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Zacks Small-Cap Research

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Durect Corp (DRRX-NASDAQ)

DUR-928 Programs Accelerating. Anticipate NASH, Psoriasis Data Later This Year.

We value DRRX using sum-of-the-parts, with most of the value related to DUR-928 based on pricing of recent NASH-targeted M&A transactions as a proxy. Our methodology also includes DCF of DRRX's current cash-generating products and earn-outs.

Current Price (03/13/19)	$0.82
Valuation	**$6.00**

OUTLOOK

Last week Durect reported financial results for their fourth quarter ending December 31st and provided a business update. Relative to the financials, revenue of $3.6M included $2.9M in product sales, mostly related to ALZET mini pumps and LACTEL biodegradable polymer products, as well as $0.8M in collaborative revenue. Total revenue was inline with our $3.6M estimate.

DUR-928 is where we continue to believe most of the upside value lies in DRRX. As a reminder, DUR-928 could have platform-like utility and is being investigated in several formulations and potential applications including oral, intravenous and topical formulas and in indications such NASH, alcoholic hepatitis (AH) and psoriasis. Durect has recently adopted somewhat of an updated strategy as it relates to DUR-928, which relates to honing their focus on accelerating timelines for those indications which they believe hold the most near-term potential to move into late-stage development – with one of those areas being NASH. Response to POSIMIR CRL anticipated, positive result could provide upside to our model. Indivior launched PERSERIS in February, analyst's sales estimates of which have recently been upwardly revised.

SUMMARY DATA

52-Week High	**$2.55**
52-Week Low	**$0.46**
One-Year Return (%)	**-57.92**
Beta	**2.16**
Average Daily Volume (sh)	**426,306**
Shares Outstanding (mil)	**162**
Market Capitalization ($mil)	**$132**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**46**
Insider Ownership (%)	**10**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**16.6**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2019 Estimate	**N/A**
P/E using 2020 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Avg.,**
Type of Stock	**Small-Growth**
Industry	**Med-Drugs**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	4.6 A	4.3 A	20.8 A	19.5 A	49.2 A
2018	3.5 A	3.4 A	8.0 A	3.6 A	18.6 A
2019	3.3 E	3.5 E	3.5 E	4.2 E	14.5 E
2020					18.1 E

Price/Sales Ratio (Industry = 2.5x)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	-$0.06 A	-$0.07 A	$0.04 A	$0.05 A	-$0.03 A
2018	-$0.05 A	-$0.04 A	-$0.02 A	-$0.05 A	-$0.16 A
2019	-$0.05 E	-$0.05 E	-$0.06 E	-$0.05 E	-$0.21 E
2020					-$0.22 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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WHAT'S NEW

Q4 Financial Results and Operational Update

Last week Durect reported financial results for their fourth quarter ending December 31st and provided a business update. Relative to the financials, revenue of $3.6M included $2.9M in product sales, mostly related to ALZET mini pumps and LACTEL biodegradable polymer products, as well as $0.8M in collaborative revenue. Total revenue was inline with our $3.6M estimate.

Product sales remain a cash cow, with gross margin at nearly 62% in Q4, up slightly from 61% in the two prior quarters. Product gross margin averaged 59% for the full year 2018, up from 49% the year earlier. As earn-outs and sales royalties essentially represent 100% margin, we continue to expect that both product sales and margins will further benefit from;

- the commencement of PERSERIS-related commercialization earn-outs (which represent 100% margin). DRRX receives single-digit royalties on sales by Indivior. In late February Indivior announced that they had launched PERSERIS. Analyst U.S. sales estimates of PERSERIS have recently been upwardly revised
- Methydur sustained release capsules (for ADHD), Taiwan regulatory approval of which Orient Pharma received in September. Orient anticipates launching ORADUR-ADHD in that country in 2019 and is also seeking regulatory clearance and commercialization partners in other Asian countries, including in China. As a reminder, DRRX receives a royalty on sales of the product by Orient and retains rights to it in North America, Europe, Japan and all other countries not specifically licensed to Orient Pharma

Operating expenses in Q4, at $9.4M, were flat from Q3'18 and down about 5% from the prior year period. For the full year, operating expenses were $37.9M, about 15% lower than in 2017. Most of the $6.9M reduction in opex relates to R&D, which fell as a result of lower spend related to certain programs, such as POSIMIR, ORADUR-ADHD and REMOXY ER, partially offset by an increase in costs associated with development progress of DUR-928. Management is guiding for flattish SG&A in 2019 but for R&D expense to increase, which largely reflects ramping activities of the DUR-928 programs.

Cash

Financial position remains very healthy and with a recent amendment to terms of the $20M term loan, which pushed back the initial principal repayment and final maturity dates by 18 months (to June 2020) and 27 months (to Nov 2022), respectively, DRRX's cash runway is substantial. Cash balance was $34.3M at year-end. Operating burn averaged approximately $4.9M per quarter through 2018. Durect expects their current cash balance to be sufficient to fund operations through at least the next 12 months.

As it relates to the operational front…

- **DUR-928** is where we continue to believe most of the upside value lies in DRRX. As a reminder, DUR-928 could have platform-like utility and is being investigated in several formulations and potential applications including oral, intravenous and topical formulas and in indications such NASH, alcoholic hepatitis (AH) and psoriasis. Durect has recently adopted somewhat of an updated strategy as it relates to DUR-928, which relates to honing their focus on accelerating timelines for those indications which they believe hold the most near-term potential to move into late-stage development – with one of those areas being NASH. Recent progress on these programs include (also see our detailed description of DUR-928 programs later in this report);

    - **New NASH Phase 1b program**
        - Ph1b open label, multi-site, U.S. study to evaluate safety, pharmacokinetics and 'signals of biological activity' of orally-administered DUR-928 over 28 consecutive days in NASH patients
        - Three doses; low, middle and high. Each cohort n= 20 patients
        - DRRX will provide more specifics re: study design following initial patient dosing
        - ***Initiation of enrollment and initial data expected in Q1'19 and 2H'19, respectively***

    - **AH Phase 2a study with IV DUR-928**
        - Includes two patient cohorts;
            - Part A: moderate AH at three dose levels; 30mg, 90mg and 150mg (n=4 per dose cohort) and
            - Part B: severe AH at 30mg, 90mg and possibly a 150mg dose (n=4 per dose cohort)

- Protocol recently amended with the goal of speeding trial completion. Protocol now allows for Part B to commence enrollment (initially with low-dose) following review by trial oversight committee, while simultaneously continuing to enroll Part A. This protocol modification allows investigators to immediately enroll these higher MELD-score patients and speed overall completion time of the trial
- Low-dose (30mg) cohort (n=4) completed among both Part A and Part B patients
- Based on positive feedback from their clinical trial investigators, dose escalation committee and expert advisors (as it relates to safety and PK review), both Part A and Part B are approved to enroll the next-highest dose (90mg). DRRX is advancing Part B to 90mg dose and recruiting Part A patients for 90mg. ***Expect to complete Part B 90mg dose this year***
- Previously, the plan was to transition the study to Dr. Craig McClain at the University of Louisville following completion of the 30mg dose of Part B. But, following positive review of this cohort, the plan is now for DRRX to continue this study and for Dr. McClain to conduct a parallel, NIH-funded, study

- **Psoriasis with topical DUR-928**
  - Plans underway for a Phase2a proof-of-concept study with topical DUR-928 in patients with mild-to-moderate plaque psoriasis
    - U.S., multi-site, randomized, double-blind (patients serve as own control)
    - Primary endpoint is change in local psoriasis scores
    - Targeting enrollment of 20 in order to obtain data on at least 15 patients
    - DUR-928 applied topically once-daily for four weeks with four-week follow-up
  - Anticipate dosing starting in Q1'19
  - ***Topline data expected in 2H'19***

- **Primary Sclerosing Cholangitis Phase 2a study with oral DUR-928**: PSC program has been discontinued as DRRX focuses DUR-928 on NASH, AH and psoriasis

- **U.S. launch of PERSERIS**. On July 30th Indivior announced that FDA approved their NDA for PERSERIS (risperidone), the first once-monthly subcutaneous risperidone-containing, long-acting injectable for the treatment of schizophrenia in adults. That triggered a $5M milestone payment to DRRX. DRRX will also receive single-digit royalties on sales by Indivior. ***On February 27, 2019, Indivior announced the U.S. launch of PERSERIS.***

- **Regulatory approval of Methydur sustained release capsules (for ADHD) in Taiwan**. Orient Pharma received notice of regulatory approval in Taiwan in September. Per DRRX's Q4'18 earnings release in early March, Orient Pharma has stated that they expect to make Methydur commercially available in Taiwan in 2019. DRRX receives a royalty on sales of the product by Orient and retains rights to it in North America, Europe, Japan and all other countries not specifically licensed to Orient Pharma. While we do not expect significant royalty-related revenue from sales in Taiwan (population ~24M), we do view this as meaningful as it may be a harbinger for accelerated development and regulatory activities in other, more meaningful markets, such as China

- **POSIMIR CRL response anticipated**. As a reminder, DRRX submitted an NDA (via 505(b)(2) pathway) to FDA for POSIMIR in April 2013. FDA responded in February 2014 with a Complete Response Letter. Following interaction with the agency, Durect conducted and completed a Phase 3 clinical trial of POSIMIR (PERSIST trial). As reported in October 2017, while results favored POSIMIR, the trial failed to meet its primary endpoint of a statistically significant reduction in pain on movement over the first 48 hours after surgery as compared to standard bupivacaine HCl. Durect has now completed a total of 16 clinical studies with POSIMIR.

  DRRX recently engaged Dr. Lee S. Simon, a physician and previous (2001 – 2003) Director of FDA's Analgesic, Anti-inflammatory and Ophthalmologic Drug Products division, to evaluate potential next-steps with POSIMIR. Based on his review of the PERSIST data, Dr. Simon advised the company to formally respond to the Complete Response Letter. As such, DRRX expects to make a full response to the CRL in 1H'19. Given an anticipated six-month FDA review period, Durect should have an answer from the agency before current year-end. As we had removed POSIMIR from our model, a 'favorable' response from FDA – most notably, a reasonably efficient pathway to U.S. marketing approval, would likely provide upside to our estimates.

Pipeline Refresher

DUR-928 Programs:

Update on Phase II of Injectable DUR-928 for AH

In late-April 2018, Durect commenced patient dosing in a **Phase 2a** clinical trial of DUR-928 in patients with **alcoholic hepatitis (AH).**

This is an open label, dose escalation study conducted in two parts.

- **Part A** includes patients with moderate alcoholic hepatitis (MELD = 11 to 20), and
- **Part B** will include patients with severe alcoholic hepatitis (MELD = 21 to 30)

The study is being conducted using **three dose levels** (30, 90 and 150 mg) in Part A, with sequential dose escalation following review of safety and PK results of the prior dose level. Patients will receive DUR-928 by intravenous infusion, and the dose may be adjusted in Part B based on the findings from Part A. Patients will be enrolled at multiple clinical sites in the U.S. and the target number of participants to complete the study is **24-36**. The objectives of this study include safety, PK and PD signals, as determined by improvement in liver biochemistry, model for end stage liver disease (MELD) scores and Lille scores, and other biomarkers.

The study protocol was recently updated with the goal of speeding trial completion. Protocol now allows for Part B (i.e. severe AH) to commence enrollment (initially with low-dose) following review by trial oversight committee, while simultaneously continuing to enroll Part A. This is expected to speed overall completion of the trial.

As of early March 2019, the low dose low-dose (30mg) cohorts among both Part A (n=4) as well as Part B (n=4) had completed enrollment. Following subsequent safety and PK review, both Part A and Part B have been approved to enroll their respective 90mg cohorts. DRRX noted on the Q4'18 call (March 7th) that they are now advancing Part B to 90mg and recruiting Part A patients for 90mg.

Previously, the plan was to transition the study to Dr. Craig McClain at the University of Louisville following completion of the 30mg dose of Part B. But, following positive review of this cohort, the plan is now for DRRX to continue this study and for Dr. McClain to conduct a parallel, NIH-funded, study

Update on DUR-928 for NASH

In January 2016, Durect initiated a single-ascending-dose **Phase 1b** clinical trial with oral DUR-928 in patients with nonalcoholic steatohepatitis **(NASH)** in **Australia.**

This Phase 1b trial of DUR-928 was a dose ranging (50 mg and 200 mg), single-ascending-dose safety and pharmacokinetic (PK) study of **oral DUR-928** in subjects with NASH and matched control subjects (MCS). This study was conducted in successive cohorts evaluating single-dose levels (first a low dose and then a high dose) of oral DUR-928. Both cohorts consisted of 10 NASH patients and 6 MCS.

Table 1. Patient Demographics (mean ±SD)

	Cohort 1 (50 mg)		Cohort 2 (200 mg)	
Demographics	NASH	MCS	NASH	MCS
# of Patients	10	6	10	6
Age (yrs)	53.4 (10.7)	56.8 (6.5)	53.2 (12.9)	54.7 (6.0)
BMI (kg/m2)	34.7 (6.2)	31.2 (2.4)	36.6 (6.4)	33.2 (4.4)
Gender (M/F)	5/5	5/1	5/5	3/3
Baseline ALT (U/L)	66.7 (18.9)	19.3 (6.5)	78.9 (45.5)	20.8 (4.8)
Cirrhotic Patients	2	--	3	--
Non-Cirrhotic Patients	6	--	5	--
Undetermined	2	--	2	--

In April 2017 Durect presented the updated **Phase 1b** data at the International Liver Congress (EASL) in Amsterdam. In both cohorts, DUR-928 was **well tolerated overall**. There was an approximate 10-30% increase in DUR-928 exposure in NASH patients compared to MCS. A single serious adverse event (shortness of breath), designated as possibly related to study drug, was reported in cohort 2 in a NASH patient with a prior history of

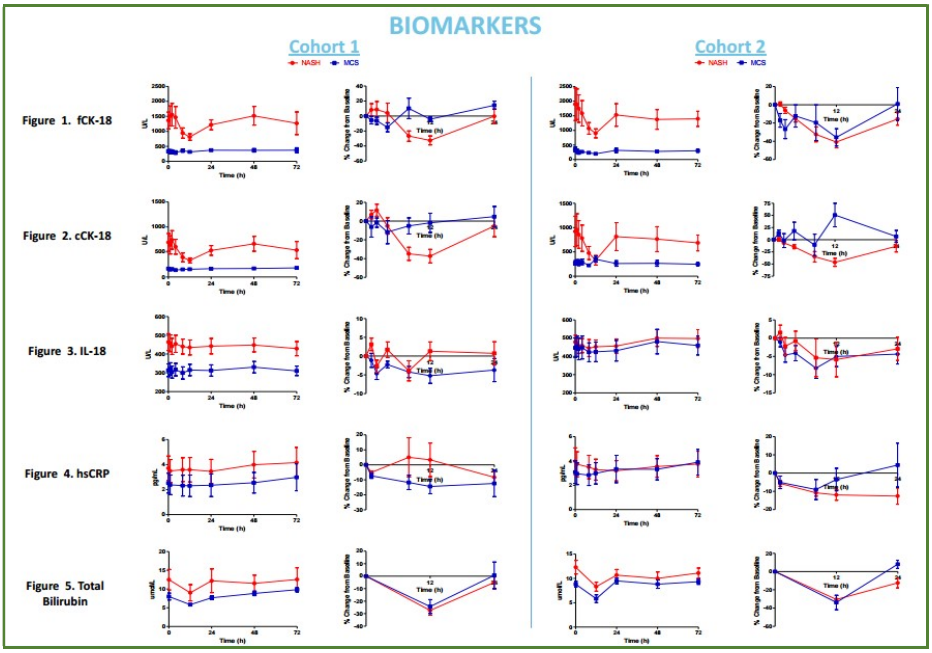
arrhythmia and an ongoing viral infection; no unusual abnormal biochemistry was observed and the symptom spontaneously resolved.

Table 2. Pharmacokinetic Parameters (mean ±SEM)

	Cohort 1		Cohort 2	
PK Parameters	NASH	MCS	NASH	MCS
Cmax (ng/mL)	113.2 (36.3)	94.0 (27.4)	332.7 (99.5)	260.5 (54.8)
Tmax (hr)	2.4 (0.8)	3.0 (1.1)	2.9 (1.2)	2.7 (1.0)
T½ (hr)	1.6 (0.2)	1.7 (0.3)	1.9 (0.4)	1.7 (0.4)
AUClast (ng*hr/mL)	512.7 (219.1)	476.5 (187.6)	1723.7 (470.9)	1316.9 (203.4)
AUCinf (ng*hr/mL)	528.1 (216.4)	487.9 (190.2)	1732.6 (470.5)	1325.5 (202.9)

Exploratory biomarker analysis indicated that a single oral dose of DUR-928 resulted in reductions from baseline in the levels of both full-length and cleaved cytokeratin-18 (CK-18), bilirubin, hsCRP and IL-18 in NASH patients.

- The decrease of full-length CK-18 (a generalized cell death marker) at 12 hours was approximately 33% in the NASH patients in the low dose cohort and approximately 41% in the high dose cohort. The decrease of cleaved CK-18 (a cell apoptosis marker) at 12 hours was approximately 37% in the NASH patients in the low dose cohort and approximately 47% in the high dose cohort.
- The decrease in total bilirubin (a liver function marker for which a decrease would be seen as positive) at 12 hours in the NASH patients was approximately 27% in the low dose cohort and approximately 31% in the high dose cohort.
- High sensitivity C-Reactive Protein (hsCRP), a marker of inflammation, trended higher at 12 hours in the NASH patients by approximately 3% in the low dose cohort but trended lower by approximately 12% in the high dose cohort.
- IL-18, an inflammatory mediator implicated in both liver and kidney diseases, trended lower at 12 hours by approximately 5% in both the low dose cohort and in the high dose cohort.



New (U.S.) NASH Phase 1b program

DRRX recently accelerated the timeline for enrolling a new Ph1b U.S. study for oral DUR-928 in NASH which had previously been anticipated in 1H 2019 (usually implying Q2) but is now expected to happen this quarter (i.e. Q1'19). DRRX disclosed that it is an open-label study evaluating orally-administered DUR-928 in NASH patients over 28 days for safety, pharmacokinetics and signals of biological activity.

While we should learn more details about the study, including specifics related to exactly what biological activity they intend to measure, when enrollment is underway (expected this quarter), we think the likely biomarkers of

interest include bilirubin, C-reactive protein (hsCRP), IL-18 and both full-length and cleaved cytokeratin 18. All of these were evaluated in their prior oral DUR-928 Phase 1b study (conducted in Australia).

As a reminder, that study showed just a single dose of DUR-928 was associated reductions in all of these biomarkers and did so with no safety issues (see our refresher, below). This 28-day study will provide a longer-duration look at both safety and biomarker effects and, depending on the results, could offer a lot more insight into later-stage study design and, potentially, even represent a valuation inflection for the share price. As such, we will be eagerly awaiting initial results, expected in the second half of this year.

DUR-928 Topical Formulation for Psoriasis

Psoriasis effects between 7M and 32M Americans. Traditional first-line prescription therapy includes steroids to address inflammation and redness. DRRX is investigating topical DUR-928 for plaque psoriasis. Durect **completed** an initial **exploratory Phase 1b** trial in **psoriasis** patients (n = 9 evaluable patients) in Australia. The decision to proceed with clinical testing in psoriasis was based on the anti-inflammatory and cell survival properties of DUR-928, including the downregulation of IL-17, full length CK-18, cleaved CK-18, as well as the results of a psoriasis study with DUR-928 in mice.

The **Phase 1b** trial was conducted with intradermal micro injections of DUR-928, and the company thinks the results warrant further investigation. As a result, the company has developed several topical formulations of DUR-928 that the company is evaluating for a topical application microplaque trial. There is a large unmet medical need for new topical drugs for psoriasis for use prior to systemic biologic treatments which often have significant associated side effects.

Plans are underway for a Phase2a proof-of-concept study with topical DUR-928 in patients with mild-to-moderate plaque psoriasis. Expected to commence in Q1'19, this will be a U.S.-based multi-site, randomized, double-blind, controlled study with targeted enrollment of ~20 anticipated, which is expected to yield ~15 evaluable patients.

Topical application will occur 1x daily for four weeks. Each patient will serve as their own control arm with DUR-928 and vehicle-control applied to separate plaques on each patient throughout the four-week duration of the study. Follow-up will occur during weeks five through eight (i.e. four weeks subsequent to treatment duration). Primary efficacy endpoint will be improvement in local psoriasis scores in the DUR-928-treated plaque compared to the vehicle-treated plaque. Topline data is expected in 2H 2019.

Update on Phase 1b Injectable DUR-928 for Kidney Disease

This trial was also conducted in **Australia**. This **Phase Ib** trial of DUR-928 was an open-label single-ascending-dose safety and pharmacokinetic study in patients **with impaired kidney function** (stage 3 and 4 chronic kidney disease) and matched control subjects. It was conducted in successive cohorts (first a low dose and then a high dose) evaluating single-dose levels of DUR-928 administered **by injection.**

The low dose cohort enrolled 6 kidney function impaired patients and 3 matched control subjects, and the high dose cohort enrolled 5 kidney function impaired patients and 3 matched control subjects. Results showed DUR-928 was well tolerated among all subjects and the PK parameters between the kidney function impaired patients and the matched control subjects were comparable.

Update on Phase 2a Study of Oral DUR-928 for PSC

As a reminder, Durect received orphan drug designation for DUR-928 to treat patients with PSC. PSC is a chronic liver disease characterized by a progressive cause of cholestasis (decrease in bile flow) with inflammation and fibrosis of bile ducts. It is an orphan medical condition for which there is no established medical treatment.

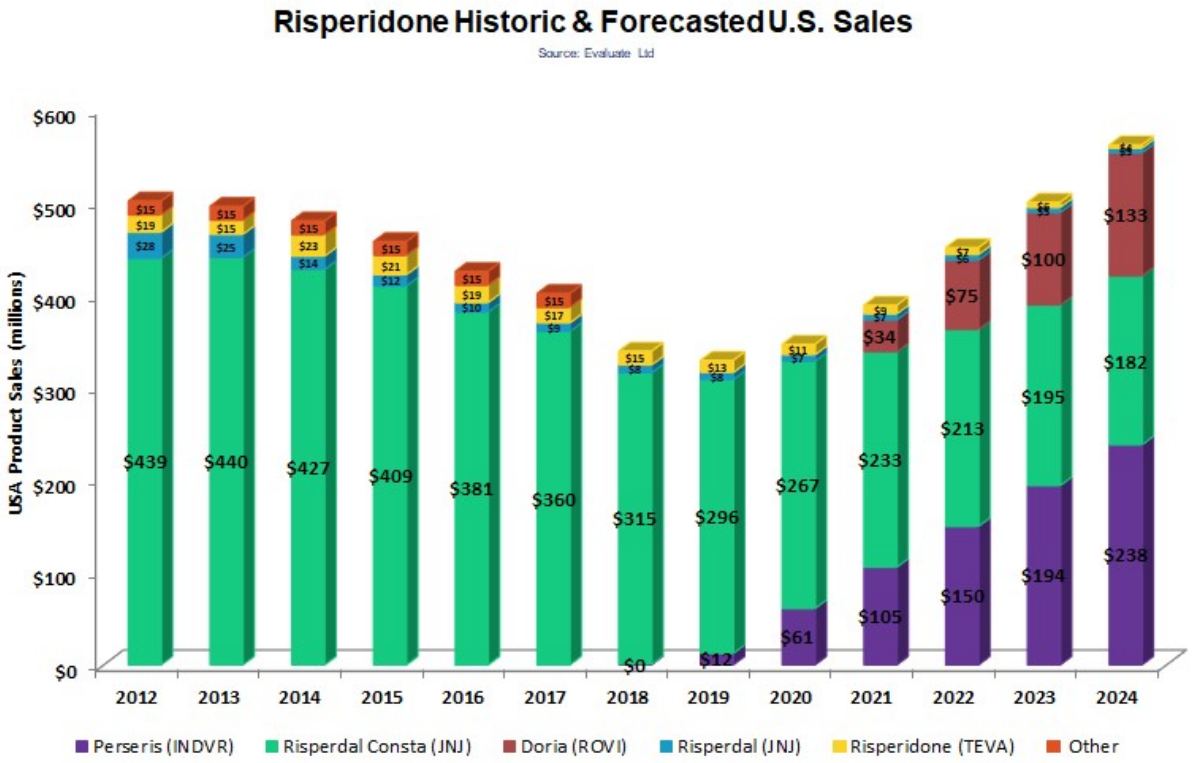
On February 26, 2018, Durect announced commencement of patient dosing in a **Phase 2a** study of DUR-928 in patients with primary sclerosing cholangitis **(PSC).** Subsequent to the commencement of enrollment, DRRX decided to discontinue their PSC trial and instead focus their time and resources on other of their ongoing programs. Citing too-slow enrollment rates, the decision was made to pull the plug on the DUR-928 primary sclerosing cholangitis trial which had only enrolled five patients between February and November 2018. Total enrollment was expected to be 30 - 40. We think that management's decision to discontinue the program fits with their prioritization strategy of focusing efforts on indications that hold the most near-term promise and which have the most potential to move into late-stage development.

PERSERIS (long-acting injectable risperidone)

In October 2017, Durect reached a $17.5 million patent purchase agreement with **Indivior UK Limited**, an affiliate of Indivior PLC (INDV.L). The deal assigned certain of Durect U.S. patent rights to Indivior for RBP-7000, Indivior's recently FDA-approved **once-monthly injectable risperidone product** for the treatment of schizophrenia. Per the agreement, Indivior made an upfront payment to Durect of $12.5 million. Then, in late-July, Indivior announced that FDA approved their NDA for PERSERIS, which triggered a $5M milestone payment to DRRX (received in Q3'18). DRRX will also receive quarterly earn-out payments based on a single-digit percentage of U.S. net sales of PERSERIS (as well as other products covered by the patent rights). On February 27, 2019, Indivior announced the U.S. launch of PERSERIS.

Risperidone (branded and unbranded) remains one of the most widely used anti-psychotics. PERSERIS addresses low compliance rates among individuals prescribed oral risperidone (taken daily), which has been shown to be a significant risk factor related to inadequate treatment of schizophrenia. As PERSERIS is the only long-acting risperidone-containing injectable, it represents the only available option that directly addresses lack of dosing adherence – which is particularly problematic among individuals with psychosis given their cognitive handicaps.[1] This long-acting benefit could draw significant interest upon launch and drive early adoption, particularly for those patients that struggle with adherence to oral risperidone therapy. Indivior noted on their Q4'18 call in February that they will be detailing the product with a sales force of approximately 50 reps. We currently model initial royalty revenue from sales of PERSERIS to DRRX commencing in 1H'19.

According to prescription data aggregated by Evaluate Pharma, U.S. and WW sales of risperidone in 2017 were approximately $380M and $1.0B, respectively. While forecasts suggest U.S. market contraction into 2019, the introduction of PERSERIS is expected to push total U.S. risperidone sales back to positive growth beginning in 2020. In fact, PERSERIS is expected to be the majority driver of U.S. risperidone sales beginning in 2019 (see chart below). Average analyst estimates forecast PERSERIS (purple bar) U.S. sales of $12M in 2019 and growing to $238M in 2024 (recently upwardly revised from prior 2024 forecast of $172M) in 2024. While this implies a healthy 82% CAGR over that period, it may still be slightly more conservative than that anticipated by Indivior, which is guiding for peak annual sales of $200M - $300M. We base our PERSERIS sales related earn-out estimates on analysts' forecasted U.S. sales of the therapy (and apply an assumed 4% royalty rate) and currently look for DRRX to recognize ~$480k, $2.4M and $4.2M of PERSERIS earn-outs in 2019, 2020 and 2021, respectively.



[1] Nielsen J., et al. Comparative Effectiveness of Risperidone Long-Acting Injectable vs FirstGeneration Antipsychotic Long-Acting Injectables in Schizophrenia: Results From a Nationwide, Retrospective Inception Cohort Study. Schizophrenia Bulletin vol. 41 no. 3 pp. 627–636, 2015

POSIMIR
POSIMIR is the company's investigational post-operative pain relief depot that utilizes the company's patented SABER technology and is intended to deliver bupivacaine to provide three days of pain relief after surgery.

In May 2017, Durect announced a development and commercialization agreement with Sandoz AG, a division of Novartis (NVS), to develop and market POSIMIR (SABER-Bupivacaine) in the U.S. Terms of that initial agreement called for Sandoz to make an upfront payment to DURECT of $20 million. DRRX was also eligible to receive up to $43 million in development and regulatory milestones, up to $230 million in sales-based milestones and a tiered double-digit royalty on product sales in the United States. The agreement was amended in May 2018 whereby Durect is now eligible for up to $30 million in milestone payments based on NDA approval. They continue to be eligible for up to an additional $230 million in sales-based milestones. Each party is also permitted to develop or commercialize competing products.

As a reminder, DRRX submitted an NDA (via 505(b)(2) pathway) to FDA for POSIMIR in April 2013. FDA responded in February 2014 with a Complete Response Letter. Following interaction with the agency, Durect conducted and completed a Phase 3 clinical trial of POSIMIR (PERSIST trial). As reported in October 2017, while results favored POSIMIR, the trial failed to meet its primary endpoint of a statistically significant reduction in pain on movement over the first 48 hours after surgery as compared to standard bupivacaine HCI. Durect has now completed a total of 16 clinical studies with POSIMIR.

DRRX recently engaged Dr. Lee S. Simon, a physician and previous (2001 – 2003) Director of FDA's Analgesic, Anti-inflammatory and Ophthalmologic Drug Products division, to evaluate potential next-steps with POSIMIR. Based on his review of the PERSIST data, Dr. Simon advised the company to formally respond to the Complete Response Letter. As such, DRRX expects to make a full response to the CRL in 1H'19. Given an anticipated six-month FDA review period, Durect should have an answer from the U.S. regulatory agency before current year-end. As we had removed POSIMIR from our model, a 'favorable' response from FDA – most notably, a reasonably efficient pathway to U.S. marketing approval, would likely provide upside to our estimates.

REMOXY
On August 6, 2018, Durect's partner Pain Therapeutics reported that it received a Complete Response Letter (CRL) from the FDA relative to their NDA REMOXY ER (oxycodone), extended-release capsules. The CRL concluded that, "The data submitted in [the] NDA do not support the conclusion that the benefits of [REMOXY] Extended-Release Capsules outweigh the risks." Following the CRL, Pain Therapeutics further announced a strategic reorganization to align its resources on advancing its drug and diagnostic assets in Alzheimer's disease.

While our assumptions will be updated if warranted, we have removed REMOXY from our model as we think it is more likely than not that the development program will be either completely discontinued or at least significantly delayed. We do note that there may be hope that REMOXY could be salvaged, however – or at least it appears that Pain Therapeutics believes that might be the case.

On November 12, 2018 they announced a meeting on January 31st with FDA to discuss their appeal of the latest CRL. The PR also lays out their case supporting the appeal, noting that they believe there were calculation errors, "material mistakes and misrepresentations made by FDA during a June 2018 Advisory Committee" and that when corrected for these, "REMOXY has properties that may deter against common methods of abuse, such as injection abuse". The PR goes on, making the case for REMOXY as less abusable than ER oxycodone, associated with lower health risks and meeting all evidentiary standards for FDA approval.

On February 5, 2019 Pain Therapeutics announced feedback from its meeting with FDA which notes that, "we walked out of this meeting feeling a bit disoriented by FDA's lack of transparency, clarity or helpfulness" and provides an implicit conclusion that, "we believe we are no closer today to product approval than we were over a year ago."

We continue to hold out little hope for a reversal by FDA. We will, however, update our assumptions and outlook regarding the approvability and commercial opportunity of REMOXY if warranted.

VALUATION

Large Market Opportunity for DUR-928

Although DUR-928 may have broad applications in many indications, we believe most of the underlying value resides in NAFLD/NASH and acute kidney injury.

Non-alcoholic fatty liver disease (NAFLD) is the build-up of extra fat in liver cells that is not caused by alcohol. It is normal for the liver to contain some fat. However, if more than 5% - 10% percent of the liver's weight is fat, then it is called a fatty liver (steatosis). The more severe form of NAFLD is called non-alcoholic steatohepatitis (NASH). NASH causes the liver to swell and become damaged.

NAFLD affects about 30% of adults and 10% of children in the US, among which 10-30% will develop NASH. 25-40% NASH patients will develop progressive liver fibrosis, while 20-30% NASH patients with advanced fibrosis will develop cirrhosis, which could lead to liver cancer. Currently there are no FDA approved medicines for the treatment of NAFLD/NASH.

Acute kidney injury (AKI) is defined as an abrupt or rapid decline in renal filtration function. This condition is usually marked by a rise in serum creatinine concentration or by azotemia (a rise in blood urea nitrogen [BUN] concentration).

Per Medscape, in the United States, approximately 1% of patients admitted to hospitals have AKI at the time of admission. The estimated incidence rate of AKI during hospitalization is 2-5%. AKI develops within 30 days postoperatively in approximately 1% of general surgery cases and arises in up to 67% of intensive care unit (ICU) patients. Approximately 95% of consultations with nephrologists are related to AKI. The appropriate nephrologist referral rate is approximately 70 cases per million populations.

The current treatment for AKI is mainly supportive in nature. No therapeutic modalities to date have shown efficacy in treating the condition. Therapeutic agents (eg, dopamine, nesiritide, fenoldopam, mannitol) are not indicated in the management of AKI and may be harmful for the patient.

Certainly, there are highly unmet medical needs in the NAFLD/NASH and acute kidney injury fields. The unique mechanism of action and the compelling animal and human data so far make DUR-928 a highly promising candidate for the management of NAFLD/NASH and kidney injury.

We value DRRX using sum-of-the-parts, with most of the value related to DUR-928 based on pricing of recent NASH-targeted M&A transactions as a proxy. Our methodology also includes discounted cash flow of DRRX's current cash-generating products and earn-outs.

DUR-928 valued at between $750M and $1B

Examples of some of the higher-profile NASH-related acquisitions include Allergan's (AGN) September 2016 purchase of Tobira Therapeutics. The deal, valued at $1.7B (inclusive of potential development and commercial milestones), brought two NASH candidates; Cenicriviroc, an oral CCR2/5 inhibitor in phase 2 and Evogliptin, an oral DPP-4 inhibitor in phase 1.

Earlier in 2018 Gilead bought Nimbus Therapeutics for $400M upfront and $800M in potential development milestones. NDI-0107976, an ACC inhibitor in phase 1 for the treatment of NASH was the main attraction for Gilead. Other recent NASH-related acquisitions are in the table below which was constructed by Evercore ISI. Preclinical and phase 1 candidates have commanded as much as $450M and $1B+, respectively, in buyouts.

We think frothiness of the NASH space coupled with the potential versatility of DUR-928 as it relates to formulations (oral, IV and topical) as well as its applicability in various conditions, including NASH, acute liver disease, PCS and even psoriasis warrants potential premium pricing. Initial human proof-of-concept in phase 1 studies for various formulations demonstrating a strong safety and drug interaction profile, in addition to compelling efficacy signals, further supports the relative value of DUR-928. Based on recent M&A transactions, DUR-928 has a relative value of between $750k and $1B. Further positive clinical trial progression would likely move valuation closer to the $1B mark.

Activity in the NASH space is high, with a number of recent acquisitions and partnerships.

Acquirer/Partner	Target	Type of Deal	Date Announced	Names of Programs	Phase of Development (at acquisition)	Total Value of Acquisition	Additional Details
Novartis	Conatus	Collaboration; NVS acquired worldwide rights to emricasan	December 2016	Emricasan	Phase 2b	Total potential value of at least $700 million	Conatus also eligible for tiered double digit royalties and option to co-commercialize
Allergan	Tobira	Acquisition	September 2016	Cenicriviroc (CVC), Evogliptin	CVC: Phase 3, Evogliptin: Phase 1	Total potential value of $1.695 billion	Upfront payment of $28.35 per share, in cash, and up to $49.84 per share in Contingent Value Rights
Allergan	Akarna	Acquisition	September 2016	AKN-083	Preclinical	>$50 million	$50 million upfront, with other milestones
Gilead	Nimbus	Acquisition	April 2016	NDI-010976 and other preclinical assets	Phase 1	Total potential value of $1.2 billion	Upfront payment of $400 million, with potential to receive $800 million in addition
Boehringer Ingelheim	Pharmaxis	Acquisition of PXS4728A program	May 2015	PXS4728A	Phase 1	Total potential value of ~$250 million for NASH	$31 million upfront, $222 million in milestone payments; in addition, royalties on sales
Merck	NGM Biopharma	Collaboration; MRK acquired 15% stake in the company	February 2015	Multiple including NP201	Preclinical	Total potential value of $450 million	$94 million upfront, 15% equity stake, up to $250 million to fund collaboration
Gilead	Phenex	Acquired NASH programs	January 2015	Multiple including Px-104	Phase 2	Total potential value of $470 million	Undisclosed upfront sum and milestones

Source: Company Press Releases

EVERCORE ISI

Current cash-generating products and earn-outs worth ~$90M

We estimate cash flow of DRRX's legacy products (Actel and Lactel) and PERSERIS earn-outs of approximately $85M over the next seven years. Discounting back to present at 12%, results in NPV of approximately $60M. We assign a 50% premium to the NPV value to reflect the likelihood of additional licensing, collaboration and earn-out opportunities materializing over the same period. We also note that this NPV value ($60M x 1.5 = $90M) may be conservative as it does not consider any assumed contribution from POSIMIR and only minimal contribution from ORADUR. Upside to either of those programs (such as ORADUR launch in, and meaningful revenue from, China or a viable development/regulatory strategy for POSIMIR), could result in relative upside to our NPV calculation.

Our sum-of-the-parts methodology values DRRX at approximately $965M, or $6.00/share

PROJECTED INCOME STATEMENT

Durect Corporation

DURECT Corp	Q1	Q2	Q3	Q4	2018 A	Q1	Q2	Q3	Q4	2019 E	2020 E	2021 E
PERSERIS Earn-outs (US)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.1	$0.2	$0.2	$0.5	$2.2	$3.6
YOY Growth	-	-	-	-	-	-	-	-	-	-	*340.0%*	*63.6%*
PERSERIS (Ex-US)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	
ORADUR-ADHD (DRRX rights)	$0	$0	$0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-
ORADUR-ADHD (Orient Pharma) **Rylty**	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.1	$0.1	$0.2	$0.4	$0.7
YOY Growth	-	-	-	-	-	-	-	-	-	-	*100.0%*	*75.0%*
DUR-928	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-
Alzet Pumps & Lactel Polymers	$2.4	$2.8	$2.3	$2.9	$10.4	$2.8	$2.9	$2.6	$3.2	$11.3	$12.5	$13.0
YOY Growth	*-42.1%*	*-9.3%*	*-11.3%*	*-12.6%*	*-20.9%*	*15.0%*	*3.0%*	*8.7%*	*10.4%*	*9.1%*	*10.6%*	*4.0%*
Total Product Sales	$2.4	$2.8	$2.3	$2.9	$10.4	$2.8	$3.0	$2.8	$3.4	$12.0	$15.1	$17.3
YOY Growth	*-42.1%*	*-9.3%*	*-11.3%*	*-12.6%*	*-20.9%*	*16.2%*	*8.0%*	*19.8%*	*19.9%*	*15.9%*	*25.8%*	*14.6%*
Collaborative Revenue	$1.1	$0.6	$5.7	$0.8	$8.2	$0.5	$0.5	$0.7	$0.8	$2.5	$3.0	$5.7
YOY Growth	*152.5%*	*-49.1%*	*1.6%*	*-95.2%*	*-65.2%*	*-54.4%*	*-22.5%*	*-88.6%*	*3.2%*	*-70.1%*	*22.4%*	*90.0%*
Revenue from sale of IP rights	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Total Revenues	**$3.5**	**$3.4**	**$8.0**	**$3.6**	**$18.6**	**$3.3**	**$3.5**	**$3.5**	**$4.2**	**$14.5**	**$18.1**	**$23.0**
YOY Growth	*-23.6%*	*-21.0%*	*-61.3%*	*-81.4%*	*-62.2%*	*-6.0%*	*2.3%*	*-56.9%*	*16.3%*	*-22.2%*	*25.3%*	*27.1%*
Cost of Goods Sold	$1.2	$1.1	$0.9	$1.1	$4.3	$1.4	$1.1	$1.0	$1.3	$4.8	$5.4	$6.1
Product Gross Margin	*50.9%*	*60.8%*	*61.1%*	*61.7%*	*58.8%*	*51.2%*	*62.1%*	*63.6%*	*61.4%*	*65.0%*	*64.1%*	*65.0%*
SG&A	$3.2	$2.8	$2.9	$3.5	$12.4	$3.3	$3.0	$3.1	$3.5	$12.9	$16.1	$18.7
% SG&A	*91.6%*	*82.5%*	*35.7%*	*97.6%*	*66.9%*	*100.6%*	*86.0%*	*89.6%*	*82.9%*	*89.3%*	*89.0%*	*81.3%*
R&D	$7.0	$6.1	$6.5	$5.9	$25.5	$6.2	$7.4	$7.7	$8.0	$29.3	$36.4	$38.1
% R&D	*199.3%*	*179.3%*	*81.4%*	*162.3%*	*137.4%*	*189.0%*	*212.0%*	*222.5%*	*189.6%*	*202.8%*	*201.1%*	*165.7%*
Operating Income	($7.8)	($6.6)	($2.3)	($6.9)	($23.6)	($7.6)	($8.0)	($8.4)	($8.6)	($32.6)	($39.8)	($39.9)
Operating Margin	-	-	-	-	-	-	-	-	-	-	-	-
Interest & Other Net	($0.5)	($0.4)	($0.4)	($0.4)	($1.7)	($0.5)	($0.5)	($0.6)	($0.6)	($2.2)	($2.4)	($1.7)
Pre-Tax Income	($8.3)	($7.0)	($2.7)	($7.3)	($25.3)	($8.1)	($8.5)	($9.0)	($9.2)	($34.8)	($42.2)	($41.6)
Taxes	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Net Income	($8.3)	($7.0)	($2.7)	($7.3)	($25.3)	($8.1)	($8.5)	($9.0)	($9.2)	($34.8)	($42.2)	($41.6)
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-
Reported EPS	($0.05)	($0.04)	($0.02)	($0.05)	($0.16)	($0.05)	($0.05)	($0.06)	($0.05)	($0.21)	($0.22)	($0.21)
YOY Growth					-	-	-	-	-	-	-	
Shares Outstanding	153.6	161.6	162.0	162.0	159.8	162.0	162.0	162.0	171.0	164.3	190.0	195.0

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