D agreement.

Depot injectable programs

Our research and development expenses for depot injectable programs increased to $1.4 million in 2021 from $862,000 in 2020 primarily due to higher employee-related costs and higher outside expenses for these programs.

Other DURECT research programs

Our research and development expenses for all other research activities increased to $1.1 million in 2021 from $861,000 in 2020, primarily due to higher employee-related costs incurred for these programs.

As of December 31, 2021 and 2020, we had 45 and 46 research and development employees, respectively.

We cannot reasonably estimate the timing and costs of our research and development programs due to the risks and uncertainties associated with developing pharmaceuticals as outlined in the “Risk Factors” section of this report. The duration of development of our research and development programs may span as many as ten years or more, and estimation of completion dates or costs to complete are highly speculative and subjective due to the numerous risks and uncertainties associated with developing pharmaceutical products, including significant and changing government regulation, the uncertainties of future preclinical and clinical study results, uncertainties related to the COVID-19 outbreak, the uncertainties with our collaborators’ commitment to and progress in the programs and the uncertainties associated with process development and manufacturing as well as sales and marketing. In addition, with respect to our development programs subject to third-party collaborations, the timing and expenditures to complete the programs are subject to the control of our collaborators. Therefore, we cannot reasonably estimate the timing and costs of the efforts necessary to complete the research and development programs. For additional information regarding these risks and uncertainties, see “Risk Factors” above.

Selling, general and administrative. Selling, general and administrative expenses are primarily comprised of salaries, benefits and stock-based compensation associated with finance, legal, business development, sales and marketing (including sales and marketing expenses for our ALZET product line) and other administrative personnel, overhead and facility costs, and other general and administrative costs. Selling, general and administrative expenses were $14.4 million and $13.6 million in 2021 and 2020, respectively. Stock-based compensation expense recognized related to selling, general and administrative personnel was $1.4 million and $1.1 million in 2021 and 2020, respectively. We expect our selling, general and administrative expenses to increase in 2022 compared to 2021 as employee retention credits are no longer available.

Selling, general and administrative expenses increased by $838,000 in 2021 compared to 2020, primarily due to an advisory fee related to the execution of the Innocoll agreement in 2021 compared with 2020.

As of December 31, 2021 and 2020, we had 24 and 26 selling, general and administrative personnel, respectively.

Other income (expense). Interest and other income were $156,000 and $517,000 in 2021 and 2020, respectively. The decrease in interest and other income in 2021 compared to 2020 was primarily the result of lower interest income generated as a result of lower interest rates associated with our cash and investments in 2021 compared with 2020.

Interest expense was $2.1 million and $2.2 million in 2021 and 2020, respectively. The decrease in interest expense in 2021 compared to 2020 was primarily due to lower interest rates associated with the term loan with Oxford Finance in 2021 compared to 2020.

Income taxes. As of December 31, 2021, we had net operating loss (NOL) carryforwards for federal income tax purposes of approximately $351.9 million, of which approximately $279.8 million will expire in the years 2022 through 2037, and approximately $72.1 million will not expire under current tax laws. As of December 31, 2021, we had federal research and development tax credits of approximately $16.5 million, which expire at various dates beginning in 2022 through 2041, if not utilized. As of December 31, 2021, we had NOL carryforwards for state income tax purposes of approximately $239.1 million, which expire in the years 2022 through 2041, and state research and development tax credits of approximately $17.1 million, which do not expire under current tax laws. Utilization of the net operating losses may be subject to a substantial annual limitation due to federal and state ownership change limitations. The annual limitation may result in the expiration of net operating losses and credits before utilization.

As of December 31, 2021 and 2020, we had net deferred tax assets of $116.4 million and $114.3 million, respectively. Deferred tax assets reflect the net tax effects of net operating loss and credit carryforwards and the temporary differences between the carrying amounts of assets and liabilities for

financial reporting and the amounts used for income tax purposes. Realization of deferred tax assets is dependent upon future earnings, if any, the timing and amount of which are uncertain. Accordingly, the net deferred tax assets have been fully offset by a valuation allowance.

Because realization of such tax benefits is uncertain, we provided a 100% valuation allowance as of December 31, 2021 and 2020. Utilization of the NOL and R&D credits carryforwards may be subject to a substantial annual limitation due to ownership change limitations that have occurred previously or that could occur in the future provided by Sections 382 and 383 of the Internal Revenue Code of 1986, as well as similar state and foreign provisions. These ownership changes may limit the amount of NOL and R&D credits carryforwards that can be utilized annually to offset future taxable income and tax, respectively. In general, an ownership change is defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating losses and other pre-change tax attributes (such as research and development credit carryforwards) to offset its post-change taxable income or taxes may be limited. Since our formation, we have raised capital through the issuance of capital stock on several occasions which, combined with the purchasing shareholders' subsequent disposition of those shares, may have resulted in a change of control, as defined by Section 382, or could result in a change of control in the future upon subsequent disposition. We issued $60.0 million of convertible notes in 2003 and subsequently all of these notes had been converted as of December 31, 2008 into approximately 19.0 million shares of our common stock. We also issued approximately 4.4 million shares of our common stock to an institutional investor in connection with an equity financing in September 2009. In December 2012, November 2013, April 2016, June 2019 and February 2021, we completed underwritten public offerings in which we sold an aggregate of approximately 14.0 million, 8.2 million and 13.8 million, 29.0 million and 20.4 million shares, respectively, of our common stock pursuant to effective registration statements. In 2016, 2017, 2018, 2019, 2020 and 2021, we issued approximately 5.2 million, 8.9 million, 9.6 million, 2.3 million, 5.3 million and 950,009 shares, respectively, of our common stock in the open market through Controlled Equity Offering sales agreements with Cantor Fitzgerald pursuant to effective registration statements. These transactions may also have resulted in a change of control as defined by Section 382 or could result in a change of control in the future upon the subsequent disposition of the shares.

We have not currently completed a study to assess whether a change in control has occurred or whether there have been multiple changes of control since our formation due to the significant complexity and cost associated with such a study and the fact that there could be additional changes in the future. If we have experienced a change of control at any time since our formation, utilization of our NOL or R&D credits carryforwards would be subject to an annual limitation under Sections 382 and 383 which is determined by first multiplying the value of our stock at the time of the ownership change by the applicable long-term tax-exempt rate, and then could be subject to additional adjustments, as required. Any limitation may result in expiration of a portion of our NOL or R&D credits carryforwards before utilization. Tax years 1998 to 2021 remain subject to future examination by the major tax jurisdictions in which we are subject to tax.

Liquidity and Capital Resources

We had cash, cash equivalents and investments totaling $70.0 million at December 31, 2021, which includes $150,000 of interest-bearing marketable securities classified as restricted investments on our balance sheet as of December 31, 2021 as compared to cash, cash equivalents, cash held in escrow, investments and restricted investments totaling $56.9 million at December 31, 2020.

We used $37.3 million and $38.7 million of cash in operating activities in the years ended December 31, 2021 and 2020, respectively. The cash provided by or used for operations was primarily to fund operations as well as working capital requirements. Our cash provided by or used in operating activities differs from our net loss in part due to the timing and recognition of up-front payments under collaborative agreements. Depending on the nature of the upfront payments received upon execution of collaborative agreements, which can either be recognized as revenue upfront in full or primarily recorded as deferred revenue and generally recognized over the period using a basis that best reflects the satisfaction of our performance obligations with the third-party collaborator pursuant to the applicable

agreement. The decrease in cash used in operating activities in 2021 compared to 2020 was primarily due to changes in accounts receivable, prepaid expenses and other assets, and accrued and other liabilities.

We generated $15.3 million and $9.4 million of cash from investing activities in the years ended December 31, 2021 and 2020, respectively. The increase in cash received from investing activities in 2021 was due to cash received from the sale of the LACTEL product line, partially offset by an increase in net purchases of available-for-sale securities. We anticipate incurring capital expenditures of approximately $100,000 over the next 12 months. The amount and timing of these capital expenditures will depend on, among other things, our research and development activities and needs, and the need for equipment replacements.

We generated $50.5 million and $15.7 million of cash from financing activities in the years ended December 31, 2021 and 2020, respectively. The increase in cash received from financing activities in 2021 was primarily due to higher net proceeds received from issuances of common stock in 2021 compared to 2020. In 2021, we completed an underwritten public offering of 20,364,582 shares of our common stock at a price of $2.2386 per share pursuant to an underwriting agreement with Cantor Fitzgerald, raising net proceeds of approximately $45.4 million. In 2021, we also raised net proceeds (net of commissions) of approximately $2.4 million from the sale of 950,009 shares of our common stock in the open market at a weighted average price of $2.60 per share pursuant to the October 2018 registration statement and 2015 Sales Agreement. In 2020, we raised net proceeds of approximately $12.3 million from the sale of 5,308,002 shares of the Company's common stock in the open market at a weighted average price of $2.39 per share pursuant to the October 2018 registration statement.

In July 2021, we filed a shelf registration statement on Form S-3 with the SEC (the "2021 Registration Statement") (File No. 333-258333), which upon being declared effective in August 2021, terminated our registration statement filed in August 2018 (File No. 333-226518) and allowed us to offer up to $250.0 million of securities from time to time in one or more public offerings, inclusive of up to $75.0 million of shares of our common stock which we may sell, subject to certain limitations, pursuant to a sales agreement dated July 30, 2021 with Cantor Fitzgerald (the "2021 Sales Agreement"). The 2021 Sales Agreement replaced a prior 2015 Sales Agreement.

As of March 3, 2022, we had up to $250.0 million of our securities available for sale under the 2021 Registration Statement, of which $75.0 million of our common stock are available pursuant to the 2021 Sales Agreement.

Any material sales in the public market of our common stock, under the 2021 Sales Agreement or otherwise under the 2021 Registration Statement, could adversely affect prevailing market prices for our common stock.

In July 2016, we entered into a Loan and Security Agreement (the Loan Agreement) with Oxford Finance LLC (Oxford Finance), pursuant to which Oxford Finance provided a $20.0 million secured single-draw term loan to us with an initial maturity date of August 1, 2020. The term loan was fully drawn at close and the proceeds may be used for working capital and general business requirements. The term loan repayment schedule provided initially for interest only payments for the first 18 months, followed by consecutive monthly payments of principal and interest in arrears starting on March 1, 2018 and continuing through the maturity date of August 1, 2020. Following five amendments, we make interest only payments under the amended Loan Agreement until June 1, 2023 and the final maturity date of the loan is September 1, 2025. The Loan Agreement provides for a floating interest rate (7.95% initially and 7.95% as of December 31, 2021) based on an index rate plus a spread and an additional payment equal to 10% of the principal amount of the term loan, which is due when the term loan becomes due or upon the prepayment of the facility. If we elect to prepay the loan, there is also a prepayment fee between 0.75% and 2.5% of the principal amount of the term loan depending on the timing of prepayment. Our debt repayment obligations under the Loan Agreement, as amended, may prove a burden to the Company as they become due, particularly following the expiration of the interest-only period.

The term loan is secured by substantially all of our assets, except that the collateral does not include any intellectual property (including licensing, collaboration and similar agreements relating thereto), and certain other excluded assets. The Loan Agreement contains customary representations, warranties and covenants by us, which covenants limit our ability to convey, sell, lease, transfer, assign or otherwise

dispose of certain assets; engage in any business other than the businesses currently engaged in by us or reasonably related thereto; liquidate or dissolve; make certain management changes; undergo certain change of control events; create, incur, assume, or be liable with respect to certain indebtedness; grant certain liens; pay dividends and make certain other restricted payments; make certain investments; and make payments on any subordinated debt.

The Loan Agreement also contains customary indemnification obligations and customary events of default, including, among other things, our failure to fulfill certain obligations under the 2016 Loan Agreement and the occurrence of a material adverse change which is defined as a material adverse change in our business, operations, or condition (financial or otherwise), a material impairment of the prospect of repayment of any portion of the loan, or a material impairment in the perfection or priority of lender's lien in the collateral or in the value of such collateral. In the event of default by us under the 2016 Loan Agreement, the lender would be entitled to exercise its remedies thereunder, including the right to accelerate the debt, upon which we may be required to repay all amounts then outstanding under the Loan Agreement. As a result, that portion of the term loan that was due more than 12 months after December 31, 2021 was classified within non-current liabilities.

Cash used in our operating activities is heavily influenced by the timing and structure of new corporate collaborations. While one feature of our business strategy is seeking new corporate collaborations, assuming no new collaborations and no milestone payments, we anticipate that cash used in operating activities will increase in the near term.

The COVID-19 pandemic is impacting our business in several ways. COVID-19 initially had a negative impact on orders for our ALZET product line as many ALZET customers reduced their activities during the pandemic. ALZET orders recovered significantly in 2021, a trend that may or may not continue as the impact of the pandemic has proven to be difficult to predict. For larsucosterol, we may experience delays in patient enrollment of the Phase 2b AHFIRM clinical trial or disruptions in supplies of larsucosterol or other items required for clinical trials. Delays and potential disruptions would increase the overall costs of development of larsucosterol. We are actively monitoring the impact of COVID-19 and the possible effects on its financial condition, liquidity, operations, clinical trials, suppliers, industry and workforce. However, the full extent, consequences, and duration of the COVID-19 pandemic and the resulting impact on the Company cannot currently be predicted. The Company will continue to evaluate the impact that these events could have on the Company's operations, financial position, and the results of operations and cash flows. Additional volatility in capital markets and/or clinical trial delays resulting from the impacts of COVID-19 may also limit our ability to raise capital on acceptable terms, if at all.

We believe that our existing cash, cash equivalents and investments will be sufficient to fund our planned operations, existing debt and contractual commitments and planned capital expenditures through at least the next 12 months from December 31, 2021. We may consume available resources more rapidly than currently anticipated, resulting in the need for additional funding. Over the next twelve months, we anticipate a limited increase in revenues primarily from the launch of POSIMIR by Innocoll. However, we expect to incur continuing losses and negative cash flows from operations for the foreseeable future.

Depending on whether we enter into additional collaborative agreements in the near term and the extent to which we earn revenues from our collaborative agreements, we may decide to raise additional capital through a variety of sources in the short-term and in the long-term, including:

- the public equity markets;
- private equity financings;
- collaborative arrangements; and/or
- public or private debt.

There can be no assurance that we will enter into additional collaborative agreements or maintain existing collaborative agreements in the near term, will earn collaborative revenues or that additional capital will be available on favorable terms, if at all. If adequate funds are not available, we may be required to significantly reduce or refocus our operations or to obtain funds through arrangements that

may require us to relinquish rights to certain of our products, technologies or potential markets, either of which could have a material adverse effect on our business, financial condition and results of operations. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of such securities would result in ownership dilution to our existing stockholders (assuming convertible debt securities were converted into shares).

Our cash and investments policy emphasizes liquidity and preservation of principal over other portfolio considerations. We select investments that maximize interest income to the extent possible given these two constraints. We satisfy liquidity requirements by investing excess cash in securities with different maturities to match projected cash needs and limit concentration of credit risk by diversifying our investments among a variety of high credit-quality issuers.

In 2021, there were no significant changes in our commercial commitments and contractual obligations. In aggregate, we are required to make future payments pursuant to our existing contractual obligations as follows (in thousands):

Contractual Obligations	2022	2023	2024	2025	Total
Term loan (1)	$ 1,612	$ 7,191	$ 9,408	$ 7,886	$ 26,097
Operating lease obligations	1,991	1,970	275	—	4,236
Total contractual cash obligations	$ 3,603	$ 9,161	$ 9,683	$ 7,886	$ 30,333

(1) Includes principal, interest payments and final payments and assumes no acceleration of obligations.

Recent Accounting Pronouncements

In June 2016, the FASB issued Accounting Standards Update No. 2016-13 (ASU 2016-13) “Financial Instruments - Credit Losses: Measurement of Credit Losses on Financial Instruments.” ASU 2016-13 requires measurement and recognition of expected credit losses for financial assets. This standard is effective for fiscal years beginning after December 15, 2022 for smaller reporting companies, including interim reporting periods within those years and must be adopted using a modified retrospective approach, with certain exceptions. Early adoption is permitted. The Company does not expect the adoption of this standard to have a material effect on its financial statements.

In March 2020, the FASB issued ASU 2020-04, Reference Rate Reform (Topic 848): Facilitation of the Effects of Reference Rate Reform on Financial Reporting. In response to concerns about structural risks of the cessation of London Interbank Offered Rate (LIBOR), the amendments in this ASU provide optional guidance for a limited time to ease the potential burden in accounting for (or recognizing the effects of) reference rate reform on financial reporting. The amendments in this ASU provide optional expedients and exceptions for applying GAAP to contracts, hedging relationships and other transactions affected by reference rate reform if certain criteria are met. The amendments in this ASU apply only to contracts and hedging relationships that reference LIBOR or another reference rate expected to be discontinued due to reference rate reform. The expedients and exceptions provided by the amendments do not apply to contract modifications made and hedging relationships entered into or evaluated after December 31, 2022. The amendments in this ASU are elective and are effective for all entities as of March 12, 2020 through December 31, 2022. The Company continues to evaluate contractual arrangements and hedging relationships that reference LIBOR.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

Interest Rate Risk

Our exposure to market risk for changes in interest rates relates primarily to our investment portfolio and to our term loan. Fixed rate securities and borrowings may have their fair market value adversely impacted due to fluctuations in interest rates, while floating rate securities may produce less income than expected if interest rates fall and floating rate borrowings may lead to additional interest expense if interest rates increase. Due in part to these factors, our future investment income may fall short of expectations due to changes in interest rates or we may suffer losses in principal if forced to sell securities

which have declined in market value due to changes in interest rates. Our interest expense on the term loan may rise if the interest rates increase.

Our primary investment objective is to preserve principal while at the same time maximizing yields without significantly increasing risk. Our portfolio includes money markets funds, certificates of deposit, commercial paper, corporate debt, and U.S. government agencies. The diversity of our portfolio helps us to achieve our investment objectives. As of December 31, 2021, 100% of our investment portfolio was composed of investments with original maturities of one year or less and approximately 70% of our investment portfolio matures less than 90 days from the date of purchase.

The following table presents the amounts of our cash equivalents and investments that may be subject to interest rate risk and the average interest rates as of December 31, 2021 by year of maturity (dollars in thousands):

	2022
Cash equivalents:	
Fixed rate	$ 2,089
Average fixed rate	0.03%
Variable rate	$ 43,822
Average variable rate	0.26%
Short-term investments:	
Fixed rate	$ 19,966
Average fixed rate	0.22%
Restricted investments:	
Fixed rate	$ 150
Average fixed rate	0.02%
Total investment securities	$ 66,027
Average rate	0.24%

As of December 31, 2021, the fair value of our term loan was estimated to be $20.6 million. The Loan Agreement provides for interest only payments through June 1, 2023, followed by consecutive monthly payments of principal and interest in arrears starting on June 1, 2023 and continuing through the maturity date of the term loan of September 1, 2025. The Loan Agreement provides for a floating interest rate (7.95% initially and 7.95% as of December 31, 2021) based on an index rate plus a spread. In addition, a payment equal to 10% of the principal amount of the term loan is due when the term loan becomes due or upon the prepayment of the facility. If the Company elects to prepay the loan, there is also a prepayment fee of between 0.75% and 2.5% of the principal amount of the term loan depending on the timing of prepayment. The obligation under the term loan is subject to interest rate risk because the interest rates under the obligation may exceed current interest rates.

Item 8. Financial Statements and Supplementary Data.

DURECT CORPORATION

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Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of DURECT Corporation

Opinion on the Financial Statements

We have audited the accompanying balance sheets of DURECT Corporation (the Company) as of December 31, 2021 and 2020, the related statements of operations and comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2021, and the related notes (collectively referred to as the "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical audit matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Prepaid and accrued contract manufacturing and clinical research expenses

Description of the Matter	During the year ended December 31, 2021, the Company incurred $31,846 thousand in research and development related expenses, of which $854 thousand was accrued as of December 31, 2021. The Company also has $1,518 thousand in prepaid contract manufacturing and clinical research expenses as of December 31, 2021. As described in Note 1 of the financial statements, the Company records accruals for its estimated costs of research and development activities, including contract services for clinical trials and related clinical manufacturing costs. Clinical trial activities performed by third parties are recorded based upon estimates of the proportion of work completed over the life of the individual clinical trial and patient enrollment rates in accordance with agreements established with third-party consultants and organizations. Estimates are determined by reviewing contracts, vendor agreements and purchase orders, and through detailed discussions with internal clinical personnel and external service providers as to the progress or stage of completion of trials or services and then applying these estimates of completion to previously agreed-upon rates and fees to be paid for such services. Auditing management's accounting estimates for both prepaid and accrued contract research expenses was especially challenging as evaluating the nature, progress, and stage of completion of the activities being performed under the Company's research and development agreements is dependent upon the accumulation of a high volume of information from internal clinical personnel and third-party service providers.

How We Addressed the Matter in Our Audit	We obtained an understanding, evaluated the design and tested, where applicable, the operating effectiveness of controls over the accounting for prepaid and accrued research and development expenses, including management's review of clinical trial progress and manufacturing activities in comparison to budgets and invoices received from third parties. Among others, our audit procedures included obtaining supporting evidence of the research and development activities performed for significant clinical trials and attending internal clinical trials and project status meetings with accounting personnel and clinical project managers to corroborate the status of significant research and development activities. We also obtained and read significant agreements and agreement amendments with the Company's third-party consultants and contract research organizations, examined the Company's documentation of trial timelines and future projections of trial progress and compared them to the Company's calculation of the estimated accrual or prepaid, and selected a sample of agreements and confirmed directly with the third parties the expenses incurred and the completeness of the terms of the arrangement. We also inspected invoices received after the balance sheet date to determine whether the services were performed prior to or after the balance sheet date and were properly recorded.

/s/ ERNST & YOUNG LLP

We have served as the Company's auditor since 1998.

Redwood City, California
March 8, 2022

DURECT CORPORATION

BALANCE SHEETS
(in thousands, except per share amounts)

	December 31, 2021	December 31, 2020
ASSETS		
Current assets:		
Cash and cash equivalents	$ 49,844	$ 21,312
Cash held in escrow	—	14,979
Short-term investments	19,966	19,421
Accounts receivable (net of allowances of $15 at December 31, 2021 and $72 at December 31, 2020)	6,477	940
Inventories, net	1,870	1,864
Prepaid expenses and other current assets	3,580	4,545
Total current assets	81,737	63,061
Property and equipment, net	227	251
Operating lease right-of-use assets	3,446	4,749
Goodwill	6,169	6,169
Long-term investments	—	1,000
Long-term restricted investments	150	150
Other long-term assets	261	261
Total assets	$ 91,990	$ 75,641
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 1,311	$ 1,678
Accrued liabilities	6,799	6,346
Deferred revenue, current portion	98	—
Term loan, current portion, net	—	884
Operating lease liabilities, current portion	1,848	1,795
Total current liabilities	10,056	10,703
Deferred revenue, non-current portion	812	812
Operating lease liabilities, non-current portion	1,824	3,202
Term loan, non-current portion, net	20,632	19,936
Other long-term liabilities	884	873
Commitments and contingencies		
Stockholders' equity:		
Preferred stock, $0.0001 par value: 10,000 shares authorized; none issued and outstanding	—	—
Common stock, $0.0001 par value: 350,000 shares authorized; 227,680 and 203,533 shares issued and outstanding at December 31, 2021 and 2020, respectively	23	20
Additional paid-in capital	583,818	529,884
Accumulated other comprehensive loss	(10)	(5)
Accumulated deficit	(526,049)	(489,784)
Stockholders' equity	57,782	40,115
Total liabilities and stockholders' equity	$ 91,990	$ 75,641

The accompanying notes are an integral part of these financial statements.

DURECT CORPORATION

STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(in thousands, except per share amounts)

	Year ended December 31,		
	2021	2020	2019
Collaborative research and development and other revenue	$ 6,331	$ 23,941	$ 18,129
Product revenue, net	7,646	6,170	6,945
Total revenues	13,977	30,111	25,074
Operating expenses:			
Cost of product revenues	1,955	1,406	1,263
Research and development	31,846	27,709	29,640
Selling, general and administrative	14,449	13,611	14,115
Total operating expenses	48,250	42,726	45,018
Loss from operations	(34,273)	(12,615)	(19,944)
Other income (expense):			
Interest and other income	156	517	1,074
Interest expense	(2,148)	(2,237)	(2,501)
Net other expense	(1,992)	(1,720)	(1,427)
Loss from continuing operations	(36,265)	(14,335)	(21,371)
Income from discontinued operations (Note 11)	—	13,753	793
Net loss	(36,265)	(582)	(20,578)
Net change in unrealized loss on available-for-sale securities, net of tax	(5)	(2)	(3)
Total comprehensive loss	$ (36,270)	$ (584)	$ (20,581)
Net income (loss) per share			
Basic and diluted			
Loss from continuing operations	$ (0.16)	$ (0.07)	$ (0.12)
Income from discontinued operations	$ —	$ 0.07	$ 0.00
Net loss per common share, basic and diluted	$ (0.16)	$ (0.00)	$ (0.12)
Weighted-average shares used in computing net income (loss) per share, basic and diluted	225,047	199,457	178,042

The accompanying notes are an integral part of these financial statements.

DURECT CORPORATION

STATEMENTS OF STOCKHOLDERS' EQUITY
(in thousands)

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Income (loss)	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2018	162,060	$ 16	$ 488,608	$ —	$ (468,624)	$ 20,000
Issuance of common stock upon exercise of stock options and purchases of ESPP shares	1,847	—	1,979	—	—	1,979
Issuance of common stock upon equity financings, net of issuance costs of $356	31,350	3	18,357	—	—	18,360
Issuance of fully vested options to settle accrued liabilities	—	—	994	—	—	994
Stock-based compensation expense from stock options and ESPP shares	—	—	2,108	—	—	2,108
Net loss	—	—	—	—	(20,578)	(20,578)
Change in unrealized gain on available-for-sale securities, net of tax	—	—	—	(3)	—	(3)
Balance at December 31, 2019	195,257	$ 19	$ 512,046	$ (3)	$ (489,202)	$ 22,860
Issuance of common stock upon exercise of stock options and purchases of ESPP shares	2,968	—	3,381	—	—	3,381
Issuance of common stock upon equity financings, net of issuance costs of $380	5,308	1	12,282	—	—	12,283
Stock-based compensation expense from stock options and ESPP shares	—	—	2,175	—	—	2,175
Net loss	—	—	—	—	(582)	(582)
Change in unrealized loss on available-for-sale securities, net of tax	—	—	—	(2)	—	(2)
Balance at December 31, 2020	203,533	$ 20	$ 529,884	$ (5)	$ (489,784)	$ 40,115
Issuance of common stock upon exercise of stock options and purchases of ESPP shares	2,832	1	3,586	—	—	3,587
Issuance of common stock upon equity financings, net of issuance costs of $395	21,315	2	47,658	—	—	47,660
Stock-based compensation expense from stock options and ESPP shares	—	—	2,690	—	—	2,690
Net loss	—	—	—	—	(36,265)	(36,265)
Change in unrealized loss on available-for-sale securities, net of tax	—	—	—	(5)	—	(5)
Balance at December 31, 2021	227,680	$ 23	$ 583,818	$ (10)	$ (526,049)	$ 57,782

The accompanying notes are an integral part of these financial statements.

DURECT CORPORATION
STATEMENTS OF CASH FLOWS
(in thousands)

	Year ended December 31,		
	2021	**2020**	**2019**
Cash flows from operating activities			
Net loss	$ (36,265)	$ (582)	$ (20,578)
Adjustments to reconcile net loss to net cash used in operating activities:			
Gain on sale of equipment	(11)	—	—
Depreciation and accretion	288	297	291
Stock-based compensation	2,688	2,170	2,108
Inventory write-down	—	194	255
Amortization of debt issuance cost	451	453	369
Net accretion/amortization on investments	(76)	(313)	87
Changes in operating lease liabilities	(22)	(61)	215
Gain on sale of LACTEL product line	—	(12,845)	—
Changes in assets and liabilities:			
Accounts receivable	(5,440)	389	(556)
Inventories	(4)	(249)	(217)
Prepaid expenses and other assets	965	(2,178)	786
Accounts payable	(367)	(241)	520
Accrued liabilities	384	(3,059)	5,142
Deferred revenue	98	(22,679)	22,679
Total adjustments	(1,046)	(38,122)	31,679
Net cash (used in) provided by operating activities	(37,311)	(38,704)	11,101
Cash flows from investing activities			
Purchases of property and equipment	(194)	(208)	(155)
Purchases of available-for-sale securities	(52,298)	(45,066)	(31,866)
Proceeds from maturities of available-for-sale securities	48,830	54,706	4,697
Proceeds from sales of available-for-sale securities	3,994	—	—
Net proceeds from sale of LACTEL product line	14,979	—	—
Net cash provided by (used in) investing activities	15,311	9,432	(27,324)
Cash flows from financing activities			
Payments on equipment financing obligations	(2)	(4)	(7)
Net proceeds from issuances of common stock upon exercise of stock options, and purchases of ESPP shares	3,587	3,381	1,979
Net proceeds from issuances of common stock in connection with equity financings	47,660	12,283	18,360
Term loan amendment cost	(713)	—	(829)
Net cash provided by financing activities	50,532	15,660	19,503
Net increase (decrease) in cash and cash equivalents	28,532	(13,612)	3,280
Cash, cash equivalents, and restricted cash, beginning of the period (1)	21,462	35,074	31,794
Cash, cash equivalents, and restricted cash, end of the period (1)	$ 49,994	$ 21,462	$ 35,074
Supplemental disclosure of cash flow information			
Cash paid for interest	$ 1,617	$ 1,678	$ 1,942
Supplementary disclosure of non-cash investing and financing information			
Cash held in escrow	$ —	$ 14,979	$ —
Fully vested options issued to settle accrued liabilities	$ —	$ —	$ 994
Operating lease right-of-use assets obtained in exchange for operating lease obligations (2)	$ —	$ —	$ 7,329

(1) Includes restricted cash of $150,000 (presented as long-term restricted investments) on the balance sheets at each of December 31, 2021, 2020 and 2019.

(2) Amounts for the twelve months ended December 31, 2019 include the transition adjustment for the adoption of Accounting Standards Update ("ASU" No. 2016-02, Leases ("Topic 842").

The accompanying notes are an integral part of these financial statements.

1. Summary of Significant Accounting Policies

Nature of Operations

DURECT Corporation (the Company) was incorporated in the state of Delaware on February 6, 1998. The Company is a biopharmaceutical company with research and development programs broadly falling into two categories: (i) new chemical entities derived from our Epigenetics Regulator Program, in which the Company attempts to discover and develop molecules which have not previously been approved and marketed as therapeutics, and (ii) Proprietary Pharmaceutical Programs, in which the Company applies its formulation expertise and technologies largely to active pharmaceutical ingredients whose safety and efficacy have previously been established but which the Company aims to improve in some manner through a new formulation. The Company has several products under development by itself and with third party collaborators. The Company also manufactures and sells osmotic pumps used in laboratory research and manufactures certain excipients for certain clients for use as raw materials in their products. In addition, the Company conducts research and development of pharmaceutical products in collaboration with third party pharmaceutical and biotechnology companies.

Basis of Presentation and Use of Estimates

The Company’s financial statements have been prepared in accordance with U.S. generally accepted accounting principles (U.S. GAAP). The preparation of the accompanying Financial Statements conforms to accounting principles generally accepted in the U.S. which requires management to make judgments, estimates and assumptions that affect the reported amounts of assets, liabilities, equity, revenues and expenses, and related disclosures. On an ongoing basis, management evaluates its estimates including, but not limited to, those related to revenue recognition, the period of performance, identification of deliverables and evaluation of milestones with respect to our collaborations, the amounts of revenues, recoverability of inventory, certain accrued liabilities including accrued clinical trial liability, and stock-based compensation. The Company bases its estimates on historical experience and on various other market-specific and other relevant assumptions that the Company believes to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results could differ materially from those estimates.

Reclassifications

Certain prior period amounts in the balance sheets have been reclassified to conform to current period presentation. The Company reclassified $97,000 and $545,0000 related to Contract research liabilities to Accrued liabilities at December 31, 2021 and 2020, respectively. Such reclassification did not impact the Company’s net loss or financial position.

Discontinued Operations

In December 2020, the Company announced its decision to sell its LACTEL Absorbable Polymer (LACTEL) product line to Evonik, which was completed on December 31, 2020. The accompanying financial statements have been recast to reflect the assets, liabilities, revenue and expenses related to the Company’s LACTEL product line as discontinued operations for the years ended December 31, 2020 and 2019 (see Note 11). The Company believes this format provides comparability with its previously filed financial statements.

Liquidity and Need to Raise Additional Capital

As of December 31, 2021, the Company has an accumulated deficit of $526.0 million as well as negative cash flows from operating activities.

The Company generally has had negative cash flows from operating activities and expects its negative cash flows to continue. The Company will continue to require substantial funds to continue research and development, including clinical trials of its product candidates. Management's plans in order to meet its operating cash flow requirements beyond the next 12 months from the date the financial statements are filed, may include seeking additional collaborative agreements for certain of its programs and achieving revenue from its collaboration and licensing agreements as well as financing activities such as public offerings and private placements of its common stock, preferred stock offerings, issuances of debt and convertible debt instruments.

There are no assurances that such additional funding will be obtained or that the Company will succeed in its future operations. If the Company cannot successfully raise additional capital when needed and implement its strategic development plan, its liquidity, financial condition and business prospects will be materially and adversely affected.

The Company believes its existing cash, cash equivalents, and investments are sufficient to fund its operating cashflow requirements for a period greater than 12 months from the date of issuance of these financial statements.

Cash, Cash Equivalents and Investments

The Company considers all highly liquid investments with maturities of 90 days or less from the date of purchase to be cash equivalents. Investments with original maturities of greater than 90 days from the date of purchase but less than one year from the balance sheet date are classified as short-term investments, while investments with maturities in one year or beyond one year from the balance sheet date are classified as long-term investments. Management determines the appropriate classification of its cash equivalents and investment securities at the time of purchase and re-evaluates such determination as of each balance sheet date. Management has classified the Company's cash equivalents and investments as available-for-sale securities in the accompanying financial statements. Available-for-sale securities are carried at fair value, with unrealized gains and losses reported as a component of accumulated other comprehensive loss. Realized gains and losses are included in interest income. There were no material realized gains or losses in the periods presented. The cost of securities sold is based on the specific identification method.

The Company invests in debt instruments of government agencies, corporations, and money market funds with high credit ratings. The Company has established guidelines regarding diversification of its investments and their maturities with the objectives of maintaining safety and liquidity, while maximizing yield.

Total cash held in escrow (related to the sale of the LACTEL product line) was $15 million as of December 31, 2020; the $15 million was released from escrow in January 2021.

Concentrations of Credit Risk

Financial instruments that potentially subject the Company to credit risk consist principally of interest-bearing investments and trade receivables. The Company maintains cash, cash equivalents and investments with various major financial institutions. The Company performs periodic evaluations of the relative credit standing of these financial institutions. In addition, the Company performs periodic evaluations of the relative credit quality of its investments.

Pharmaceutical companies and academic institutions account for a substantial portion of the Company's trade receivables. The Company provides credit in the normal course of business to its customers and collateral for these receivables is generally not required. The risk associated with this concentration is limited to a certain extent due to the large number of accounts and their geographic dispersion. The Company monitors the creditworthiness of its customers to which it grants credit terms in

the normal course of business. The Company maintains reserves for estimated credit losses and, to date, such losses have been immaterial in all periods presented.

Customer and Product Line Concentrations

A portion of the Company's revenue is derived from its ALZET osmotic pump product line, and the sale of certain excipients for POSIMIR and Methydur and one marketed animal health product.

Revenue from the sale of products from the ALZET product line accounted for 46%, 20% and 27% of total revenue for 2021, 2020 and 2019, respectively.

Innocoll accounted for 37% of the Company's total revenue for 2021. Gilead accounted for 76% and 68% of the Company's total revenue for 2020 and 2019, respectively.

Total revenue by geographic region for the years 2021, 2020 and 2019 are as follows (in thousands):

	Year ended December 31,		
	2021	2020	2019
United States	$ 5,690	$ 26,894	$ 21,957
Europe	6,630	1,386	906
Japan	1,015	1,174	1,472
Others	642	657	739
Total	$ 13,977	$ 30,111	$ 25,074

Revenue by geography is determined by the location of the customer.

Inventories

Inventories are stated at the lower of cost or net realizable value, with cost determined on a first-in, first-out basis. The Company may be required to expense previously capitalized inventory costs upon a change in management's judgment due to new information that suggests that the inventory will not be saleable. If the Company is able to subsequently sell products made with raw materials that were previously written down, the Company will report an unusually high gross profit as there will be no associated cost of goods for these materials.

The Company's inventories consisted of the following (in thousands):

	December 31,	
	2021	2020
Raw materials	$ 143	$ 136
Work in-process	712	796
Finished goods	1,015	932
Total inventories	$ 1,870	$ 1,864

Property and Equipment

Property and equipment are stated at cost less accumulated depreciation, which is computed using the straight-line method over the estimated useful lives of the assets, which range from three to five years. Leasehold improvements are amortized using the straight-line method over the estimated useful lives of the assets, or the terms of the related leases, whichever are shorter.

Goodwill

Goodwill is periodically assessed and evaluated for impairment. The Company operates in one operating segment and also has only one reporting unit, which is the research, development and manufacturing of pharmaceutical products. The Company assesses the impairment of goodwill at least annually and whenever events or changes in circumstances indicate that the carrying value may not be

recoverable. Factors the Company considers important which could trigger an impairment review include the following:

- significant decline in our stock price for a prolonged period;
- our market capitalization relative to net book value;
- new information affecting the commercial value of the asset;
- significant underperformance relative to historical or projected future operating results;
- significant changes in the manner of our use of the acquired assets or the strategy for the Company's overall business; and
- significant negative industry or economic trends.

The Company evaluates goodwill for impairment at least annually. To date, the Company has not recorded any impairment charge related to goodwill.

Impairment of Long-Lived Assets

The Company reviews long-lived assets, including property and equipment, intangible assets, and other long-term assets, for impairment whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable.

An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of the asset and its eventual disposition is less than its carrying amount. Impairment, if any, is calculated as the amount by which an asset's carrying value exceeds its fair value, typically using discounted cash flows to determine fair value. Through December 31, 2021, there have been no material impairment losses.

Leases

Effective January 1, 2019, the Company adopted Topic 842 using the modified retrospective transition method approach with a cumulative-effect adjustment as of January 1, 2019. The Company elected the package of practical expedients permitted under the transition guidance within the new standard, which among other things, allowed the Company to carry forward the historical lease classification of those leases in place as of January 1, 2019.

The adjustments due to the adoption of Topic 842 primarily related to the recognition of an operating lease right-of-use asset and corresponding operating lease liability for the Company's leased properties. The Company's operating lease right-of-use asset and liability were recognized at the adoption date of ASC 842 based on the present value of lease payments over the remaining lease term at the adoption date. In determining the net present value of lease payments, we used our incremental borrowing rate of 13.8% based on the information available, including remaining lease term, at the adoption date of ASC 842. As of December 31, 2021, the weighted-average remaining lease term was 1.99 years for the Company's leased properties.

There was no effect from the adoption of Topic 842 on the Company's Statement of cash flows.

Stock-Based Compensation

The Company accounts for share-based payments using a fair-value based method for costs related to all share-based payments, including stock options and stock issued under the Company's employee stock purchase plan (ESPP). The Company estimates the fair value of share-based payment awards on the date of grant using an option-pricing model. See Note 9 for further information regarding stock-based compensation.

Revenue Recognition

Product Revenue, Net

The Company sells osmotic pumps used in laboratory research and manufactures certain excipients for pharmaceutical clients for use as raw materials in their products.

Revenues from product sales are recognized when the customer obtains control of the Company's product, which occurs at a point in time, typically upon shipment to the customer. The Company expenses incremental costs of obtaining a contract as and when incurred if the expected amortization period of the asset that the Company would have recognized is one year or less.

Trade Discounts and Allowances: The Company provides certain customers with discounts that are explicitly stated in the Company's contracts and are recorded as a reduction of revenue in the period the related product revenue is recognized.

Product Returns: Consistent with industry practice, the Company generally offers customers a limited right of return for products that have been purchased from the Company. The Company estimates the amount of its product sales that may be returned by its customers and records this estimate as a reduction of revenue in the period the related product revenue is recognized. The Company currently estimates product return liabilities using its historical sales information. The Company expects product returns to be minimal.

Collaborative Research and Development and Other Revenue

The Company enters into license agreements, under which it licenses certain rights to its product candidates to third parties. The terms of these arrangements typically include payment to the Company of one or more of the following: non-refundable, up-front license fees; reimbursement of development costs incurred by the Company under approved work plans; development, regulatory, intellectual property and commercial milestone payments; payments for manufacturing supply services the Company provides itself or through its contract manufacturers; and royalties on net sales of licensed products. Each of these payments results in collaborative research and development revenues, except for revenues from royalties on net sales of licensed products, which are classified as other revenues.

In determining the appropriate amount of revenue to be recognized as it fulfills its obligations under each of its agreements, the Company performs the following steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) the Company satisfies each performance obligation. As part of the accounting for these arrangements, the Company must develop assumptions that require judgment to determine the stand-alone selling price for each performance obligation identified in the contract. The Company uses key assumptions to determine the standalone selling price, which may include forecasted revenues, development timelines, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success. The Company expects to recognize revenue for the variable consideration currently being constrained when it is probable that a significant revenue reversal will not occur.

Licenses of intellectual property: If the license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenues from non-refundable, up-front fees allocated to the license when the license is transferred to the customer and the customer is able to use and benefit from the license. For licenses that are bundled with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, up-front fees. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue

recognition. Any such adjustments are recorded on a cumulative catch-up basis, which would affect collaborative research and development revenues and net income (loss) in the period of adjustment.

Milestone Payments: At the inception of each arrangement that includes development milestone payments, the Company evaluates whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the control of the Company or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. The transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis, for which the Company recognizes revenue as or when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, the Company re-evaluates the probability of achievement of such development milestones and any related constraint, and if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect collaborative research and development revenues and net income (loss) in the period of adjustment.

Manufacturing Supply Services: Arrangements that include a promise for future supply of raw materials or drug product for either clinical development or commercial supply at the customer’s discretion are generally considered as options. The Company assesses if these options provide a material right to the customer and if so, they are accounted for as separate performance obligations. If the Company is entitled to additional payments when the customer exercises these options, any additional payments are recorded in collaborative research and development revenue when the customer obtains control of the goods, which is upon delivery.

Royalties and Earn-outs: For arrangements that include sales-based royalties or earn-outs, including milestone payments based on first commercial sale or the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, the Company has not recognized material royalty revenue resulting from the Company’s collaborative arrangements or material earn-out revenues from any of the Company’s patent purchase agreements.

Research and development revenue related to services performed under the collaborative arrangements with the Company’s third-party collaborators is recognized as the related research and development services are performed. These research payments received under each respective agreement are not refundable and are generally based on reimbursement of qualified expenses, as defined in the agreements. Research and development expenses under the collaborative research and development agreements generally approximate or exceed the revenue recognized under such agreements over the term of the respective agreements. Deferred revenue may result when the Company does not expend the required level of effort during a specific period in comparison to funds received under the respective agreement.

The Company receives payments from its customers based on development cost schedules established in each contract. Up-front payments are recorded as deferred revenue upon receipt or when due and may require deferral of revenue recognition to a future period until the Company performs its obligations under these arrangements. Amounts are recorded as accounts receivable when the Company’s right to consideration is unconditional. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the customer and the transfer of the promised goods or services to the customer will be one year or less.

Prepaid and Accrued Contract Research Expenses

The Company incurs significant costs associated with third party consultants and organizations for pre-clinical studies, clinical trials, contract research and manufacturing, validation, testing, regulatory advice and other research and development-related services. The Company is required to estimate periodically the cost of services rendered but unbilled based on management's estimates of project status. If these good faith estimates are inaccurate, actual expenses incurred could materially differ from these estimates.

Research and development expenses are primarily comprised of salaries and benefits associated with research and development personnel, overhead and facility costs, preclinical and non-clinical development costs, clinical trial and related clinical manufacturing costs, contract services, and other outside costs. Research and development costs are expensed as incurred. Research and development costs paid to third parties under sponsored research agreements are recognized as the related services are performed. In addition, reimbursements of research and development expenses incurred by the Company's partners are recorded as collaborative research and development revenue.

Comprehensive Loss

Components of other comprehensive loss are comprised entirely of unrealized gains and losses on the Company's available-for-sale securities for all periods presented. Total comprehensive loss has been disclosed in the Company's Statements of Comprehensive Loss.

Segment Reporting

The Company operates in one operating segment, which is the research, development and manufacturing of pharmaceutical products.

Net Loss Per Share

Basic net loss per share is calculated by dividing the net loss by the weighted-average number of common shares outstanding. Diluted net loss per share is computed using the weighted-average number of common shares outstanding and common stock equivalents (i.e., options to purchase common stock) outstanding during the period, if dilutive, using the treasury stock method for options.

The numerators and denominators in the calculation of basic and diluted net loss per share were as follows (in thousands except per share amounts):

	Year Ended December 31,		
	2021	2020	2019
Numerators:			
Net loss	$ (36,265)	$ (582)	$ (20,578)
Denominators:			
Weighted average shares used to compute basic net loss per share	225,047	199,457	178,042
Effect of dilutive securities:			
Dilution from stock options	—	—	—
Dilution from ESPP	—	—	—
Dilutive common shares	—	—	—
Weighted average shares used to compute diluted net loss per share	225,047	199,457	178,042
Net loss per share:			
Basic	$ (0.16)	$ (0.00)	$ (0.12)
Diluted	$ (0.16)	$ (0.00)	$ (0.12)

The computation of diluted net loss per share for 2021, 2020 and 2019 excludes the impact of options to purchase 8.3 million, 7.5 million and 21.4 million shares of common stock outstanding at December 31, 2021, 2020 and 2019, respectively, as such impact would be antidilutive.

Shipping and Handling

Costs related to shipping and handling are included in cost of revenues for all periods presented.

Recent Accounting Pronouncements

In June 2016, the FASB issued Accounting Standards Update No. 2016-13 (ASU 2016-13) “Financial Instruments - Credit Losses: Measurement of Credit Losses on Financial Instruments.” ASU 2016-13 requires measurement and recognition of expected credit losses for financial assets. This standard is effective for fiscal years beginning after December 15, 2022 for small reporting companies, including interim reporting periods within those years and must be adopted using a modified retrospective approach, with certain exceptions. Early adoption is permitted. The Company does not expect the adoption of this standard to have a material effect on its financial statements.

In March 2020, the FASB issued ASU 2020-04, Reference Rate Reform (Topic 848): Facilitation of the Effects of Reference Rate Reform on Financial Reporting. In response to concerns about structural risks of the cessation of London Interbank Offered Rate (LIBOR), the amendments in this ASU provide optional guidance for a limited time to ease the potential burden in accounting for (or recognizing the effects of) reference rate reform on financial reporting. The amendments in this ASU provide optional expedients and exceptions for applying GAAP to contracts, hedging relationships and other transactions affected by reference rate reform if certain criteria are met. The amendments in this ASU apply only to contracts and hedging relationships that reference LIBOR or another reference rate expected to be discontinued due to reference rate reform. The expedients and exceptions provided by the amendments do not apply to contract modifications made and hedging relationships entered into or evaluated after December 31, 2022. The amendments in this ASU are elective and are effective for all entities as of March 12, 2020 through December 31, 2022. The Company continues to evaluate contractual arrangements and hedging relationships that reference LIBOR.

2. Strategic Agreements

The collaborative research and development and other revenues associated with the Company’s major third-party collaborators are as follows (in thousands):

	Year ended December 31,		
	2021	2020	2019
Collaborator/Counterparty			
Innocoll (1)	$ 4,100	$ —	$ —
Gilead (2)	—	22,879	17,133
Other (3)	2,231	1,062	996
Total collaborative research and development and other revenue	$ 6,331	$ 23,941	$ 18,129

(1) The Company signed a license agreement with Innocoll on December 21, 2021, pursuant to which Innocoll agreed to pay a nonrefundable upfront license fee of $4.0 million and $1.3 million primarily for the sale of manufacturing supplies and excipients. In December 2021, upon the transfer of control of the license, the manufacturing supplies and excipients, and equipment to Innocoll, the Company recognized $4.1 million as collaborative research and development and other revenue, $1.1 million as product revenue, and a reduction of $0.1 million in net equipment (see Note 2 Strategic Agreements - Agreement with Innocoll in the financial statements)

(2) The Company signed a license agreement with Gilead on July 19, 2019. Amounts related to recognition of upfront fees and milestone payments were zero, $22.7 million, and $12.3 million for the twelve months ended December 31, 2021, 2020 and 2019, respectively. The Company received a nonrefundable upfront license fee and a milestone payment totaling $35.0 million in 2019 which was being recognized as revenue as its obligation was being satisfied using the cost-to-cost input method (see Note 2. Strategic Agreements - Agreement with Gilead Sciences, Inc. in the financial statements). In June 2020, the Company received notice that Gilead was terminating the License Agreement and a related R&D agreement between Gilead and the Company. As a result, the Company recognized all its remaining deferred revenue as there were no remaining substantive performance obligations to be provided to Gilead by the Company as of the date when the termination notice was received. Amounts recognized as revenue during each of the twelve months ended December 31, 2020 and 2019 also included the Company's reimbursable collaborative research and development services performed under its agreement with Gilead.

(3) Includes: (a) amounts related to earn-out revenue from Indivior UK Limited (Indivior) with respect to PERSERIS net sales; (b) feasibility programs; (c) research and development activities funded by Santen Pharmaceutical Co. Ltd. (Santen); and (d) royalty revenue from OP Pharma with respect to Methydur net sales. Since 2018, the parties have been working together on a limited set of research and development activities funded by Santen.

As of December 31, 2021, the Company had potential milestones of up to $208.0 million that the Company may receive in the future under its collaborative arrangements, of which $23.0 million are development-based milestones, $10.0 million are patent-based milestones and $175.0 million are sales-based milestones. Within the category of development-based milestones, $2.0 million are related to early-stage clinical testing (defined as Phase 1 or 2 activities), $3.0 million are related to late-stage clinical testing (defined as Phase 3 activities), $3.0 million are related to regulatory filings and $15.0 million are related to regulatory approvals. No milestone payments were received between December 31, 2021 and March 3, 2022, and we do not anticipate receiving any of these milestone revenues other than $2.0 million of a sales-based milestone triggered by the first commercial sale of POSIMIR by Innocoll.

Agreement with Innocoll

On December 21, 2021, the Company entered into a license agreement with Innocoll Pharmaceuticals Limited ("Innocoll"). Pursuant to the Innocoll Agreement, the Company has granted Innocoll an exclusive, royalty-bearing, sublicensable right and license to develop, manufacture and commercialize in the United States, POSIMIR®, the Company's FDA-approved post-surgical pain product, with respect to all uses and applications in humans. The Innocoll Agreement provides for the assignment of the Company's supply agreement with its contract manufacturing organization to Innocoll and also provides Innocoll with the right, within the United States, to expand the approved indications of POSIMIR. The Company retains, outside the United States, all of the global rights to POSIMIR.

Upon execution of the Innocoll Agreement, Innocoll agreed to pay the Company an initial non-refundable, upfront fee of $4.0 million as well as a fee in the amount of $1.3 million primarily to cover the manufacturing supplies and excipients and certain equipment transferred to Innocoll pursuant to the terms of the Innocoll Agreement, and certain recently incurred DURECT expenses the parties negotiated for Innocoll to reimburse. The Company will also receive $2.0 million upon the first commercial sale of POSIMIR in the United States. The Company is eligible to receive additional milestone payments of up to $130.0 million in the aggregate, depending on the achievement of certain regulatory, commercial, and intellectual property milestones with respect to POSIMIR. In addition, upon commercialization, the Company will earn low to mid double-digit royalties from net sales of POSIMIR in the United States.

The Innocoll Agreement includes customary representations and warranties on behalf of the Company and Innocoll, including representations as to the licensed intellectual property, regulatory

matters and compliance with applicable laws. The Innocoll Agreement also provides for certain mutual indemnities for breaches of representations, warranties and covenants.

The Company also evaluated Innocoll's future purchases of an excipient from the Company and concluded that these purchases are option rights, and are at market rates, and do not constitute a material right performance obligation. As such, these future purchases have been excluded from the initial allocation of transaction price and the Company will account for them as separate contracts when and if Innocoll elects to issue purchase orders for the excipient.

During December 2021, an upfront fee of $4.0 million as well as a fee in the amount of $1.2 million to cover reimbursed expenses, the manufacturing supplies and excipients transferred to Innocoll pursuant to the terms of the Innocoll Agreement was recognized as revenue when the performance obligations were satisfied in December 2021 and $0.1 million was recorded as a net reduction in equipment in December 2021. At December 31, 2021, the Company included $5.3 million due from Innocoll in accounts receivable on its balance sheet; these funds were received in January 2022.

Agreement with Gilead Sciences, Inc.

On July 19, 2019, the Company entered into a license agreement (the "Gilead Agreement") with Gilead Sciences, Inc. ("Gilead"). Pursuant to the Gilead Agreement, the Company granted Gilead the exclusive worldwide rights to develop and commercialize a long-acting injectable HIV product utilizing DURECT's SABER® technology. Gilead also received exclusive access to the SABER platform for HIV and Hepatitis B Virus (HBV) and the exclusive option to license additional SABER-based products directed to HIV and HBV.

Under the terms of the Gilead Agreement, Gilead made a non-refundable upfront payment to DURECT of $25 million, and in October 2019, the Company also received a $10 million milestone payment from Gilead for further development of the product candidate.

During the twelve months ended December 31, 2019, the upfront and milestone consideration of $35 million received in 2019 associated with the Primary Services was being recognized as revenue when the first performance obligation was being satisfied using the cost-to-cost input method, which the Company believes best depicts the transfer of control to the customer. Under the cost-to-cost input method, the extent of progress towards completion is measured based on the ratio of actual costs incurred to the total estimated costs. Revenue is recorded as a percentage of the transaction price based on the extent of progress towards completion. The estimate of the Company's measure of progress, which can include additional Primary Services, if any, and the estimate of any additional consideration for those additional Primary Services, are included in the transaction price which is updated at each reporting date, and revenue is recognized on a cumulative catchup basis. As such, management applies a certain amount of judgment in estimating both the Primary Services and the corresponding timeline to through completion of the first performance obligation, which are key inputs when using the cost-to-cost input method.

During the twelve months ended December 31, 2019, the Company recognized $12.3 million of the deferred revenue within collaborative research and development and other revenues. The Company also recognized $4.8 million from Gilead during the twelve months ended December 31, 2019 from feasibility related collaborative research and development services.

In June 2020, Gilead terminated the Gilead Agreement and a related R&D agreement between Gilead and the Company. As a result, the Company recognized $22.7 million as revenue during the year ended December 31, 2020, which represented all of the remaining upfront fee and milestone payment that had previously been deferred as there were no remaining substantive performance obligations to be provided to Gilead by the Company as of the date when the termination notice was received.

The following table presents changes in the Company's contract assets and liabilities for the twelve months ended December 31, 2020 (in thousands) as a result of entering the Gilead Agreement:

	Balance at January 1, 2020	Additions	Deletions	Balance at December 31, 2020
Balance Sheet				
Assets				
Accounts receivable	$ 494	$ 200	$ (694)	$ —
Total contract asset	$ 494	$ 200	$ (694)	$ —
Liabilities				
Deferred revenue, current portion	$ 22,679	$ 9,174	$ (31,853)	$ —
Total contract liabilities	$ 22,679	$ 9,174	$ (31,853)	$ —

Patent Purchase Agreement with Indivior

In September 2017, we entered into an agreement with Indivior (the "Indivior Agreement"), under which we assigned to Indivior certain patents that may provide further intellectual property protection for PERSERIS, Indivior's extended-release injectable suspension for the treatment of schizophrenia in adults. In consideration for such assignment, Indivior made non-refundable upfront and milestone payments to DURECT totaling $17.5 million. Additionally, under the terms of the agreement with Indivior, DURECT receives quarterly earn-out payments into 2026 that are based on a single digit percentage of U.S. net sales of PERSERIS. Indivior commercially launched PERSERIS in the U.S. in February 2019. The Indivior Agreement contains customary representations, warranties and indemnities of the parties.

Agreement with Santen Pharmaceutical Co., Ltd.

On December 11, 2014, the Company and Santen Pharmaceutical Co., Ltd. (Santen) entered into a definitive agreement (the Santen Agreement). Pursuant to the Santen Agreement, the Company granted Santen an exclusive worldwide license to the Company's proprietary SABER formulation platform and other intellectual property to develop and commercialize a sustained release product utilizing the Company's SABER technology to deliver an ophthalmology drug. Santen controls and funds the development and commercialization program, and the parties established a joint management committee to oversee, review and coordinate the development activities of the parties under the Santen Agreement.

In connection with the Santen agreement, Santen paid the Company an upfront fee of $2.0 million in cash and agreed to make contingent cash payments to the Company of up to $76.0 million upon the achievement of certain milestones, of which $13.0 million are development-based milestones and $63.0 million are commercialization-based milestones including milestones requiring the achievement of certain product sales targets (none of which has been achieved as of December 31, 2020). Santen will also pay for certain Company costs incurred in the development of the licensed product. If the product is commercialized, the Company 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. In January 2018, the Company was notified by Santen that due to a shift in priorities, Santen elected to reallocate research and development resources and put the Company's program on pause until further notice. While the main program is on pause, the parties are working together on a limited set of research and development activities funded by Santen. As of December 31, 2021, the cumulative aggregate payments received by the Company under this agreement were $3.3 million.

3. Financial Instruments

Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. The Company's valuation techniques

used to measure fair value maximize the use of observable inputs and minimize the use of unobservable inputs. The Company follows a fair value hierarchy based on three levels of inputs, of which the first two are considered observable and the last unobservable, that may be used to measure fair value. These levels of inputs are the following:

- Level 1—Quoted prices in active markets for identical assets or liabilities.
- Level 2—Inputs other than Level 1 that are observable, either directly or indirectly, such as quoted prices for similar assets or liabilities; quoted prices in markets that are not active; or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.
- Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

The Company's financial instruments are valued using quoted prices in active markets or based upon other observable inputs. The following table sets forth the fair value of the Company's financial assets that were measured at fair value on a recurring basis as of December 31, 2021 (in thousands):

	Level 1	Level 2	Level 3	Total
Money market funds	$ 2,089	$ —	$ —	$ 2,089
Certificates of deposit	—	150	—	150
Commercial paper	—	62,495	—	62,495
Corporate debt	—	1,293	—	1,293
Total	$ 2,089	$ 63,938	$ —	$ 66,027

The following table sets forth the fair value of our financial assets that were measured at fair value on a recurring basis as of December 31, 2020 (in thousands):

	Level 1	Level 2	Level 3	Total
Money market funds	$ 522	$ —	$ —	$ 522
Certificates of deposit	—	150	—	150
Commercial paper	—	32,213	—	32,213
Municipal bonds	—	6,305	—	6,305
U.S. Government agencies	—	1,000	—	1,000
Total	$ 522	$ 39,668	$ —	$ 40,190

The Company's financial instruments are valued using quoted prices in active markets or based upon other observable inputs. Money market funds are classified as Level 1 financial assets. Certificates of deposit, commercial paper, corporate debt securities, and U.S. Government agency securities are classified as Level 2 financial assets. The fair value of the Level 2 assets is estimated using pricing models using current observable market information for similar securities. The Company's Level 2 investments include U.S. government-backed securities and corporate securities that are valued based upon observable inputs that may include benchmark yields, reported trades, broker/dealer quotes, issuer spreads, two-sided markets, benchmark securities, bids, offers and reference data including market research publications. The fair value of commercial paper is based upon the time to maturity and discounted using the three-month treasury bill rate. The average remaining maturity of the Company's Level 2 investments as of December 31, 2021 is less than twelve months and these investments are rated by S&P and Moody's at AAA or AA- for securities and A1 or P1 for commercial paper.

The following is a summary of available-for-sale securities as of December 31, 2021 and 2020 (in thousands):

	December 31, 2021			
	Amortized Cost	Unrealized Gain	Unrealized Loss	Estimated Fair Value
Money market funds	$ 2,089	$ —	$ —	$ 2,089
Certificates of deposit	150	—	—	150
Commercial paper	62,505	—	(10)	62,495
Corporate debt	1,293	—	—	1,293
	$ 66,037	$ —	$ (10)	$ 66,027
Reported as:				
Cash and cash equivalents	$ 45,913	$ —	$ (2)	$ 45,911
Short-term investments	19,974	—	(8)	19,966
Long-term restricted investments	150	—	—	150
	$ 66,037	$ —	$ (10)	$ 66,027

	December 31, 2020			
	Amortized Cost	Unrealized Gain	Unrealized Loss	Estimated Fair Value
Money market funds	$ 522	$ —	$ —	$ 522
Certificates of deposit	150	—	—	150
Commercial paper	32,213	2	(2)	32,213
Municipal bonds	6,310	—	(5)	6,305
U.S. Government agencies	1,000	—	—	1,000
	$ 40,195	$ 2	$ (7)	$ 40,190
Reported as:				
Cash and cash equivalents	$ 19,619	$ 1	$ (1)	$ 19,619
Short-term investments	19,426	1	(6)	19,421
Long-term investments	1,000	—	—	1,000
Long-term restricted investments	150	—	—	150
	$ 40,195	$ 2	$ (7)	$ 40,190

The following is a summary of the cost and estimated fair value of available-for-sale securities at December 31, 2021, by contractual maturity (in thousands):

	December 31, 2021	
	Amortized Cost	Estimated Fair Value
Mature in one year or less	$ 63,798	$ 63,788
Mature after one year through five years	150	150
	$ 63,948	$ 63,938

There were no securities that have had an unrealized loss for more than 12 months as of December 31, 2021.

As of December 31, 2021, unrealized losses on available-for-sale investments are not attributed to credit risk and are considered to be temporary. The Company believes that it is more-likely-than-not that

investments in an unrealized loss position will be held until maturity or the recovery of the cost basis of the investment. To date, the Company has not recorded any impairment charges on marketable securities related to other-than-temporary declines in market value.

4. Property and Equipment

Property and equipment consist of the following (in thousands):

	December 31,	
	2021	2020
Equipment	$ 10,696	$ 10,890
Leasehold improvements	8,474	8,428
Construction-in-progress	—	42
	19,170	19,360
Less accumulated depreciation and amortization	(18,943)	(19,109)
Property and equipment, net	$ 227	$ 251

Depreciation expense was $132,000, $297,000 and $291,000 in 2021, 2020 and 2019, respectively.

As of December 31, 2021, the Company has recorded $638,000 as a liability which was included in other long-term liabilities on its balance sheet for asset retirement obligations associated with the estimated restoration cost for its leased buildings.

5. Restricted Investments

As of December 31, 2021 and 2020, the Company had $150,000 recorded as restricted investments, which primarily served as collateral for letters of credit securing a leased facility in California.

6. Commitments

Operating Leases

The Company has lease arrangements for its facilities in California and Alabama as follows.

Location	Approximate Square Feet	Operation	Expiration
Cupertino, CA	30,149 sq. ft.	Office, Laboratory and Manufacturing	Lease expires 2024 (with an option to renew for an additional five years)
Cupertino, CA	20,100 sq. ft.	Office and Laboratory	Lease expires 2024 (with an option to renew for an additional five years)
Vacaville, CA	24,634 sq. ft.	Manufacturing	Lease expires 2023 (with an option to renew for an additional five years)

Under these leases, the Company is required to pay certain maintenance expenses in addition to monthly rent. Rent expense is recognized on a straight-line basis over the lease term for leases that have scheduled rental payment increases. Rent expense under all operating leases was $1.9 million for each of the years ended December 31, 2021, 2020 and 2019. In determining the net present value of lease payments, the Company used its incremental borrowing rate of 13.8% based on the information available, including remaining lease term, at the adoption date of ASC 842. As of December 31, 2021 and 2020, the weighted-average remaining lease term was 1.99 years and 2.99 years, respectively, for the Company’s leased properties.

Future minimum payments under these noncancelable leases are as follows (in thousands):

Year ending December 31,	Operating Leases
2022	1,991
2023	1,970
2024	275
	4,236
Less Present value adjustment	(564)
Operating lease liabilities recognized	$ 3,672

7. Accrued Liabilities

Accrued liabilities as of December 31, 2021 and 2020 were comprised as follows (in thousands):

	December 31,	
	2021	2020
Accrued compensation and benefits	$ 4,099	$ 3,463
Accrued contract research and manufacturing cost	757	1,027
Accrued clinical costs	97	545
Others	1,846	1,311
Total	$ 6,799	$ 6,346

8. Term Loan

In July 2016, the Company entered into a $20.0 million secured single-draw term loan with Oxford Finance LLC (Oxford Finance). The Company and Oxford Finance entered into five subsequent amendments to the Loan Agreement in February 2018, November 2018, December 2019, March 2021 and May 2021. For amendments 1-3 and 5, the Company paid Oxford Finance loan modification fees of $100,000, $900,000, $825,000 and $712,500 respectively. As amended, the Loan Agreement provides for interest only payments through June 1, 2023, followed by consecutive monthly payments of principal and interest in arrears starting on June 1, 2023 and continuing through the maturity date of the term loan of September 1, 2025. The Loan Agreement provides for a floating interest rate (7.95% initially and 7.95% as of December 31, 2021) based on an index rate plus a spread. In addition, a payment equal to 10% of the principal amount of the term loan is due when the term loan becomes due or upon the prepayment of the facility. If the Company elects to prepay the loan, there is also a prepayment fee of between 0.75% and 2.5% of the principal amount of the term loan depending on the timing of prepayment. The $150,000 facility fee that was paid at the original closing, the loan modification fees and other debt offering/issuance costs have been recorded as debt discount on the Company’s balance sheet and together with the final $2.0 million payment are being amortized to interest expense using the effective interest method over the revised term of the loan.

The term loan is secured by substantially all of the assets of the Company, except that the collateral does not include any intellectual property (including licensing, collaboration and similar agreements relating thereto), and certain other excluded assets. The 2016 Loan Agreement contains customary representations, warranties and covenants by the Company, which covenants limit the Company’s ability to convey, sell, lease, transfer, assign or otherwise dispose of certain assets of the Company; engage in any business other than the businesses currently engaged in by the Company or reasonably related thereto; liquidate or dissolve; make certain management changes; undergo certain change of control events; create, incur, assume, or be liable with respect to certain indebtedness; grant certain liens; pay

dividends and make certain other restricted payments; make certain investments; and make payments on any subordinated debt.

The Loan Agreement also contains customary indemnification obligations and customary events of default, including, among other things, the Company's failure to fulfill certain obligations of the Company under the Loan Agreement and the occurrence of a material adverse change which is defined as a material adverse change in the Company's business, operations, or condition (financial or otherwise), a material impairment of the prospect of repayment of any portion of the loan, or a material impairment in the perfection or priority of lender's lien in the collateral or in the value of such collateral. In the event of default by the Company under the Loan Agreement, the lender would be entitled to exercise its remedies thereunder, including the right to accelerate the debt, upon which the Company may be required to repay all amounts then outstanding under the Loan Agreement, which could harm the Company's financial condition. The conditionally exercisable call option related to the event of default is considered to be an embedded derivative which is required to be bifurcated and accounted for as a separate financial instrument. In the periods presented, the value of the embedded derivative is not material, but could become material in future periods if an event of default became more probable than is currently estimated.

The fair value of the term loan approximates the carrying value. Future maturities and interest payments under the term loan as of December 31, 2021, are as follows (in thousands):

2022	1,612
2023	7,191
2024	9,408
2025	7,886
Total minimum payments	26,097
Less amount representing interest	(4,246)
Gross balance of term loan	21,851
Less unamortized debt discount	(1,219)
Carrying value of term loan	20,632
Less term loan, current portion, net	—
Term loan, non-current portion, net	$ 20,632

9. Stockholders' Equity

Common Stock

In November 2015, the Company filed a shelf registration statement on Form S-3 with the SEC, which allowed the Company to offer up to $125.0 million of securities from time to time in one or more public offerings of its common stock. In addition, the Company entered into a Controlled Equity Offering sales agreement with Cantor Fitzgerald, under which the Company may sell, subject to certain limitations, up to $40 million of common stock through Cantor Fitzgerald, acting as agent. In August 2018, the Company filed a new shelf registration statement on Form S-3 with the SEC, which upon being declared effective in October 2018, terminated the November 2015 registration statement and allowed the Company to offer up to $175.0 million of securities from time to time in one or more public offerings, inclusive of up to $75.0 million of additional shares of common stock which the Company may sell, subject to certain limitations, under the 2015 Sales Agreement through Cantor Fitzgerald, acting as agent.

On June 20, 2019, the Company entered into a transaction to sell 29,000,000 shares of our common stock to certain investors in a registered offering at a price of $0.52 per share, raising total gross proceeds to the Company of approximately $15.1 million. In 2020, the Company raised net proceeds of approximately $12.3 million from the sale of 5,308,002 shares of the Company's common stock in the

open market at a weighted average price of $2.39 per share pursuant to the October 2018 registration statement.

In February 2021, the Company completed an underwritten public offering of 20,364,582 shares of its common stock at a price of $2.2386 per share pursuant to an underwriting agreement with Cantor Fitzgerald & Co., raising total gross proceeds to the Company of approximately $45.6 million before deducting estimated offering expenses payable by the Company. Total stock issuance costs related to this financing were approximately $195,000. After deducting estimated offering expenses payable by the Company, the net proceeds to the Company were approximately $45.4 million.

In 2019, the Company raised net proceeds of approximately $3.5 million from the sale of 2,349,820 shares of the Company's common stock in the open market at a weighted average price of $1.55 per share pursuant to the October 2018 registration statement. In 2021, the Company raised net proceeds (net of commissions) of approximately $2.4 million from the sale of 950,009 shares of the Company's common stock in the open market at a weighted average price of $2.60 per share pursuant to the 2018 Registration Statement and the 2015 Sales Agreement.

In July 2021, the Company filed a shelf registration statement on Form S-3 with the SEC (the "2021 Registration Statement") (File No. 333-258333), which upon being declared effective in August 2021, terminated the 2018 Registration Statement and allows the Company to offer up to $250.0 million of securities from time to time in one or more public offerings, inclusive of up to $75.0 million of shares of the Company's common stock which the Company may sell, subject to certain limitations, pursuant to a sales agreement dated July 30, 2021 with Cantor Fitzgerald & Co. (the "2021 Sales Agreement"). The 2021 Sales Agreement replaced the 2015 Sales Agreement.

Description of Stock-Based Compensation Plans

2000 Stock Plan (Incentive Stock Plan)

In January 2000, the Company's Board of Directors and stockholders adopted the DURECT Corporation 2000 Stock Plan, under which incentive stock options and non-statutory stock options and stock purchase rights may be granted to employees, consultants and non-employee directors. The 2000 Stock Plan was amended by written consent of the Board of Directors in March 2000 and written consent of the stockholders in August 2000.

In April 2005, the Board of Directors approved certain amendments to the 2000 Stock Plan. At the Company's annual stockholders meeting in June 2005, the stockholders approved the amendments of the 2000 Stock Plan to: (i) expand the types of awards that the Company may grant to eligible service providers under the Stock Plan to include restricted stock units, stock appreciation rights and other similar types of awards (including other awards under which recipients are not required to pay any purchase or exercise price) as well as cash awards; and (ii) include certain performance criteria that may be applied to awards granted under the Stock Plan.

At the Company's annual stockholders meeting in June 2010, the stockholders approved amendments of the 2000 Stock Plan to: (i) provide that the number of shares that remain available for issuance will be reduced by two shares for each share issued pursuant to an award (other than an option or stock appreciation right) granted on or after the date of the 2010 Annual Meeting; (ii) expand the types of transactions that might be considered repricings and option exchanges for which stockholder approval is required; (iii) provide that shares tendered or withheld in payment of the exercise price of an option or withheld to satisfy a withholding obligation, and all shares with respect to which a stock appreciation right is exercised, will not again be available for issuance under the Stock Plan; (iv) require that options and stock appreciation rights have an exercise price or base appreciation amount that is at least fair market value on the grant date, except in connection with certain corporate transactions, and that stock appreciation rights may not have longer than a 10-year term; (v) add new performance goals that may be used to provide "performance-based compensation" under the 2000 Stock Plan; (vi) extend the term of

the 2000 Stock Plan to the date that is ten (10) years following the stockholders meeting; and (vii) expand the treatment of outstanding awards in connection with certain changes of control of the Company to cover mergers in which the consideration payable to stockholders is not solely securities of the successor corporation.

At the Company's annual stockholders meeting in June 2011, June 2014, June 2016 and June 2018, the stockholders approved amendments of the 2000 Stock Plan to increase the number of shares of the Company's common stock available for issuance by 5,500,000 shares, 4,000,000 shares, 5,000,000 shares and 7,500,000 shares, respectively, each of which had previously been approved by the Board of Directors.

At the Company's annual stockholders meeting in June 2019, the stockholders approved amendments of the 2000 Stock Plan to extend the term of the 2000 Stock Plan to the date that is ten (10) years following the stockholders meeting.

A total of 46,296,500 shares of common stock have been reserved for issuance under this plan. The plan expires in June 2029.

In April 2013, the Board of Directors approved certain amendments to the 2000 Stock Plan to: (i) increase the number of stock options granted to a non-employee director on the date which such person first becomes a director from 30,000 to 70,000 shares of common stock; each option shall have a ten-year term, become exercisable in installments of one-third of the total number of options granted on each anniversary of the grant and have a two-year period following termination of Director status in which the former director can exercise the option; (ii) modify the exercise period for future option grants to a non-employee director in which a former director can exercise the option following termination of Director status from a one year period to a two-year period.

Options granted under the 2000 Stock Plan expire no later than ten years from the date of grant. Options may be granted with different vesting terms from time to time not to exceed five years from the date of grant. The option price of an incentive stock option granted to an employee or of a nonstatutory stock option granted to any person who owns stock representing more than 10% of the total combined voting power of all classes of stock of the Company (or any parent or subsidiary) shall be no less than 110% of the fair market value per share on the date of grant. The option price of an incentive stock option granted to any other employee shall be no less than 100% of the fair market value per share on the date of grant.

As of December 31, 2021, 6,793,921 shares of common stock were available for future grant and options to purchase 25,362,025 shares of common stock were outstanding under the 2000 Stock Plan.

2000 Employee Stock Purchase Plan

In August 2000, the Company adopted the 2000 Employee Stock Purchase Plan. This purchase plan is implemented by a series of overlapping offering periods of 24 months' duration, with new offering periods, other than the first offering period, beginning on May 1 and November 1 of each year and ending April 30 and October 31, respectively, two years later. The purchase plan allows eligible employees to purchase common stock through payroll deductions at a price equal to the lower of 85% of the fair market value of the Company's common stock at the beginning of each offering period or at the end of each purchase period. The initial offering period commenced on the effectiveness of the Company's initial public offering.

In April 2010, the Board of Directors approved certain amendments to the 2000 Employee Stock Purchase Plan. At the Company's annual stockholders meeting in June 2010, the stockholders approved the amendments of the 2000 Employee Stock Purchase Plan to: (i) increase the number of shares of our common stock authorized for issuance under the ESPP by 250,000 shares; (ii) extend the term of the ESPP to the date that is ten (10) years following the stockholders meeting; (iii) provide for six-month consecutive offering periods beginning on November 1, 2010; (iv) revise certain provisions to reflect the

final regulations issued under Section 423 of the Code by the Internal Revenue Service; and (v) provide for the cash-out of options outstanding under an offering period in effect prior to the consummation of certain corporate transactions as an alternative to providing for a final purchase under such offering period.

In March 2015, the Board of Directors approved certain amendments to the 2000 Employee Stock Purchase Plan. At the Company's annual stockholders meeting in June 2015, the stockholders approved the amendments of the 2000 Employee Stock Purchase Plan to: (i) increase the number of shares of our common stock authorized for issuance under the ESPP by 350,000 shares; and (ii) extend the term of the ESPP to the date that is ten (10) years following the stockholders meeting. At each of the Company's annual stockholders meeting in June 2017 and in June 2020, the stockholders approved amendments of the 2000 Employee Stock Purchase Plan to increase the number of shares our common stock authorized for issuance under the ESPP by 350,000 shares and to re-approve its material terms.

The plan expires in June 2030. A total of 2,900,000 shares of common stock have been reserved for issuance under this plan. As of December 31, 2021, 383,412 shares of common stock were available for future grant and 2,866,588 shares of common stock have been issued under the 2000 Employee Stock Purchase Plan.

As of December 31, 2021, shares of common stock reserved for future issuance consisted of the following:

	December 31, 2021
Stock options outstanding	25,362,025
Stock options available for grant	6,793,921
Employee Stock Purchase Plan	383,412
	32,539,358

A summary of stock option activity under all stock-based compensation plans is as follows:

	Number of Options	Weighted Average Exercise Price Per Share	Weighted Average Remaining Contractual Term (in Years)	Aggregate Intrinsic Value (in millions)
Outstanding at December 31, 2020	27,274,439	$ 1.45	4.98	$ 19.6
Options granted	2,882,926	$ 1.94		
Options exercised	(2,718,024)	$ 1.27		
Options forfeited	(87,614)	$ 2.02		
Options expired	(1,989,702)	$ 3.18		
Outstanding at December 31, 2021	25,362,025	$ 1.39	5.11	$ 1.7
Exercisable at December 31, 2021	20,902,088	$ 1.30	4.43	$ 1.5
Vested and expected to vest at December 31, 2021	25,362,025	$ 1.39	5.11	$ 1.7

The weighted-average grant date fair value of options granted during the years ended December 31, 2021, 2020 and 2019 was $1.94, $2.12 and $0.61 per share, respectively. The aggregate intrinsic value in the table above represents the total intrinsic value (i.e., the difference between the Company's closing stock price on the last trading day of 2021 and the exercise price, multiplied by the number of in-the-money options) that would have been received by the option holders had all option holders exercised their in-the-money options on December 31, 2021. This amount changes based on the fair market value of the Company's common stock. The total intrinsic value of options exercised was $3.1 million, $3.6 million and $1.7 million for the years ended December 31, 2021, 2020 and 2019, respectively.

In lieu of providing cash bonuses to certain employees, in January 2019 the Company granted its employees stock options to purchase 2.3 million shares of the Company's common stock, which vested immediately on the grant date. The weighted-average grant-date fair value of all options granted with exercise prices equal to fair market value was $0.43 in 2019 determined by the Black-Scholes option valuation method. There were no options granted with exercise prices lower than fair market value.

Expenses for non-employee stock options are recorded over the vesting period of the options, which closely approximates the non-employee's performance period, with the value determined by the Black-Scholes option valuation method and remeasured over the vesting term.

As of December 31, 2021, the Company had three stock-based equity compensation plans, which are described above. The employee stock-based compensation cost that has been included in the statements of operations and comprehensive loss is shown as below (in thousands):

	Year ended December 31,		
	2021	2020	2019
Cost of product revenues	$ 19	$ 13	$ 13
Research and development	1,245	981	746
Selling, general and administrative	1,424	1,085	1,269
	$ 2,688	$ 2,079	$ 2,028

Because the Company had a net operating loss carryforward as of December 31, 2021, no excess tax benefits for the tax deductions related to stock-based compensation expense were recognized in the statement of operations. Additionally, no incremental tax benefits were recognized from stock options exercised during 2021, which would have resulted in a reclassification to reduce net cash provided by operating activities with an offsetting increase in net cash provided by financing activities.

Determining Fair Value

Valuation and Expense Recognition. The Company estimates the fair value of stock options granted using the Black-Scholes option valuation model. The Company recognizes the expense on a straight-line basis. The expense for options is recognized over the requisite service periods of the awards, which is generally the vesting period.

Expected Term. The expected term of options granted represents the period of time that the options are expected to be outstanding. The Company determines the expected life using historical options experience. This develops the expected life by taking the weighted average of the actual life of options exercised and cancelled and assumes that outstanding options are exercised uniformly from the current holding period through the end of the contractual life.

Expected Volatility. The Company estimates the volatility of its common stock at the date of grant based on the historical volatility of the Company's common stock.

Risk-Free Rate. The Company bases the risk-free rate that it uses in the Black-Scholes option valuation model on the implied yield in effect at the time of option grant on U.S. Treasury zero-coupon issues with substantially equivalent remaining terms.

Dividends. The Company has never paid any cash dividends on its common stock and the Company does not anticipate paying any cash dividends in the foreseeable future. Consequently, the Company uses an expected dividend yield of zero in the Black-Scholes option valuation model.

The Company used the following assumptions to estimate the fair value of options granted (including fully vested options issued in January 2019) and shares purchased under its stock plans and employee stock purchase plan for the years ended December 31, 2021, 2020 and 2019:

	Year ended December 31,		
	2021	2020	2019
Stock Options			
Risk-free rate	0.8-1.5%	0.5-1.4%	1.5-2.7%
Expected dividend yield	—	—	—
Expected term (in years)	7.0-7.8	7.0-7.3	7.5-10.0
Volatility	85-86%	84-87%	79-83%
Forfeiture rate (1)	0.0%	0.0%	0.0%

(1) The Company accounts for forfeitures as they occur.

	Year ended December 31,		
	2021	2020	2019
Employee Stock Purchase Plan			
Risk-free rate	0.04%	0.1%	1.6-2.5%
Expected dividend yield	—	—	—
Expected term (in years)	0.5	0.5	0.5
Volatility	56-71%	78-124%	60-103%

There were 113,858, 102,006 and 111,909 shares purchased under the Company’s employee stock purchase plan during the years ended December 31, 2021, 2020 and 2019, respectively. Included in the statement of operations and comprehensive loss for the year ended December 31, 2021, 2020 and 2019 was $57,000, $86,000 and $27,000, respectively, in stock-based compensation expense related to the recognition of expenses related to shares purchased under the Company’s employee stock purchase plan.

As of December 31, 2021, $4.0 million of total unrecognized compensation costs related to nonvested stock options is expected to be recognized over the respective vesting terms of each award through 2025. The weighted average term of the unrecognized stock-based compensation expense is 2.4 years.

The following table summarizes information about stock options outstanding at December 31, 2021:

	Options Outstanding			Options Exercisable		
Range of Exercise Price	Number of Options Outstanding	Weighted-Average Remaining Contractual Life (In years)	Weighted-Average Exercise Price	Number of Options Exercisable	Weighted-Average Exercise Price
$0.57 - $0.57	140,000	7.31	$ 0.57	93,334	$ 0.57
$0.58 - $0.58	2,709,747	7.01	$ 0.58	2,314,983	$ 0.58
$0.58 - $0.88	2,976,137	2.92	$ 0.82	2,970,355	$ 0.82
$0.91 - $1.20	2,639,110	4.18	$ 1.14	2,485,672	$ 1.15
$1.21 - $1.22	2,178,534	1.31	$ 1.21	2,133,534	$ 1.21
$1.24 - $1.24	2,692,189	5.97	$ 1.24	2,609,901	$ 1.24
$1.26 - $1.31	2,546,570	4.77	$ 1.31	2,396,570	$ 1.31
$1.33 - $2.03	4,536,609	7.37	$ 1.78	2,056,738	$ 1.58
$2.04 - $2.10	2,545,271	2.86	$ 2.09	2,405,271	$ 2.09
$2.11 - $2.80	2,397,858	7.56	$ 2.26	1,435,730	$ 2.33
$0.57 - $2.80	25,362,025	5.11	$ 1.39	20,902,088	$ 1.30

The Company received $3.4 million, $3.2 million and $1.9 million in cash from option exercises under all stock-based compensation plans for the years ended December 31, 2021, 2020 and 2019, respectively.

10. Income Taxes

The Company accounts for income taxes using the liability method under ASC 740, *Income Taxes*. Under this method, deferred tax assets and liabilities are determined based on temporary differences resulting from the different treatment of items for tax and financial reporting purposes. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to reverse. Additionally, the Company must assess the likelihood that deferred tax assets will be recovered as deductions from future taxable income. The Company has provided a full valuation allowance on the Company's deferred tax assets because the Company believes it is more likely than not that its deferred tax assets will not be realized. The Company evaluates the realizability of its deferred tax assets on a quarterly basis. The Company recorded a deferred tax liability of $244,000 on its balance sheet at both December 31, 2021 and 2020 that arose from tax amortization of an indefinite-lived intangible asset. The Company also recorded a deferred tax expense of zero in the years ended December 31, 2021, 2020 and 2019. The Company recorded no tax expense in each of 2021, 2020 and 2019.

The reconciliation of income tax expenses (benefit) at the statutory federal income tax rate of 21%, to net income tax benefit included in the statements of operations and comprehensive loss for the years ended December 31, 2021, 2020 and 2019 is as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
U.S. federal taxes benefit at statutory rate	$ (7,616)	$ (122)	$ (4,321)
Change in valuation allowance	2,266	(2,022)	3,142
Stock-based compensation	641	268	879
Research and development tax credits	(954)	(1,132)	(1,004)
Expiring net operating losses	5,612	2,991	1,252
Other	51	17	52
Total income tax (benefit) provision	$ —	$ —	$ —

In 2021, 2020 and 2019, total income tax provision (benefit) expense was zero. Deferred tax assets and liabilities reflect the net tax effects of net operating loss and research and other credit carryforwards and the temporary differences between the carrying amounts of assets and liabilities for financial reporting and the amounts used for income tax purposes.

Significant components of the Company's deferred tax assets and liabilities are as follows (in thousands):

	December 31,	
	2021	2020
Deferred tax assets:		
Net operating loss carryforwards	90,114	87,197
Research and other credits	19,197	19,153
Deferred revenue	202	223
Stock-based compensation	2,741	3,840
Other	4,962	5,204
Total deferred tax assets	117,216	115,617
Valuation allowance for deferred tax assets	(116,358)	(114,323)
Deferred tax liabilities - Right of use asset	(1,102)	(1,538)
Net deferred tax assets and liabilities	$ (244)	$ (244)

The Company recognizes deferred tax assets to the extent that the Company believes that these assets are more likely than not to be realized. In making such a determination, all available positive and negative evidence is considered, including future reversals of existing taxable temporary differences, projected future taxable income, tax-planning strategies, and results of recent operations. If it is determined that the Company would be able to realize deferred tax assets in the future in excess of their net recorded amount, the Company would make an adjustment to the deferred tax asset valuation allowance, which would cause a provision benefit to be recognized. The recognition and measurement of tax benefits requires significant judgment. Judgments concerning the recognition and measurement of tax benefit might change as new information becomes available. Given the Company's history of operating losses, the net deferred tax assets have been fully offset by a valuation allowance. The valuation allowance increased by $2.0 million and $4.6 million during 2021 and 2019, and decreased by $2.9 million during 2020 and, respectively.

As of December 31, 2021, the Company had net operating loss carryforwards for federal income tax purposes of approximately $351.9 million, of which approximately $279.8 million will expire in the years 2022 through 2037, and approximately $72.1 million which do not expire, and federal research and development tax credits of approximately $16.5 million, which expire at various dates beginning in 2022 through 2041, if not utilized.

As of December 31, 2021, the Company had net operating loss carryforwards for state income tax purposes of approximately $239.1 million, which expire in the years 2022 through 2041, if not utilized, and state research and development tax credits of approximately $17.1 million, which do not expire.

Utilization of the net operating losses may be subject to a substantial annual limitation due to federal and state ownership change limitations. The annual limitation may result in the expiration of net operating losses before utilization.

At December 31, 2021 and December 31, 2020, the Company had unrecognized tax benefits of approximately $12.4 million and $10.9 million, respectively (none of which, if recognized, would affect the Company's effective tax rate). The Company does not believe there will be any material changes in its unrecognized tax positions over the next twelve months.

A reconciliation of the beginning and ending amount of unrecognized tax benefits is as follows (in thousands):

	December 31,	
	2021	2020
Balance at beginning of the year	$ 10,888	$ 9,078
Increase related to prior year tax positions	911	1,136
Increase related to current year tax positions	622	674
Balance at end of the year	$ 12,421	$ 10,888

Interest and penalty costs related to unrecognized tax benefits, if any, are classified as a component of interest and other income, net in the Statements of Operations and Comprehensive Loss. The Company did not recognize any interest and penalties expenses related to unrecognized tax benefits for the years ended December 31, 2021, 2020 and 2019.

The Company files income tax returns in the U.S. federal jurisdiction and various state jurisdictions. The Company is subject to U.S. federal and state income tax examination for calendar tax years ending 1999 through 2020 due to unutilized net operating losses and research credits.

California Assembly Bill 85 (AB 85) was signed into law in June 2021. The legislation suspended the use of California Net Operating Loss deductions for 2020, 2021, and 2022 for certain taxpayers and imposed a limitation on the use of certain California Tax Credits for 2020, 2021, and 2022. The carryover periods for Net Operating Loss deductions disallowed by this provision were extended. Subsequent to the yearend balance sheet date, California enacted Senate Bill 113, which removed the net operating loss suspension and limited use of business tax credits for 2022. The Senate Bill 113 will have no income tax impact as the Company continues to record full valuation allowance against the deferred tax assets due to the cumulative tax losses. The Company will continue to monitor possible California net operating loss and credit limitation in future periods.

Beginning in 2022, the Tax Cuts and Jobs Act eliminates the option to deduct research and development expenditures when incurred and requires taxpayers to capitalized and amortize domestic expenditures over five years and foreign expenditures over fifteen years. While it is possible Congress may modify or repeal this provision before it becomes effective, the Company has no assurance these provisions will be modified or repealed. Therefore, based on current assumptions, this could potentially create a deferred tax asset balance, expected to be offset by valuation allowance, beginning in 2022.

11. Discontinued Operations

On December 31, 2020, the Company completed the sale of its LACTEL Absorbable Polymers product line to Evonik. Under the terms of the Asset Purchase Agreement, Evonik paid DURECT approximately $15.1 million, and also agreed to assume certain liabilities with respect to the transferred assets.

As a result of the sale of the LACTEL product line, the operating results from our LACTEL product line have been excluded from continuing operations and presented as discontinued operations in the accompanying Statements of Operations and Comprehensive Loss for all periods presented. During the twelve months ended December 31, 2020, we recorded a gain on sale of the LACTEL product line of $12.8 million, upon the completion of sale to Evonik. The results of operations and gain from discontinued operations presented below include certain allocations that management believes fairly reflect the utilization of services provided to the LACTEL product line. The allocations do not include amounts related to general corporate administrative expenses or interest expense. Therefore, these results of operations do not necessarily reflect what the results of operations would have been had the LACTEL product line operated as a stand-alone entity.

The components of income from discontinued operations as reported in the Company's statement of operations were as follows (in thousands):

	Year ended December 31,	
	2020	2019
Product revenue, net	$ 4,918	$ 4,490
Total revenues	4,918	4,490
Operating expenses:		
Cost of product revenues	3,019	2,880
Research and development	476	569
Selling, general and administrative	515	248
Total costs and expenses	4,010	3,697
Income from discontinued operations	908	793
Other income:		
Gain on sale of the LACTEL product line	12,845	—
Net income from discontinued operations	$ 13,753	$ 793
Net income per share		
Basic and diluted	$ 0.07	$ 0.00
Weighted-average shares used in computing net income per share basic and diluted		
Basic and diluted	199,457	178,042

The following table presents certain non-cash items related to discontinued operations, which are included in the Company's statement of cash flows (in thousands):

	Years ended December 31, 2020	Years ended December 31, 2019
Depreciation	$ 198	$ 241
Stock-based compensation expense	91	81
Goodwill	229	—
Loss on disposal of property and equipment	129	—
	$ 647	$ 322
Gain on sale of the LACTEL product line	$ 12,845	$ —
Non-cash items, net	$ (12,198)	$ 322

12. Subsequent Events

On February 9, 2022, the Company received a deficiency letter from the Listing Qualifications Department of the Nasdaq Stock Market ("Nasdaq") notifying the Company that for the last 30 consecutive business days the bid price for the Company's common stock had closed below the minimum $1.00 per share requirement for continued inclusion in Nasdaq Capital Market pursuant to Nasdaq Listing Rule 5550(a)(2) (the "Minimum Bid Price Requirement"). The deficiency letter does not result in the immediate delisting of the Company's common stock from Nasdaq.

The Company has been provided an initial period of 180 calendar days, or until August 8, 2022, to regain compliance with the Minimum Bid Price Requirement. If the Company is not in compliance with the Minimum Bid Price Requirement by August 8, 2022, the Company may be afforded a second 180 calendar day period to regain compliance. To qualify, the Company would be required to meet the continued listing requirement for market value of publicly held shares and all other initial listing standards required by Nasdaq, except for the minimum bid price requirement.

The Company intends to monitor the closing bid price of its common stock and may, if appropriate, consider available options to regain compliance with the Minimum Bid Price Requirement, which could include effecting a reverse stock split. However, there can be no assurance that the Company will be able to regain compliance with the Minimum Bid Price Requirement.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure.

Not applicable.

Item 9A. Controls and Procedures.

Disclosure Controls and Procedures

As required by paragraph (b) of Exchange Act Rules 13a-15 or 15d-15, DURECT's management, including our Chief Executive Officer and Chief Financial Officer, conducted an evaluation as of the end of the period covered by this report, of the effectiveness of DURECT's disclosure controls and procedures as defined in Exchange Act Rule 13a-15(e) and 15d-15(e). Based on that evaluation, our Chief Executive Officer and Chief Financial Officer concluded that DURECT's disclosure controls and procedures were effective as of the end of the period covered by this report.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Exchange Act Rules 13a-15(f) and 15d-15(f). Under the supervision of our Chief Executive Officer and Chief Financial Officer and with the participation of our management, we conducted an evaluation of the effectiveness of our internal control over financial reporting as of December 31, 2021 based on the framework in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 Framework). Based on that evaluation, our management concluded that our internal control over financial reporting was effective as of December 31, 2021.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting identified in connection with the evaluation required by paragraph (d) of Exchange Act Rules 13a-15 or 15d-15 that occurred during our last fiscal quarter that have materially affected or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The names of the executive officers of the Company and their ages, titles and biographies as of the date hereof are incorporated by reference from Part I, Item 1, above.

Information required by this item will be contained in our definitive proxy statement to be filed with the Securities and Exchange Commission on Schedule 14A in connection with our 2022 Annual Meeting of Stockholders (the Proxy Statement), which is expected to be filed not later than 120 days after the end of our fiscal year ended December 31, 2021, under the headings "Election of Directors," "The Board, Board Committees and Meetings," "Code of Ethics," and "Section 16(a) Beneficial Ownership Reporting Compliance," and is incorporated herein by reference.

Item 11. Executive Compensation

Information required by this item will be contained in the Proxy Statement under the headings "Executive Compensation," "Director Compensation," and "Compensation Committee Report" and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

Information required by this item will be contained in the Proxy Statement under the headings "Common Stock Ownership of Certain Beneficial Owners and Management" and "Equity Compensation Plan Information," and is incorporated herein by reference.

Item 13. Certain Relationships, Related Transactions and Director Independence

Information required by this item will be contained in the Proxy Statement under the headings "Certain Relationships," "Other Transactions," and "The Board, Board Committees and Meetings," and is incorporated herein by reference.

Item 14. Principal Accountant Fees and Services

Information required by this item will be contained in the Proxy Statement under the heading "Fees Billed for Services Rendered by Principal Accountant," and is incorporated herein by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules.

(a) The following documents are filed as part of this report:

(1) *Financial Statements*

The Index to financial statements in Item 8 of this report is incorporated herein by reference as the list of the financial statements required as part of this report.

(2) *Financial Statement Schedules*

See Schedule II—Valuation and Qualifying Accounts, immediately following Item 16 of this Form 10-K.

Schedules not listed above have been omitted because the information required to be set forth therein is not applicable or is not present in amounts sufficient to require submission of the schedule, or because the information required is included in the financial statements or notes thereto.

(3) The list of exhibits are filed as part of or furnished with this annual report on Form 10-K as applicable.

Exhibit Index

Exhibit Number	Description
3.1	Amended and Restated Certificate of Incorporation of the Company (incorporated by reference to Exhibit 3.3 to the Company's Registration Statement on Form S-1, as amended (File No. 333-35316), initially filed on April 20, 2000).
3.2	Certificate of Amendment of the Amended and Restated Certificate of Incorporation of the Company (incorporated by reference to Exhibit 3.4 to the Company's Post-Effective Amendment No. 1 to the Company's Registration Statement on Form S-3, filed on July 1, 2010.
3.3	Certificate of Amendment to the Amended and Restated Certificate of Incorporation of DURECT Corporation (incorporated by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K, as filed with the SEC on June 20, 2018).
3.4	Certificate of Designation of Rights, Preferences and Privileges of Series A Participating Preferred Stock of DURECT Corporation (incorporated by reference to Exhibit 3.3 to the Company's Registration Statement on Form S-3 (File No. 333-128979) initially filed on October 13, 2005).
3.5	Certificate of Amendment to Certificate of Designation of Rights, Preferences and Privileges of Series A Participating Preferred Stock of DURECT Corporation (incorporated by reference to Exhibit 3.7 to the Company's Quarterly Report on Form 10-Q (File No. 000-31615) filed on August 5, 2010).
3.6	Certificate of Amendment to the Amended and Restated Certificate of Incorporation of the Company (incorporated by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K filed on June 16, 2021).
3.7	Certificate of Correction to the Charter Amendment (incorporated by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K/A filed on June 25, 2021).
3.8	Amended and Restated Bylaws of the Company (incorporated by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K (File No. 000-31615), filed on December 17, 2014).
4.1	Description of Securities of the Registrant (incorporated by reference to Exhibit 4.2 to the Company's annual report on Form 10-K (File No. 000-31615), filed on March 5, 2020).
10.1+	Form of Indemnification Agreement between the Company and each of its Officers and Directors (incorporated by reference to Exhibit 10.1 to the Company's Registration Statement on Form S-1, as amended (File No. 333-35316), initially filed on April 20, 2000).
10.2+	2000 Stock Plan, as amended (incorporated by reference to Exhibit 10.2 to the Company's annual report on Form 10-K (File No. 000-31615), filed on March 5, 2020).

Exhibit Number	Description
10.3+	2000 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.4 to the Company's Registration Statement on Form S-1, as amended (File No. 333-35316), initially filed on April 20, 2000).
10.4	Modified Net Single Tenant Lease Agreement between the Company and DeAnza Enterprises, Ltd. dated as of February 18, 1999 (incorporated by reference to Exhibit 10.11 to the Company's Registration Statement on Form S-1, as amended (File No. 333-35316), initially filed on April 20, 2000).
10.5	Lease between the Company and Renault & Handley Employee Investments Co. with commencement date of January 1, 2005 (incorporated by reference to Exhibit 10.36 to the Company's Annual Report on Form 10-K (File No. 000-31615) filed on March 11, 2004).
10.6	First Lease Extension between the Company and Renault & Handley Employee Investments Co. effective March 1, 2009 (incorporated by reference to Exhibit 10.54 to the Company's Quarterly Report on Form 10-Q (File No. 000-31615) filed on May 7, 2009).
10.7	Second Amendment to Lease between De Anza Enterprises and the Company dated as of August 6, 2009 (incorporated by reference to Exhibit 10.56 to the Company's Quarterly Report on Form 10-Q (File No. 000-31615) filed on November 2, 2009).
10.8	Third Amendment to Lease between De Anza Enterprises and the Company dated as of December 21, 2010 (incorporated by reference to Exhibit 10.63 to the Company's Annual Report on Form 10-K (File No. 000-31615) filed with the SEC on March 3, 2011).
10.9	Fourth Amendment to Lease between De Anza Enterprises and the Company dated as of August 20, 2013 (incorporated by reference to Exhibit 10.71 to the Company's Quarterly Report on Form 10-Q (File No. 000-31615) filed with the SEC on November 5, 2013).
10.10	Addendum II to Lease between the Company and Northwest Asset Management Company dated as of August 27, 2013 (incorporated by reference to Exhibit 10.72 to the Company's Quarterly Report on Form 10-Q (File No. 000-31615) filed with the SEC on November 5, 2013).
10.11	Second Amendment to Lease between Handley Management Corporation, as successor-by-merger to Renault & Handley Employee Investments Co. and the Company dated November 11, 2013 (incorporated by reference to Exhibit 10.73 to the Company's Annual Report on Form 10-K (File No. 000-31615) filed with the SEC on February 27, 2014).
10.12**	License Agreement between the Company and Santen Pharmaceutical Co., Ltd. dated December 11, 2014 (incorporated by reference to Exhibit 10.28 to the Company's Annual Report on Form 10-K (File No. 000-31615) filed with the SEC on March 3, 2015).
10.13**	Exclusive License Agreement between the Company and Virginia Commonwealth University Intellectual Property Foundation dated December 5, 2012 (incorporated by reference to Exhibit 10.29 to the Company's Annual Report on Form 10-K (File No. 000-31615) filed with the SEC on March 3, 2015).

Exhibit Number	Description
10.14	Loan and Security Agreement between the Company and Oxford Finance LLC dated July 28, 2016. (incorporated by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q (File No. 000-31615) filed with the SEC on November 1, 2016).
10.15	First Amendment to Loan and Security Agreement between the Company and Oxford Finance LLC dated February 28, 2018 (incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed March 5, 2018).
10.16	Second Amendment to Loan and Security Agreement between the Company and Oxford Finance LLC dated November 1, 2018 (incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed November 5, 2018).
10.17	Addendum III to Lease between the Company and Northwest Asset Management Company dated as of April 10, 2018 (incorporated by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q (File No. 000-31615) filed with the SEC on August 2, 2018).
10.18	Fifth Amendment to Lease between De Anza Enterprises and the Company dated as of August 15, 2018 (incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K, as filed with the SEC on August 17, 2018).
10.19	Third Amendment to Lease between Handley Management Corporation, as successor-by-merger to Renault & Handley Employee Investments Co. and the Company dated September 17, 2018 (incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K, as filed with the SEC on September 21, 2018).
10.20	Amendment No. 1 to Exclusive License Agreement between the Company and Virginia Commonwealth University Intellectual Property Foundation dated July 2, 2015 (incorporated by reference to Exhibit 10.4 to the Company's Quarterly Report on Form 10-Q (File No. 000-31615) filed with the SEC on November 8, 2018).
10.21	Amendment No. 2 to Exclusive License Agreement between the Company and Virginia Commonwealth University Intellectual Property Foundation dated March 6, 2018 (incorporated by reference to Exhibit 10.5 to the Company's Quarterly Report on Form 10-Q (File No. 000-31615) filed with the SEC on November 8, 2018).
10.22++	License Agreement between the Company and Gilead Sciences, Inc. dated July 19, 2019 (incorporated by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q (File No. 000-31615) filed with the SEC on November 5, 2019).
10.23	Third Amendment to Loan and Security Agreement between the Company and Oxford Finance LLC dated December 31, 2019 (incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K, as filed with the SEC on January 6, 2020).
10.24	Asset purchase agreement between the Company and Evonik Corporation dated December 4, 2020 (incorporated by reference to Exhibit 10.32 to the Company's Annual Report on Form 10-K (File No. 000-31615) filed with the SEC on March 5, 2021).

Exhibit Number	Description
10.25	Executive Change of Control Policy, as amended December 9, 2020 (incorporated by reference to Exhibit 10.33 to the Company's Annual Report on Form 10-K (File No. 000-31615) filed with the SEC on March 5, 2021).
10.26*	Fourth Amendment to Loan and Security Agreement between the Company and Oxford Finance LLC dated March 3, 2021.
10.27	Fifth Amendment to Loan and Security Agreement between the Company and Oxford Finance LLC dated May 28, 2021 (incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K, as filed on June 2, 2021).
10.28*++	License agreement by and between the Company and Innocoll Pharmaceuticals Limited dated December 21, 2021.
23.1*	Consent of Independent Registered Public Accounting Firm.
31.1*	Rule 13a-14(a) Section 302 Certification.
31.2*	Rule 13a-14(a) Section 302 Certification.
32.1***	Certificate pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2***	Certificate pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because XBRL tags are embedded within the Inline XBRL document.
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101)

* Filed herewith.
** Confidential treatment granted with respect to certain portions of this Exhibit.
*** Furnished, not filed.
\+ Indicates a management contract or compensatory plan or arrangement.
++ Certain portions of this exhibit (indicated by "[***]") have been omitted in accordance with Item 601(b)(10) of Regulation S-K.

Item 16. Form 10-K Summary.

The Company has elected not to include summary information.

SCHEDULE II—VALUATION AND QUALIFYING ACCOUNTS

Year Ended December 31, 2021, 2020 and 2019
(in thousands)

	Balance at beginning of the year	Additions (Reductions) to allowances	Deductions	Balance at end of the year
Allowance for doubtful accounts				
Year ended December 31, 2021	$ (72)	$ 56	$ 1	$ (15)
Year ended December 31, 2020	$ (27)	$ (46)	$ 1	$ (72)
Year ended December 31, 2019	$ (83)	$ 56	$ —	$ (27)

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

DURECT CORPORATION

By: /s/ James E. Brown

James E. Brown
President and Chief Executive Officer

Date: March 8, 2022

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ James E. Brown **James E. Brown**	President, Chief Executive Officer and Director (Principal Executive Officer)	March 8, 2022
/s/ Michael H. Arenberg **Michael H. Arenberg**	Chief Financial Officer (Principal Accounting Officer)	March 8, 2022
/s/ MOHAMMAD AZAB **Mohammad Azab**	Director	March 8, 2022
/s/ Simon X. Benito **Simon X. Benito**	Director	March 8, 2022
/s/ Terrence F. Blaschke **Terrence F. Blaschke**	Director	March 8, 2022
/s/ Gail M. Farfel **Gail M. Farfel**	Director	March 8, 2022
/s/ PETER S. GARCIA **Peter S. Garcia**	Director	March 8, 2022
/s/ David R. Hoffmann **David R. Hoffmann**	Director, Chairman of the Board	March 8, 2022
/s/ GAIL J. MADERIS **Gail J. Maderis**	Director	March 8, 2022
/s/ Judith J. Robertson **Judith J. Robertson**	Director	March 8, 2022