Zacks Small-Cap Research

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Arrowhead Research (ARWR-NASDAQ)

ARWR: Strong balance sheet, New clinical candidate nominated, on track to complete Phase II a and initiate Phase IIb of ARC-520 – maintaining Outperform

Current Recommendation	**Outperform**
Prior Recommendation	N/A
Date of Last Change	06/11/2013
Current Price (08/15/14)	$13.94
Twelve- Month Target Price	**$28.00**

OUTLOOK

ARWR is a clinical stage biotech company focused on RNAi targeted therapy using DPC platform technology.

We are optimistic about the Company's lead program ARC-520 for HBV. ARWR presented Phase I data recently and is on track to release top line data of Phase IIa in 3Q14. The Company plans to initiate Phase IIb of ARC-520 in 4Q14. The Company just announced its second clinical candidate ARC-AAT for liver disease.

Balance sheet is strong.

We are optimistic about the prospect of ARWR. And maintain our Outperform rating on its shares.

SUMMARY DATA

52-Week High	**$26.57**
52-Week Low	**$3.80**
One-Year Return (%)	**248.52**
Beta	**2.83**
Average Daily Volume (sh)	**3,300,582**
Shares Outstanding (mil)	**53**
Market Capitalization ($mil)	**$723**
Short Interest Ratio (days)	**3.12**
Institutional Ownership (%)	**59**
Insider Ownership (%)	**2**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2013 Estimate	**N/A**
P/E using 2014 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**Small-Growth**
Industry	**Biotechnology**
Zacks Rank in Industry	**N/A**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2013	0.16 A	0.04 A	0.04 A	0.04 A	0.29 A
2014	0.04 A	0.04 A	0.04 A	0.04 E	0.17 E
2015					0.30 E
2016					0.30 E

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

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2013	-$0.33 A	-$0.41 A	-$0.18 A	-$0.35 A	-$1.24 A
2014	-$0.19 A	-$0.25 A	-$0.24 A	-$0.25 E	-$0.94 E
2015					-$0.86 E
2016					-$0.87 E

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

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WHAT'S NEW

- **Balance sheet remains strong;**
- **Update on ARC-520 Phase IIb study;**
- **New clinical candidate announced and targeting liver disease;**
- **We raise our price target to $28 per share anticipating positive Phase IIa data;**

Arrowhead Reported Fiscal 2014 Third Quarter Financial Results with a Strong Balance Sheet

On August 12, 2014, Arrowhead Research Corporation (ARWR) announced financial results for its fiscal 2014 third quarter ended June 30, 2014 and provided an update on the **Phase IIa** study of ARC-520.

There was no meaningful revenue for the fiscal third quarter of 2014.

R&D expenses were $6.4 million for fiscal 3Q14, compared to $1.8 million for fiscal 3Q13.

SG&A expenses were $4.0 million for fiscal 3Q14, compared to $2.6 million for fiscal 3Q13.

Total operating expenses for the quarter were $12.7 million, compared to $6.4 million for the quarter ended June 30, 2013.

Net loss for the fiscal third quarter of 2014 was $11.6 million ($0.22 per share), compared to a net loss of $6.1 million ($0.23 per share) for the quarter ended June 30, 2013.

Net cash used in operating activities for the first nine months of fiscal 2014 was $24.5 million, compared with $13.6 million in the prior year period.

The Company's balance sheet remains strong. As of June 30, 2014, the company's cash and investments of cash were $188.5 million.

In February, 2014, Arrowhead closed an underwritten offering of 6,325,000 shares of common stock. The offering was priced at $18.95 per share and the company received gross proceeds of approximately $120 million.

The Company's current cash should be able to fund the planned Phase IIb and Phase III trial. The strengthened balance sheet will allow the Company to accelerate the development of its pipeline.

Update on ARC-520 Phase IIa Study

The Phase IIa trial began doing patients on March 24, 2014 in Hong Kong.

The Phase IIa study was planned to enroll up to 16 chronic HBV patients in **two dose cohorts** with patients receiving either ARC-520 or placebo **in combination with entecavir**. **Primary endpoints** will be safety and tolerability as well as depth and duration of surface antigen knock down. Patients will be followed until surface antigen levels return to baseline.

The company has **completed dosing** of 1 mg/kg and 2 mg/kg dose cohorts. ARC-520 continues to be well tolerated, with no dropouts or serious adverse events reported. The overall rate of AEs has been lower in the Phase IIa than in the Phase I normal volunteer study and safety labs continue to show no indication of end organ toxicity.

Initial blinded data suggest that the magnitude of HBsAg knockdown is similar to non-human primate studies, including the chronically infected chimpanzee reported on previously. Duration of knockdown

appears to be substantially more sustained than in non-human primates, with patients in the 2 mg/kg group still demonstrating substantial knockdown after 8 weeks, which is the most recent time point available.

HBsAg levels appear to continue to decline in a number of patients at the 8 week time point in the 2 mg/kg group.

Based on the initial review, dosing less frequent than once monthly will be explored in Phase IIb.

Due to the excellent safety profile of ARC-520, and because Arrowhead thought that ARC-520 could demonstrate even deeper knockdown of HBsAg, the company decided to explore 3 mg/kg in patients. The company has begun dosing that cohort. Arrowhead sees limited downside risk at this dose, because it completed a **3 mg/kg** cohort in healthy volunteers and that safety profile was quite positive and consistent with all other groups tested.

We are pleased to see that the trial remains on schedule to meet the previously stated goal of releasing **top line** results in the third quarter.

Phase IIb Will Be Initiated in 4Q14

Based on the Phase IIa data, **Phase IIb** study of ARC-520 will begin in 4Q14 that will test two dose levels in e-antigen negative anti-antigen positive patients on entecavir or tenofovir. Preparation of this Phase IIb study is underway. The Phase IIb will be a multi-dose, multi-national, and will likely include sites in the US, Europe and Asia. The Phase IIb study is designed to provide a read out on ARC-520's ability to achieve functional cure, among other outcome measures. We estimate top line results from the Phase IIb trial will be available in **mid-2015**.

We are pleased that the company is on track to advance ARC-520. Based on preclinical and the Phase I clinical studies, we are highly confident that the Phase IIa and Phase IIb trial will have a high possibility to be successful.

We expect Arrowhead will be able to initiate **pivotal Phase III** trial of ARC-520 in late 2015 or early 2016, and data should be available in late 2016. NDA could be filed in 1H2017, and the FDA approval is in late 2017 or early 2018.

We think ARC-520 is the primary value driver in near- and mid-term for Arrowhead. The successful development of ARC-520 is critical to Arrowhead because the HBV market offers opportunities for substantial revenues, and because validation of the Company's RNAi delivery technology opens broad opportunities both for other therapeutic programs and licensing opportunities.

In this regard, the completion of the Phase I study and the initiation of the Phase IIa of ARC-520 represent an important milestone for Arrowhead in achieving its long term growth goal. One of the attractive features of RNAi and of DPCs specifically is once the safety profile in man for the delivery system has been established, additional targets and candidates can be studied rapidly. Therefore the Phase I trial of ARC-520 will provide the company with the data needed to accelerate the development of its pipeline and bring additional candidates into the clinic.

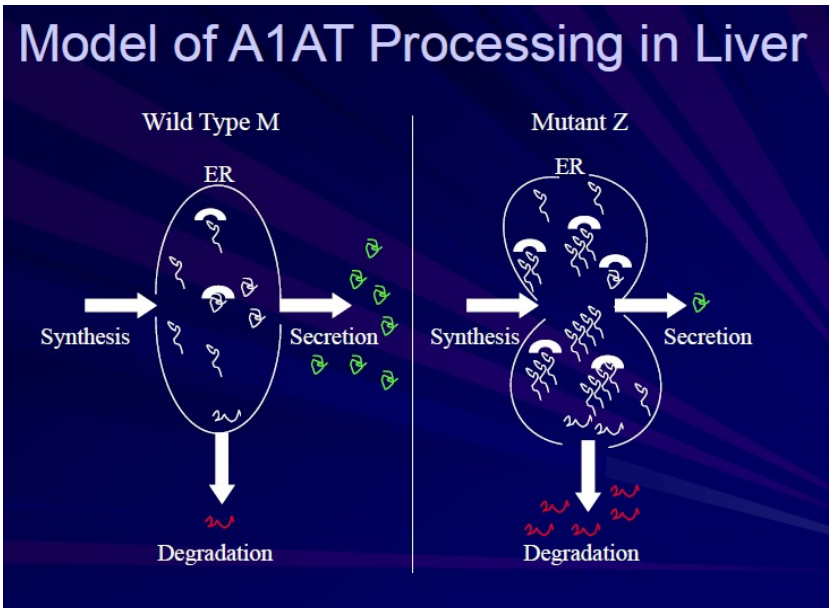
New Clinical Candidate ARC-AAT Announced

On June 19, 2014 at Analyst Day held in New York City, Arrowhead announced its second clinical candidate **ARC-AAT** for the treatment of Alpha-1 antitrypsin deficiency (**AATD**)-associated **liver disease.**

AATD is an autosomal recessive genetic disorder associated with liver disease in children and adults and pulmonary disease in adults. Alpha-1 antitrypsin is a **protease inhibitor** of a circulating glycoprotein of the serpin family encoded by the AAT gene and primarily synthesized in the liver. The physiologic

function of AAT is inhibition of neutrophil proteases to protect healthy tissues during inflammation and prevent tissue damage. This is especially important **in the lung**.

The Z mutant is the most common disease variant and has a single amino acid substitution that results in improper protein folding causing severe impairment of secretion from hepatocytes. This lack of secretion leads to **accumulation** of mutant **Z-AAT** polymers, which form globules in the hepatocyte endoplasmic reticulum. This triggers continuous hepatocyte injury, leading to fibrosis, cirrhosis, and increased risk of hepatocellular carcinoma.



Source: Company presentation

Approximately 96-98% of AATD-related disease is due to the homozygous PiZZ genotype. The mean estimated prevalence of AATD in the U.S is 1 per 3000-5000, or approximately 100,000 patients.

Estimated U.S. PiZZ AATD Prevalence	Publication
80,000	Stolk et al, Internat J COPD, 2006
70,000	Stoller J, Aboussouan L, Am J Respir Crit Care Med, 2012
47,000	De Serres FJ Chest, 122,5(2002)
34,000	De Serres FJ, Ther Adv Respir Dis 6(5) 2012, 277-295
100,000	Alpha-1 Antitrypsin Deficiency Diagnosis and Standards, American Thoracic Society, 2003.
70,500	Stoller J, Lancet 2005; 365: 2225-36
62,800-157,000	Teckman, COPD 10(S1):35-43 2013
61,605	O Brien ML et al, J Pediatric 1978
Mean U.S. Prevalence ~76,000	

Source: Company presentation

AATD is also an important cause of **pediatric liver disease** with an estimated prevalence in children of approximately 20,000 patients, and 50-80% likely to manifest liver disease during childhood.

AATD Liver Disease in Children	Estimated U.S. Prevalence
Total PiZZ prevalence in children	20,000
Liver disease during childhood (50-80%)	10,000-16,000
Severe liver disease (20%)	2,000-3,200
Liver Fibrosis	500-800
Transplant	250-400

Source: Company presentation

AATD is considered to be a relatively **high prevalence orphan disease**, and it is frequently misdiagnosed or undiagnosed. European prevalence is estimated to be 1 per 2500.

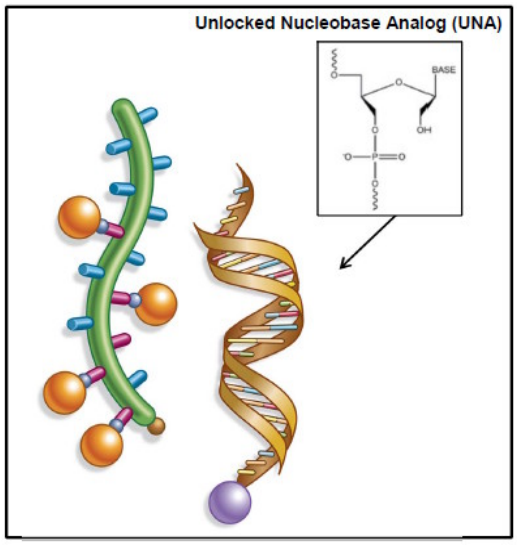
PiZZ individuals have severe deficiency of functional AAT leading to pulmonary disease and hepatocyte injury and liver disease. **Lung disease** is frequently treated with AAT **augmentation therapy**. However, augmentation therapy does nothing to treat liver disease, and there is no specific therapy for hepatic manifestations. There is a significant unmet need as **liver transplant** is currently the only available cure.

Arrowhead's ARC-AAT Targets the AAT Gene

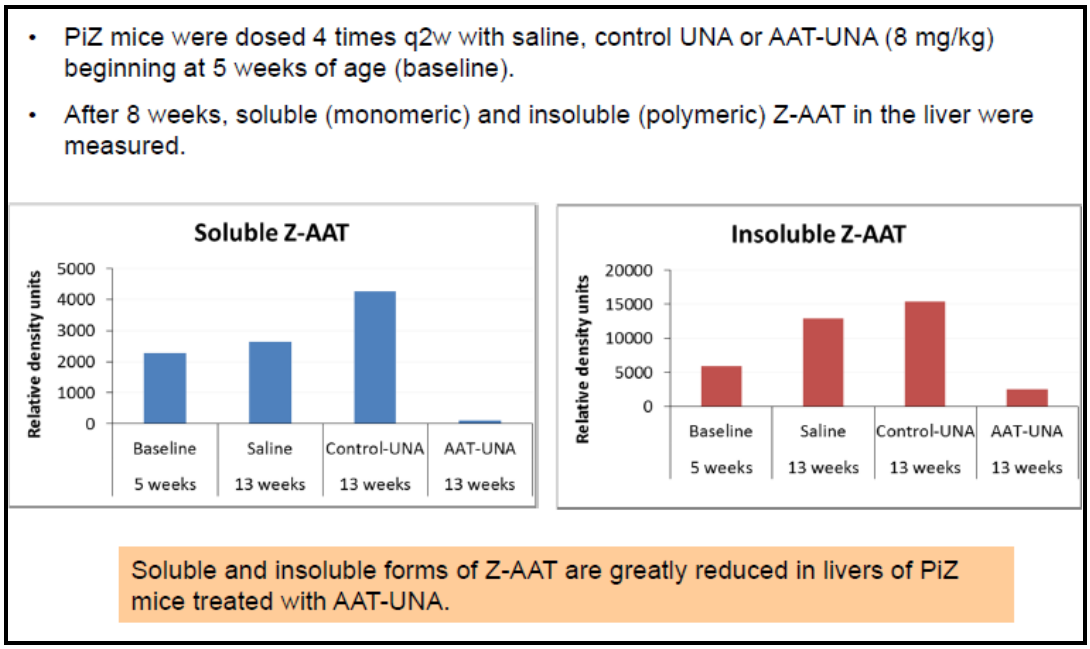
ARC-AAT is an RNAi therapeutic based on the Company's Dynamic Polyconjugate **(DPC**) platform technology. ARC-AAT is designed to treat liver disease associated with Alpha-1 antitrypsin deficiency (AATD). The rational for the design of ARC-AAT is based on the following assumptions: inhibition of Z-AAT production by silencing AAT gene can

- Prevent accumulation of disease causing protein,
- Allow clearance of accumulated protein,
- Prevent repeated cycles of cellular damage and tissue repair,

The RNAi selection process is rigorous for ARC-AAT. Arrowhead has developed a novel unlocked nucleobase analog (**UNA)**-containing RNAi molecule designed for systemic delivery using the DPC delivery system. Incorporation of UNA into the ARC-ATT is associated with improved duration.

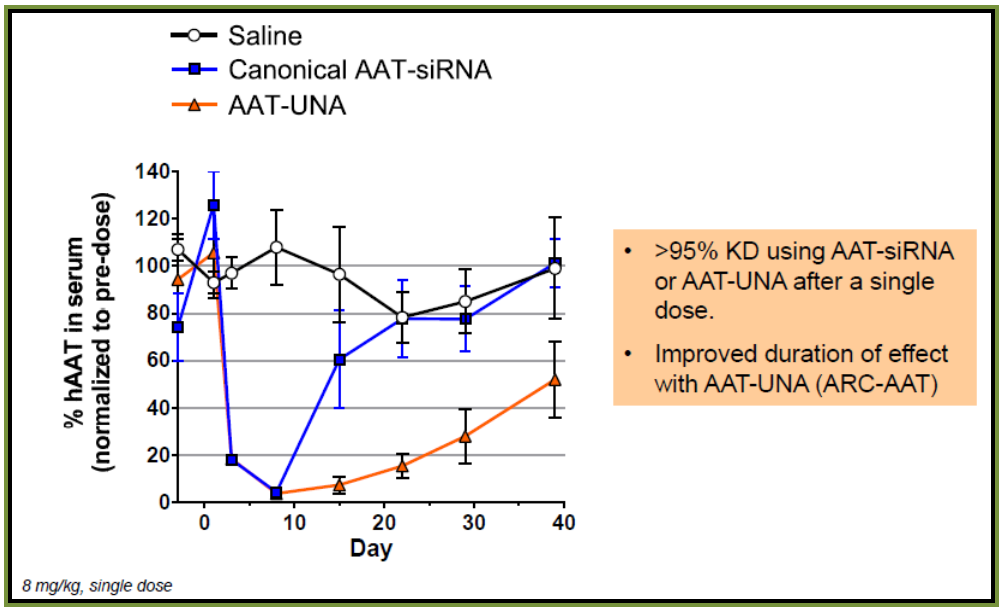


In preclinical PiZ **mouse model**, which is genetically modified to produce the mutant human AAT (Z-AAT), ARC-AAT induced a greater than 95 percent reduction in circulating AAT after a single dose. After eight weeks of treatment in multi-dose studies, soluble (monomeric) and insoluble (polymeric) forms of Z-AAT were greatly reduced in the livers of PiZ mice treated with ARC-AAT. In addition, liver globule burden was substantially reduced from baseline levels and in comparison to treatment with saline, which showed progressive globule formation.



Source: Company presentation

The addition of the UNA slowed the rebound in production of AAT compared to canonical siRNAs, and produced a substantially improved duration of effect. In **primate** studies, knockdown of AAT in serum persisted for over ten weeks with greater than 80 percent knockdown observed at the six-week time point.



Source: Company presentation

Clinical Development Plan for ARC-AAT

Based on the preclinical results, Arrowhead plans to file an IND application for ARC-AAT in 4Q14.

According to management, initial testing will be in **adult patients** with signs of liver injury, with the intention of preventing additional injury and improving liver histology. In the future, additional studies may be initiated to investigate treatment of children, including those with severe hepatic disease who may otherwise require liver transplant.

Arrowhead has signed an agreement with the Alpha-1 Project (TAP), a subsidiary of the **Alpha-1 Foundation**. Under the terms of the agreement, TAP will partially fund the development of ARC-AAT. In addition to the funding, TAP will make its scientific advisors available to Arrowhead, assist with patient recruitment for clinical trials thanks to the Alpha-1 Foundation Patient Research Registry, and engage in other collaborative efforts that support the development of ARC-AAT.

We are pleased to see that Arrowhead is diversifying its pipeline by nominating a second clinical candidate, which further de-risk its pipeline. In the absence of specific therapy other than liver transplant for AATD associated liver disease, we believe RNAi holds great potential.

With the experience of two candidates ARC-520 and ARC-AAT, the DPC platform, as well as a strong balance sheet, we believe Arrowhead is well positioned to further diversify its pipeline down the road.

We remain bullish on Arrowhead shares

We maintain our Outperform rating on Arrowhead shares, and raise our price target to $28 from previous $18.75 per share.

Recent pullback provides a buying opportunity. Current market price does not reflect the intrinsic value of the Company. At current market price, we think there is still enough room for further price appreciation.

Recent clinical advancement from RNAi companies such as Alnylam Pharmaceuticals and other small companies has validated the RNAi platform. The $700 million investment by Sanofi in Alnylam pushed the valuation of Alnylam to $5 billion at current market price.

Currently, Arrowhead shares are trading at around $14 per share, which values the Company at about $742 million in market cap based on 53 million outstanding shares. Of course, ARWR's pipeline is not as diversified as that of Alnylam and its lead program of ARC-520 is still in Phase II trial. The Company just announced second clinical candidate targeting AATD associated liver disease. ARWR looks more like an early stage Alnylam. The Company's DPC platform technology has the potential to target any indication.

The Company's anti-HBV drug candidate ARC-520 has demonstrated compelling efficacy data and safety profile in animal studies and is safe and well tolerated in humans. The positive Phase I data of ARC-520 further de-risk Arrowhead. ARC-520 has the potential for functional cure of HBV infection. We estimate that ARC-520 could be approved in the US in 2017 and has a blockbuster potential.

Our financial model indicates that ARWR will be profitable in 2018 with EPS of $0.64 per share. EPS will grow to $1.77 per share in 2019 based on total revenue of $250 million. We think ARWR shares should be valued using 40 x P/E multiple, and 20% discount rate. Based on this relative value metrics, our model shows that ARWR should be valued at $28 per share. Our price target values Arrowhead at $1.48 billion in market cap, which we think is a fair value to Arrowhead.

Following are the near term catalysts:

- 3Q14, to release top line results from the Phase IIa study;

- 4Q14, to initiate multi-dose Phase IIb study or ARC-520;
- 4Q14, to file an IND for ARC-AAT.

PROJECTED INCOME STATEMENT

-		2014 (Sept)					2015 (Sept)	2016 (Sept)	2017 (Sept)	2018 (Sept)	2019 (Sept)
$ in millions except per share data	FY	Q1	Q2	Q3	Q4	FYE	FYE	FYE	FYE	FYE	FYE
Revenue	$0.29	$0.04	$0.04	$0.04	$0.04	$0.17	$0.30	$0.30	$10.00	$125.00	$250.00
YOY Growth								-	*3233.3%*	*1150.0%*	*100.0%*
Total Revenues	**$0.29**	**$0.04**	**$0.04**	**$0.04**	**$0.04**	**$0.17**	**$0.30**	**$0.30**	**$10.00**	**$125.00**	**$250.00**
YOY Growth	*97.6%*	*-73.0%*	*0.0%*	*0.0%*	*-1.7%*	*-40.2%*	*72.9%*	*0.0%*	*3233.3%*	*1150.0%*	*100.0%*
Cost of Revenue	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$1.5	$18.8	$35.0
Gross Income	**$0.3**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.2**	**$0.3**	**$0.3**	**$8.5**	**$106.3**	**$215.0**
Gross Margin	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*85.0%*	*85.0%*	*86.0%*
R&D	$8.7	$3.1	$5.2	$6.4	$7.2	$21.9	$23.0	$25.0	$15.5	$17.0	$20.0
% R&D	*2999.2%*	*7286.1%*	*11923.3%*	*14610.7%*	*16744.2%*	*12646.5%*	*7666.7%*	*8333.3%*	*155.0%*	*13.6%*	*8.0%*
SG&A	$10.2	$3.0	$4.4	$4.0	$4.5	$16.0	$18.5	$20.0	$25.0	$27.5	$32.0
% SG&A	*3499.0%*	*6966.5%*	*10161.3%*	*9227.2%*	*10465.1%*	*9209.3%*	*6166.7%*	*6666.7%*	*250.0%*	*22.0%*	*12.8%*
Other expenses	$6.0	$0.9	$1.6	$2.3	$1.4	$6.2	$5.5	$7.0	$8.5	$10.0	$12.0
% Other	*2073.1%*	*2150.1%*	*3643.9%*	*5290.8%*	*3255.8%*	*3592.8%*	*1833.3%*	*2333.3%*	*85.0%*	*8.0%*	*4.8%*
Operating Income	**($24.6)**	**($7.0)**	**($11.2)**	**($12.7)**	**($13.1)**	**($44.0)**	**($46.7)**	**($51.7)**	**($40.5)**	**$51.8**	**$151.0**
Operating Margin	-	-	-	-	-	-	-	-	-	-	*60.4%*
Other Income (Net)	($6.6)	($3.6)	($2.7)	$1.1	($0.5)	($5.8)	($0.5)	($0.5)	($0.5)	($0.5)	($0.5)
Pre-Tax Income	**($31.1)**	**($10.6)**	**($13.9)**	**($11.6)**	**($13.6)**	**($49.8)**	**($47.2)**	**($52.2)**	**($41.0)**	**$51.3**	**$150.5**
Net Taxes (benefit)	$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%*
Reported Net Income	**($31.1)**	**($10.6)**	**($13.9)**	**($11.6)**	**($13.6)**	**($49.8)**	**($47.2)**	**($52.2)**	**($41.0)**	**$51.3**	**$150.5**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
Net Margin	-	-	-	-	-	-	-	-	-	-	-
Weighted avg. Shares Out	*24.0*	*37.7*	*44.3*	*51.9*	*53.0*	*46.7*	*55.0*	*60.0*	*70.0*	*80.0*	*85.0*
Reported EPS	**($1.30)**	**($0.28)**	**($0.31)**	**($0.22)**	**($0.26)**	**($1.06)**	**($0.86)**	**($0.87)**	**($0.59)**	**$0.64**	**$1.77**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
One time charge	$7.00	$3.62	$2.73	($1.07)	$0.50	$5.78	$0.00	$0.00	$0.00	$0.00	$0.00
Non GAAP Net Income	**($24.1)**	**($7.0)**	**($11.2)**	**($12.7)**	**($13.1)**	**($44.0)**	**($47.2)**	**($52.2)**	**($41.0)**	**$51.3**	**$150.5**
Non GAAP EPS	**($1.01)**	**($0.19)**	**($0.25)**	**($0.24)**	**($0.25)**	**($0.94)**	**($0.86)**	**($0.87)**	**($0.59)**	**$0.64**	**$1.77**

Source: Company filing and Zacks Investment Research estimates

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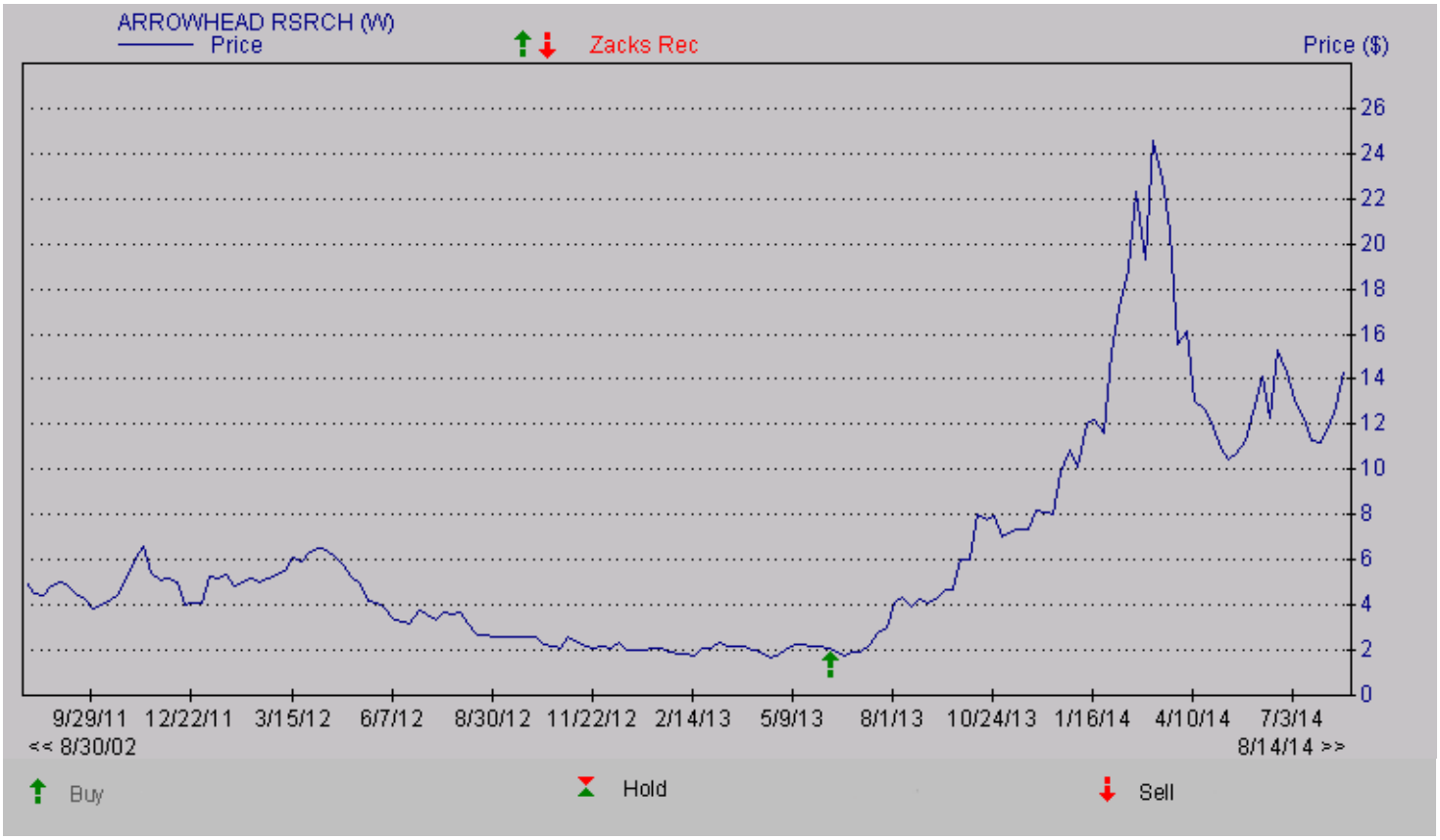
HISTORICAL ZACKS RECOMMENDATIONS



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Hold/Neutral: The analyst expects that the company will perform in line with the broader U.S. equity market over the next one to two quarters.
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