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Zacks Small-Cap Research

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Durect Corp (DRRX-NASDAQ)

DRRX: Pipeline Update: Focus Is On Accelerating DUR-928 in NASH and Other High-Potential Indications

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 (01/11/19)	$0.62
Valuation	**$6.00**

OUTLOOK

Durect provided a corporate/pipeline update. Much of the focus was on DUR-928. Noteworthy is that the company announced a somewhat updated strategy as it relates to DUR-928 - specifically that they intend to hone their focus on accelerating timelines for those indications which they believe hold the most near-term potential to move into late-stage development. One of those areas is clearly NASH – an indication with significant unmet need and one that, if DRRX can build on the prior Phase 1b data, could represent meaningful upside to the share price in our opinion. Encouragingly, management accelerated the timeline for initial dosing of their new Ph1b study of DUR-928 in NASH – previously expected to happen in 1H'19 (which often implies Q2), this is now slated for this quarter. Initial data expected 2H 2019.

Meanwhile DUR-928 in psoriasis and AH also continue to make progress. Psoriasis data also expected later this year. As it relates to AH, once Part B low-dose completes, the study transitions to Dr. McClain of the U of Louisville, a recognized KOL in AH, and be funded by an NIH grant.

Regarding PERSERIS, launch still slated for this quarter, supported by ~50 reps. DRRX receives single-digit earn outs on net sales.

We are maintaining our $6/share price target.

SUMMARY DATA

52-Week High	**$2.55**
52-Week Low	**$0.46**
One-Year Return (%)	**-46.15**
Beta	**2.21**
Average Daily Volume (sh)	**379,947**
Shares Outstanding (mil)	**162**
Market Capitalization ($mil)	**$100**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**49**
Insider Ownership (%)	**4**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**20.1**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2018 Estimate	**N/A**
P/E using 2019 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)
2016	3.6 A	3.2 A	3.7 A	3.5 A	14.0 A
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 E	18.5 E
2019					14.5 E

Price/Sales Ratio (Industry = 2.5x)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	-$0.06 A	-$0.07 A	-$0.06 A	-$0.06 A	-$0.26 A
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 E	-$0.16 E
2019					-$0.22 E

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

WHAT'S NEW

Pipeline update
Earlier this week Durect provided a corporate and pipeline update. Much of the focus was, as expected, on DUR-928. Particularly noteworthy is that the company announced a somewhat updated strategy as it relates to DUR-928 - specifically that they intend to hone their focus on accelerating timelines for those indications which they believe hold the most near-term potential to move into late-stage development. One of those areas is clearly NASH – an indication with significant unmet need and one that, if DRRX can build on the prior Phase 1b data, could represent meaningful upside to the share price in our opinion. **As it relates to DUR-928 in NASH**…

- they have 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
    - management also provided initial details of the trial design including that it will be…open-label evaluating orally-administered DUR-928 in NASH patients over 28 days for safety, pharmacokinetics and "signals of biological activity"
    - DRRX anticipates initial data from this study to be announced in the second half of this year

  While we may know more about specifics in terms of exactly what biological activity they intend to measure when DRRX provides additional details about the study design (expected later this quarter), comments on the call suggest that biomarkers of interest include bilirubin, C-reactive protein (hsCRP), IL-18 and both full-length and cleaved cytokeratin 18 – all of which 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 later this year.

As it relates to DUR-928 in psoriasis, DRRX expects the Phase 2a proof-of-concept study evaluating topical DUR-928 in patients with mild-to-moderate plaque psoriasis to commence dosing this quarter (i.e. Q1'19) and if all goes to plan, to announce topline data in the second half of this year. These timelines are unchanged from prior expectations. Psoriasis represents a sizeable market, afflicting up to 32M Americans, and an unmet need for new topical drugs to treat the condition prior to use of systemic biologics, which often have significant associated side effects.

As a reminder, this new study follows an initial exploratory Phase 1b trial in psoriasis patients (n = 9 evaluable patients) using intradermal micro injections of DUR-928 which was conducted 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 **Phase2a trial of injectable DUR-928 in alcoholic hepatitis** is ongoing with two patients now having enrolled in Part B (i.e. severe AH patients) of the study at the 30mg (i.e. low) dose. 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.

As a reminder, the study was recently updated with the intention of speeding it along – allowing for Part B to enroll as Part A (moderate AH) completes at the same dose level. Part A completed enrollment (n=4) at the low-dose in early November, at which time Part B commenced at the same 30mg dose. **Once Part B completes DRRX will transition the study to Dr. Craig McClain at the University of Louisville**, a recognized KOL in AH who was recently awarded an NIH grant which will be used to fund the study to completion (following Part B 30mg dosing). Target number of patients to complete the study is 24 to 36. Objectives include safety, PK and PD signals, as determined by improvement in liver biochemistry, MELD and Lille scores, and other biomarkers.

The **DUR-928 PSC program is being discontinued.** Citing too-slow enrollment rates, management noted that they are pulling the plug on the DUR-928 primary sclerosing cholangitis trial. The trial commenced patient dosing in late-February 2018 but as of November had only enrolled five patients with total enrollment expected to have been 30 - 40. While DRRX had noted that it was enrolling at a pace similar to that of other (non-related) PSC studies,

their 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.

As it relates to other development programs….

- **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. DRRX noted that they received notice from Sandoz AG, with which they had a development and commercialization agreement related to POSIMIR, that they are returning U.S. rights to Durect**.**

  The decision follows a recent change in leadership at Sandoz as well as the announcement by Durect in October 2017 that the Phase 3 clinical trial for POSIMIR did not meet its primary efficacy endpoint of reduction in pain on movement over the first 48 hours after surgery as compared to standard bupivacaine HCl. While results trended in favor of POSIMIR versus the comparator, they did not achieve statistical significance. Management noted on the Q3'18 call in November that they were evaluating next steps of the program.

  Given the failure in Phase 3, we had removed POSIMIR from our model – as such, this decision by Sandoz has no effect on our estimates or valuation. DRRX is seeking a termination fee from Sandoz – the process related to which has been initiated.

- **PERSERIS** was introduced to the U.S. market in November 2018 but is set to make its official domestic launch next month. Durect's partner for PERSERIS, Indivior, expects to support the launch with 40 to 60 reps. In the meantime, Indivior is working on payor access and generating awareness among prescribers. As a reminder, PERSERIS is the first once-monthly subcutaneous risperidone-containing, long-acting injectable for the treatment of schizophrenia in adults. Indivior estimates peak sales of the drug in the range of $200M to $300M. Durect receives 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). PERSERIS launch timelines and related activities are inline with our prior (and current) expectations. See our refresher on PERSERIS below.

Refresher on Prior Phase 1b Oral Study of DUR-928 for NASH

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	--

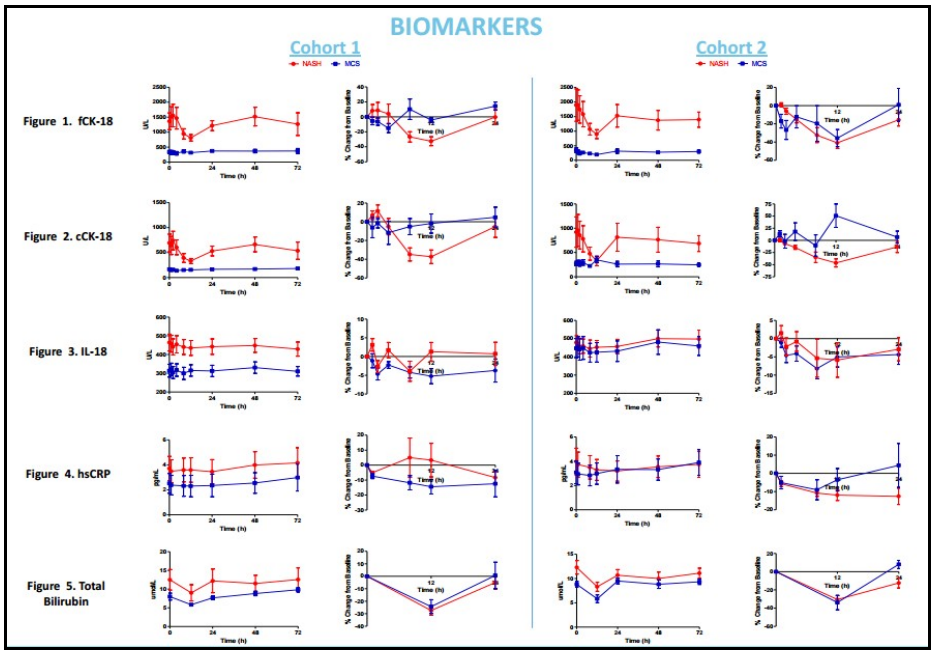
In April 2017 Durect presented the updated **Phase 1b** data at the International Liver Congress (EASL) in Amsterdam. In both cohorts, DUR-928 was **well tolerated overall**. There was an approximate 10-30% increase in DUR-928 exposure in NASH patients compared to MCS. A single serious adverse event (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, 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.

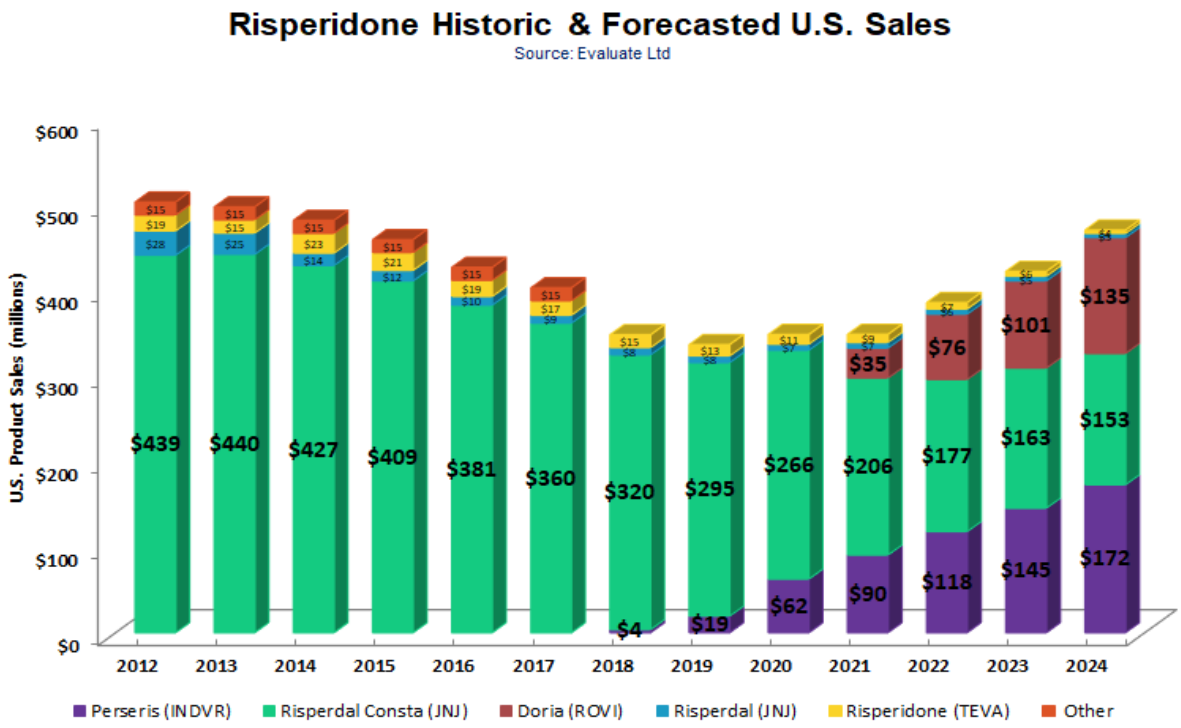


Refresher on PERSERIS

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 into 2026. 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 had initial product available in Q4'18 and expects to officially launch it in February, supported with a sales force of between 40 and 60 U.S. reps. We continue to 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 as soon as this year (see chart below). Average analyst estimates forecast PERSERIS (purple bar) U.S. sales of $19M in 2019 and growing to $172M in 2024. While this implies a healthy 55% 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 ~$760k and $2.5M of PERSERIS earn-outs in 2019 and 2020, 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

PROJECTED INCOME STATEMENT

Durect Corporation

DURECT Corp	Q1	Q2	Q3	Q4	2017A	Q1	Q2	Q3	Q4	2018 E	2019 E	2020 E
PERSERIS Earn-outs (US)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.8	$2.5
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	*226.3%*
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
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-
ORADUR-ADHD (Orient Pharma) **Rylty**	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.2	$0.4
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	*100.0%*
DUR-928	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-
Alzet Pumps & Lactel Polymers	$4.1	$3.1	$2.6	$3.3	$13.1	$2.4	$2.8	$2.3	$2.5	$10.0	$11.0	$12.0
YOY Growth	*29.6%*	*9.5%*	*-22.0%*	*17.5%*	*7.8%*	*-42.1%*	*-9.3%*	*-11.3%*	*-23.4%*	*-23.6%*	*9.9%*	*9.1%*
Total Product Sales	$4.1	$3.1	$2.6	$3.3	$13.1	$2.4	$2.8	$2.3	$2.5	$10.0	$12.0	$14.9
YOY Growth	*29.6%*	*9.5%*	*-22.0%*	*17.5%*	*7.8%*	*-42.1%*	*-9.3%*	*-11.3%*	*-23.4%*	*-23.6%*	*19.5%*	*24.4%*
Collaborative Revenue	$0.4	$1.3	$5.6	$16.3	$23.6	$1.1	$0.6	$5.7	$1.1	$3.1	$2.5	$2.5
YOY Growth	*3.6%*	*241.8%*	*1491.5%*	*2105.0%*	*1154.1%*	*152.5%*	*-49.1%*	*1.6%*	*-93.2%*	*-86.7%*	*-20.0%*	*0.0%*
Revenue from sale of IP rights			$12.5		$12.5	$0.0	$0.0	$0.0	$0.0	0.0%	0.0%	0.0%
Total Revenues	**$4.6**	**$4.3**	**$20.75**	**$19.5**	**$49.17**	**$3.49**	**$3.41**	**$8.04**	**$3.60**	**$18.5**	**$14.5**	**$17.4**
YOY Growth	*26.6%*	*36.8%*	*454.3%*	*455.5%*	*250.6%*	*-23.6%*	*-21.0%*	*-61.3%*	*-81.6%*	*-62.3%*	*-22.0%*	*20.2%*
Cost of Goods Sold	$1.5	$0.9	$3.1	$1.1	$6.6	$1.2	$1.1	$0.9	$1.0	$4.2	$4.2	$5.2
Product Gross Margin	*62.7%*	*69.7%*	*-17.4%*	*67.5%*	*49.3%*	*50.9%*	*60.8%*	*61.1%*	*60.0%*	*62.0%*	*65.0%*	*65.0%*
SG&A	$3.0	$3.7	$3.1	$3.3	$13.2	$3.2	$2.8	$2.9	$2.9	$11.8	$14.5	$17.2
% SG&A	*66.6%*	*85.2%*	*15.1%*	*16.9%*	*26.8%*	*91.6%*	*82.5%*	*35.7%*	*80.6%*	*63.5%*	*100.3%*	*99.0%*
R&D	$7.5	$9.1	$8.4	$6.6	$31.6	$7.0	$6.1	$6.5	$7.3	$26.9	$32.4	$36.8
% R&D	*165.3%*	*210.2%*	*40.4%*	*33.8%*	*64.3%*	*199.3%*	*179.3%*	*81.4%*	*202.8%*	*145.2%*	*224.3%*	*211.7%*
Operating Income	($7.6)	($9.4)	$6.1	$8.6	($2.2)	($7.8)	($6.6)	($2.3)	($7.6)	($24.3)	($36.7)	($41.8)
Operating Margin	-	-	-	-	-	-	-	-	-	-	-	*-240.7%*
Interest & Other Net	($0.5)	($0.6)	($0.0)	($0.3)	($1.5)	($0.5)	($0.4)	($0.4)	($0.6)	($1.9)	($2.6)	($2.4)
Pre-Tax Income	($8.1)	($9.9)	$6.1	$8.2	($3.7)	($8.3)	($7.0)	($2.7)	($8.2)	($26.2)	($39.3)	($44.2)
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	($8.1)	($9.9)	$6.1	$8.2	($3.7)	($8.3)	($7.0)	($2.7)	($8.2)	($26.2)	($39.3)	($44.2)
YOY Growth	-	-	-	-	-					-	*49.7%*	*12.6%*
Reported EPS	($0.06)	($0.07)	$0.04	$0.05	($0.03)	($0.05)	($0.04)	($0.02)	($0.05)	($0.16)	($0.22)	($0.23)
YOY Growth					-					-	-	-
Shares Outstanding	141.8	142.5	147.2	150.8	145.6	153.6	161.6	162.0	164.0	160.3	175.0	190.0

Brian Marckx, CFA. Zacks Investment Research

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