Zacks Small-Cap Research

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Grant Zeng, CFA
312-265-9466
gzeng@zacks.com

scr.zacks.com
10 S. Riverside Plaza, Chicago, IL 60606

DURECT Corporation

(DRRX-NASDAQ)

DRRX: *DUR-928 on track to enter into Phase II studies, POSIDUR Phase III initiated, and Remoxy NDA filing in 1Q16----Buy*

Current Recommendation	**Buy**
Prior Recommendation	Hold
Date of Last Change	04/30/2015
Current Price (01/07/16)	$1.76
Target Price	**$6.00**

Update

Durect just initiated a new Phase III trial with POSIDUR this fall designed to satisfy the U.S. FDA's request for additional information. Another late stage candidate Remoxy will be filed for NDA in 1Q16 by its partner Pain Therapeutics.

We are especially optimistic about the company's lead epigenomic regulator program DUR-928, which holds great market potential for multiple indications, such as for the management of NAFLD/NASH and acute kidney injury.

We continue to be positive about the Durect story and rate the company shares a Buy rating.

SUMMARY DATA

52-Week High	**$3.23**
52-Week Low	**$0.83**
One-Year Return (%)	**122.09**
Beta	**0.47**
Average Daily Volume (sh)	**402,443**
Shares Outstanding (mil)	**121**
Market Capitalization ($mil)	**$230**
Short Interest Ratio (days)	**15.10**
Institutional Ownership (%)	**N/A**
Insider Ownership (%)	**N/A**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**14.7**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2015 Estimate	**N/A**
P/E using 2016 Estimate	**N/A**

Risk Level	**High,**
Type of Stock	**Small-Growth**
Industry	**Med-Drugs**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	6.3 A	4.6 A	4.3 A	4.3 A	19.4 A
2015	4.8 A	4.4 A	4.7 A	5.1 E	19.1 E
2016					21.0 E
2017					30.7 E

Earnings per Share
(EPS is operating earnings before non recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	-$0.03 A	-$0.05 A	-$0.06 A	-$0.05 A	-$0.20 A
2015	-$0.04 A	-$0.05 A	-$0.05 A	-$0.06 E	-$0.20 E
2016					-$0.23 E
2017					-$0.17 E

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WHAT'S NEW

DURECT Announces Positive Phase I Data for Injectable DUR-928

On Jan 6, 2016, DURECT (DRRX) announced the successful completion of a **Phase I** clinical trial with an **injectable formulation** of DUR-928 intended for acute use indications.

The Phase I trial of injectable DUR-928 was a single-site, randomized, double-blinded, placebo-controlled, single-ascending-dose study that evaluated the safety, tolerability and pharmacokinetics of 4 doses of DUR-928 when administered through an intramuscular injection. Total of **24 healthy volunteers** in four cohorts were enrolled in the study with 16 receiving DUR-928 and 8 receiving placebo.

Peak plasma concentrations were over 100 fold higher than endogenous levels. DUR-928 was well-tolerated at all dose levels, with no treatment-related adverse events reported and plasma levels were dose proportional.

Before the highest dose was added to the single-ascending-dose study, the company proceeded to a multi-dose cohort including **10 healthy volunteers**, in which study participants received DUR-928 for 5 consecutive days (n = 8 on drug, 2 on placebo) with what at the time was the highest dose in the prior study. No 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.

The completion of the Phase I trial of injectable DUR-928 is on track with the company's development plan and is an important milestone in the development of DUR-928.

What's next for DUR-928?

Durect plans to move into **Phase II** trial in 2016 for both oral DUR-928 and injectable DUR-928, which will be conducted in Australia.

The company is currently finalizing protocols with the assistance of its scientific consultants and is evaluating potential indications for DUR-928 in order to prioritize the development program. Long term opportunities fall into four broad categories:

- orphan acute indications;
- broader acute indications;
- orphan chronic indications, and
- broader chronic indications.

DURECT's initial Phase II studies will be designed to show an efficacy signal in patients suffering from one orphan acute condition such as acute **kidney injury** and one broad chronic indication such as **NAFLD/NASH**. We will provide update when the company provides more detail on the Phase II studies in the future.

	2015			
	H1	H2	2016	Potential Indications
DUR-928 Oral Dose (chronic)	Phase I	Phase II Planning	Phase II	NAFLD / NASH, various orphan metabolic conditions
DUR-928 Injectable Dose (acute)	Pre-clinical	Phase I	Phase II	Acute Kidney Injury, various orphan acute injuries
Other NCE's (acute and chronic)	Pre-clinical	Pre-clinical	Phase I	NAFLD / NASH, various orphan indications

DUR-928 Holds Great Potential for Multiple Indications

Among Durect's multiple candidates, DUR-928 may be the most promising one in our view because this compound has the potential to target multiple indications including NAFLD/NASH and acute kidney injury.

The Background

DUR-928 came from DURECT's Epigenomic Regulator Program, which is a collaborative effort between DURECT and the Department of Internal Medicine at Virginia Commonwealth University (VCU), the VCU Medical Center, and the McGuire VA Medical Center. During the course of this program, a number of compounds that may have therapeutic utility have been identified, including the lead molecule DUR-928. DURECT holds the exclusive worldwide right to develop and commercialize DUR-928 and related molecules discovered in the program.

DUR-928 is an endogenous (produced naturally by the body), orally bioavailable small molecule that modulates the activity of several nuclear receptors that play an important regulatory role in lipid homeostasis, inflammation and cell survival. Studies have showed that DUR-928 modulates the activity of more than 240 genes, including ACC, FAS, HMGR, Cyp7A1, LXR, PPARγ, NFκB/IκB, TNFα, IL-1α, IL-6, COX-2, PCSK9, and others.

The broad biologic activities indicate that DUR-925 may have a broad range of clinical applications including acute organ injury, ischemia or reperfusion injury, and chronic liver disease such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

Compelling Animal Data

Durect has completed **multiple animal studies** with compelling efficacy and safety data. These studies involved 7 different animal models involving three animal species.

Four of these models represent **acute organ injury**, which include:

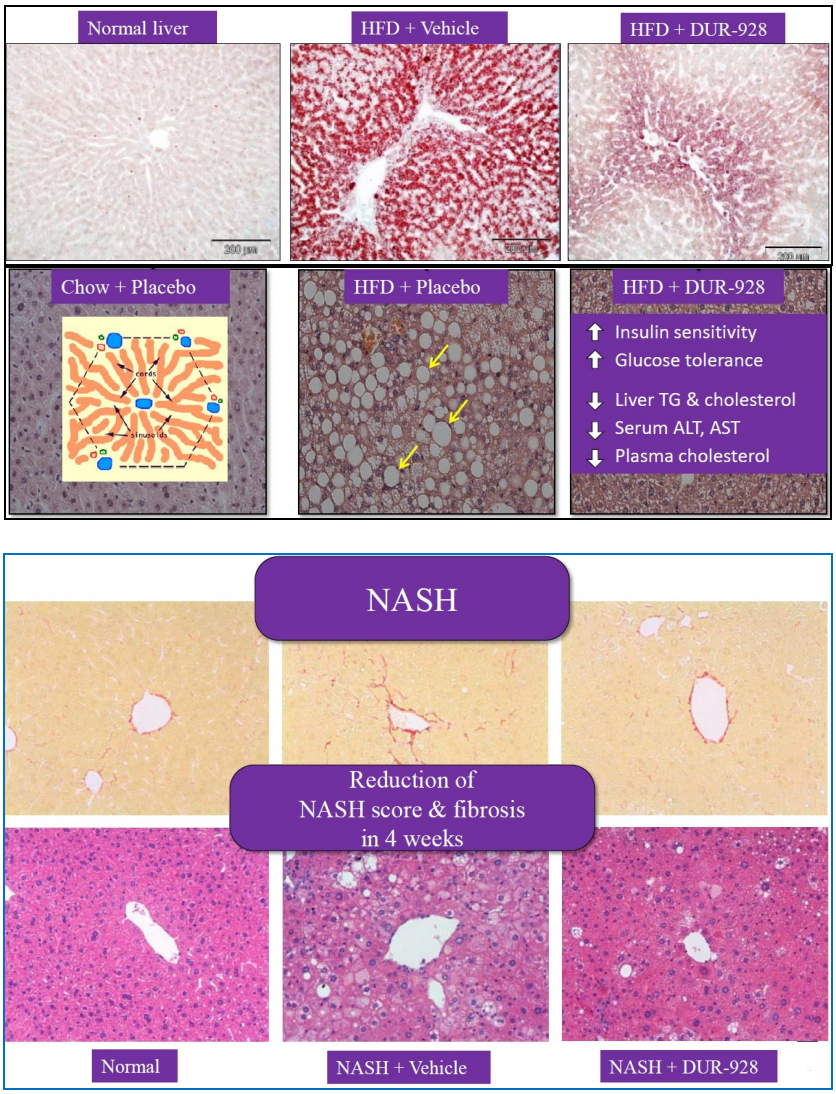
- liver toxicity mouse;
- endotoxin induced septic shock mouse;
- renal ischemia/reperfusion rat; and
- brain ischemia/stroke rat;

Three represent **chronic disorder animal models**. They are:

- high fat diet mouse;

- high fat diet hamster; and
- nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) mouse.

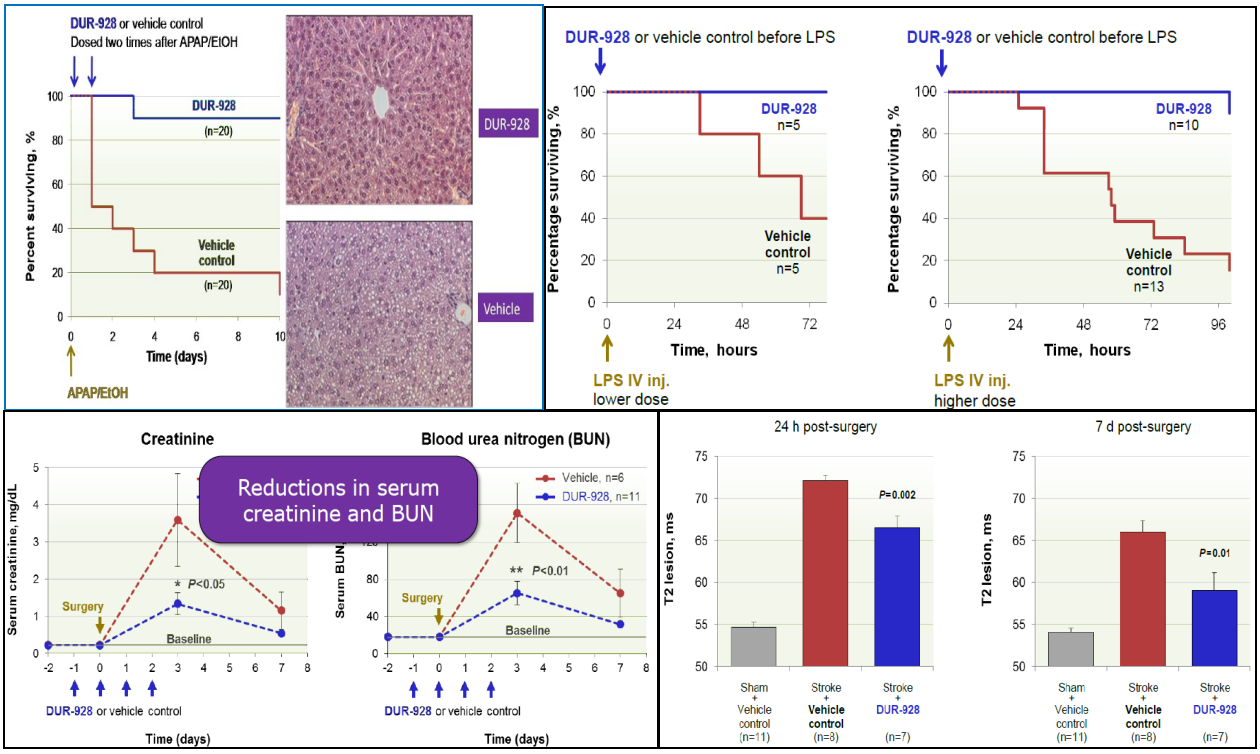
In the three chronic disorder animal models, DUR-928 treatment led to significant improvement in liver morphology and improvement in NAFLD/NASH score and fibrosis.



Top three panels represent the high fat diet mouse model. Middle three panels represent high fat diet hamster model. The bottom six panels represent NAFLD/NASH mouse model.

In all four acute organ injury models, DUR-928 treatment led significant increase in survival.

- In a chemical induced mouse liver toxicity model (upper left panel), 90% mice lived in the DUR-928 group while 90% mice died on the vehicle group.
- In an endotoxin-induced septic shock mouse model (upper right panel), 90-100% mice survived on the DUR-928 group, while only 15-40% mice lived on the vehicle group.
- In an acute kidney injury rat model (lower left panel), DUR-928 significantly reduced creatinine and blood urea nitrogen (BUN) in serum, indicating the organ protection by DUR-928.
- In a brain injury rat model (lower right panel), DUR-928 significantly reduced the T2 lesion (measure of cell viability).



Animal pharmacokinetics and toxicity studies have shown DUR-928 to be orally bioavailable and safe at all doses tested to date.

An injectable formulation, envisioned for use in acute conditions, is currently undergoing animal testing. The company plans to use the oral version of DUR-928 for chronic use and the injectable DUR-928 for acute use.

Positive Phase I Data Reported for Oral Formulation

DURECT recently has completed and reported positive results from two **Phase I** clinical trials with an **oral formulation** of DUR-928.

The initial Phase I trial of DUR-928 was a single-site, randomized, double-blinded, placebo-controlled, **single-ascending-dose** study that evaluated the safety, tolerability and pharmacokinetics of DUR-928 when **orally administered** in 30 subjects. After the completion of the initial single-dose trial, the company subsequently conducted a Phase I **multiple-ascending-dose**, oral administration trial in 20 healthy subjects, evaluating DUR-928 in two consecutive 10-subject cohorts, the first receiving DUR-928 at a lower dose and the second at a higher dose.

In both Phase I clinical trials, DUR-928 was well-tolerated at all dose levels, with no clinically significant changes in vital signs, laboratory values or ECG parameters, no severe or serious drug-related adverse events reported and no subjects withdrawing from the study. Peak plasma concentrations achieved were at least 100-fold higher than endogenous levels, no accumulation in plasma concentrations were observed with repeat dosing, and dose related increases in plasma concentrations were observed with peak plasma concentration at approximately 2 – 6 hours after dosing.

DURECT is now moving on to a multiple-dose **Phase I** trial with the **injectable formulation**. Assuming no adverse safety results from this trial, DURECT would then be positioned to commence patient trials in 2016 with an injectable formulation as well as with an oral formulation.

Large Market Opportunity for DUR-928

Although DUR-928 may have broad applications in many indications, we believe the initial focus will be 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).

According to 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.

Attractive Valuation

We continue to be optimistic about Durect story and maintain our Buy rating for its shares. We reiterate our price target of $6.00 per share based on the progress the company has made in advancing its candidates.

Durect is a late development stage biotech company. Its two Phase III candidates are Posidur and Remoxy. The company and its partner Pain Therapeutics plans to submit a NAD for Remoxy in the 1Q16 and we expect the drug to be approved by the end of 2016.

The company has initiated a new Phase III PERSIST trial with its clinical candidate Posidur. We estimate top line data will be available in 4Q16 or 1Q17 and the FDA approval will take place in late 2017 or early 2018.

Based on our financial model, we expect the company will become profitable in 2018 with an EPS of $0.11 based on total revenue of $70 million, which include royalty revenue from Posidur and Remoxy,

existing product sales and collaborative revenue. EPS will increase to $0.19 in 2020 based on total revenue of $96 million. Based on this model, we come up with a fair value of the company at $3.00 per share, which values the company at $360 million in market cap.

But remember this valuation only considers the company's existing products and the two late stage candidates of Remoxy and Posidur. As we discussed above, among the company's multiple candidates, we are especially optimistic about the company's epigenomic regulator program DUR-928, which holds great potential for multiple indications, such as NASH and acute kidney injury. Based on probability adjusted NPV analysis, we have a fair value of $3 for DUR-928.

We believe even with the only NAFLD/NASH indication, the market is big enough for DUR-928 to support the company's long term growth and valuation. If we look at the valuation of similar companies, we will have some sense how DUR-928 will impact Durect's valuation. We notice that three companies have similar NASH programs. ICPT and RPTP's NASH programs are in Phase II and FGEN's is in Phase I/II. Our $3.00 per share values Durect's DUR-928 program at $360 million in market cap based on 120 million outstanding shares, which is still conservative compared to its peers in our view.

Together our fair value for Durect is $6.00 per share, which values the company at $720 million in market cap. If the company can show positive DUR-928 data for NASH and/or acute kidney injury in the planned Phase II trials, share price can easily double.

Company	Ticker	NASH stage	Current Share Price	Market Cap ($billion)
Intercept Pharmaceuticals	ICPT	Phase II	$135.74	$3.30
FibroGen, Inc.	FGEN	Phase I/II	$27.07	$1.66
Raptor Pharmaceuticals	RPTP	Phase II	$4.29	$0.37
Average			**$55.70**	**$1.78**
DURECT Corporation	DRRX	Phase I/II	$1.76	$0.21

Source: Zacks Investment Research

INCOME STATEMENT

DURECT Corp	2014 A	Q1A	Q2A	Q3A	Q4E	2015 E	2016 E	2017 E	2018 E	2019 E	2020 E
Posidur (Royalty)	$0	$0	$0	$0	$0	$0	$0	$0	$26	$12	$32
YOY Growth	-	-	-	-	-	-	-	-	-	-	*161.9%*
Remoxy (Royalty)	$0	$0	$0	$0	$0	$0	$1.0	$9.7	$22.4	$28.9	$40.3
YOY Growth	-	-	-	-	-	-	-	-	*131.4%*	*28.8%*	*39.7%*
Alzet Pumps & Lactel Polymers	$11.1	$3.0	$2.7	$2.7	$3.0	$11.4	$11.5	$11.5	$11.5	$11.5	$11.5
YOY Growth	*-5.0%*	*9.1%*	*-6.4%*	*7.4%*	*-0.4%*	*2.2%*	*1.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Collaborative Revenue	$8.3	$1.7	$1.8	$2.1	$2.1	$7.7	$8.5	$9.5	$10.0	$11.0	$12.0
YOY Growth	*130.0%*	*-50.5%*	*2.5%*	*17.1%*	*67.1%*	*-7.1%*	*10.9%*	*11.8%*	*5.3%*	*10.0%*	*9.1%*
Total Revenues	**$19.4**	**$4.8**	**$4.4**	**$4.7**	**$5.1**	**$19.1**	**$21.0**	**$30.7**	**$69.9**	**$63.6**	**$95.9**
YOY Growth	*26.6%*	*-24.2%*	*-3.1%*	*11.4%*	*19.5%*	*-1.8%*	*10.2%*	*46.1%*	*127.7%*	*-8.9%*	*50.8%*
Cost of Goods Sold	$5.7	$1.0	$1.0	$0.9	$1.1	$4.0	$4.5	$4.8	$5.0	$5.2	$5.5
Product Gross Margin	*49.0%*	*66.9%*	*61.6%*	*67.1%*	*63.0%*	*64.7%*	*60.9%*	*58.3%*	*56.5%*	*54.8%*	*52.2%*
SG&A	$12.3	$2.8	$2.7	$3.2	$3.2	$11.9	$13.0	$14.0	$15.0	$16.0	$18.0
% SG&A	*63.3%*	*59.1%*	*61.3%*	*67.0%*	*62.7%*	*62.6%*	*61.9%*	*45.6%*	*21.5%*	*25.1%*	*18.8%*
R&D	$22.4	$5.4	$5.6	$6.7	$7.5	$25.2	$30.0	$32.0	$35.0	$40.0	$45.0
% R&D	*115.6%*	*112.4%*	*127.0%*	*140.3%*	*147.1%*	*132.0%*	*142.9%*	*104.3%*	*50.1%*	*62.9%*	*46.9%*
Operating Income	($21.0)	($4.4)	($4.9)	($6.0)	($6.7)	($22.0)	($26.5)	($20.1)	$14.9	$2.4	$27.4
Operating Margin	*-108.2%*	-	-	-	-	*-115.7%*	*-126.2%*	*-65.5%*	*21.3%*	*3.8%*	*28.6%*
Interest & Other Net	($1.0)	($0.4)	($0.5)	($0.5)	($0.5)	($2.0)	($2.0)	($1.0)	($1.0)	($1.0)	($1.0)
Pre-Tax Income	($22.0)	($4.9)	($5.5)	($6.5)	($7.2)	($24.0)	($28.5)	($21.1)	$13.9	$1.4	$26.4
Taxes	$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%*
Net Income	($22.0)	($4.9)	($5.5)	($6.5)	($7.2)	($24.0)	($28.5)	($21.1)	$13.9	$1.4	$26.4
YOY Growth	-	-	-	-	-	-	-	-	-	*-89.7%*	*1756.3%*
Reported EPS	($0.20)	($0.04)	($0.05)	($0.05)	($0.06)	($0.20)	($0.23)	($0.17)	$0.11	$0.01	$0.19
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
Shares Outstanding	111.6	113.8	118.8	120.5	122.0	118.8	122.0	125.0	130.0	135.0	140.0

Source: company filings and Zacks estimates

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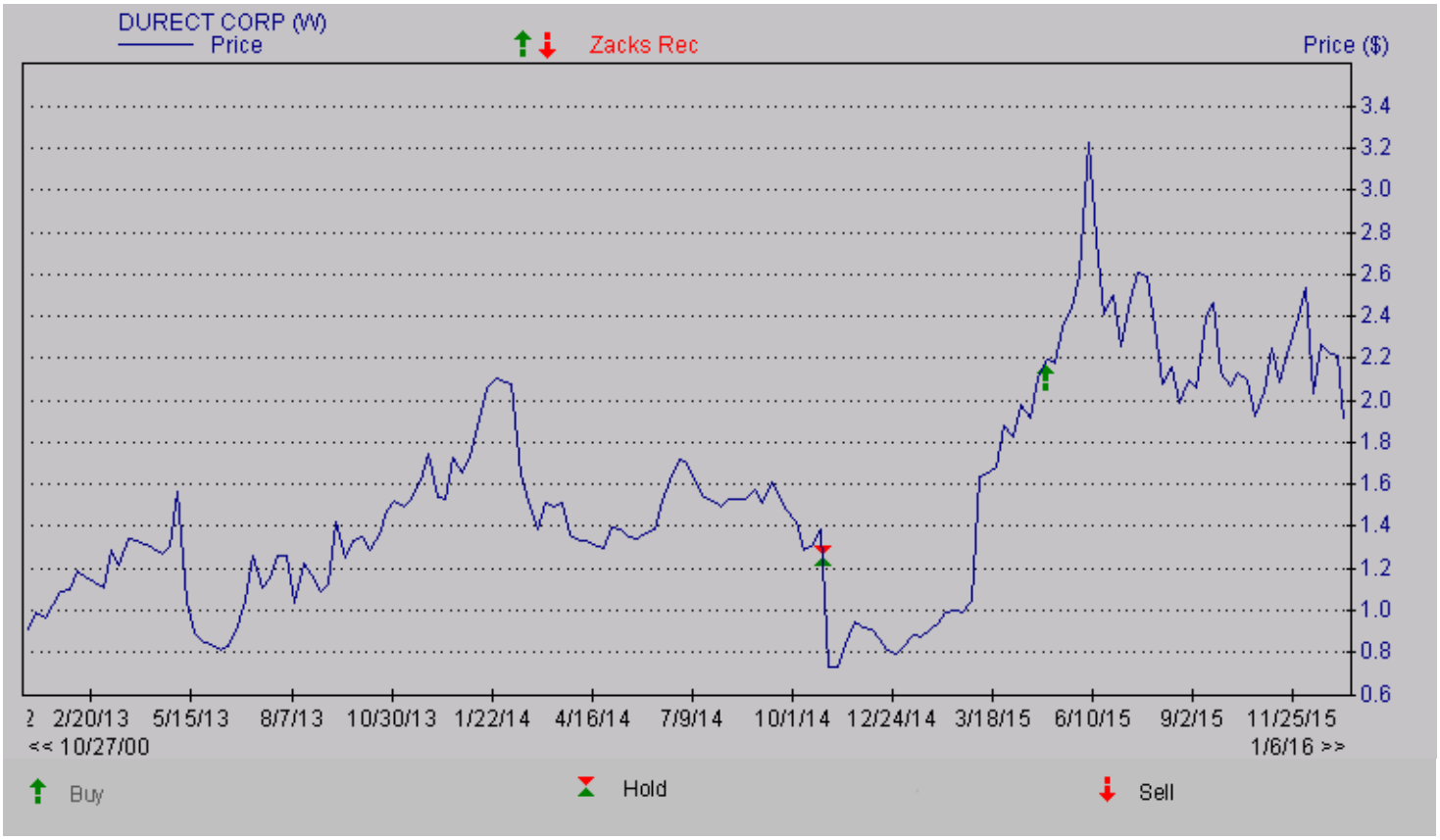

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Sell/Underperform: The analyst expects the company will underperform the broader U.S. Equity market over the next one to two quarters.

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