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September 10, 2018
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Arrowhead Pharm (ARWR-NASDAQ)

ARWR: Positive clinical data presented for ARO-HBV, Amgen collaboration programs are advancing; New clinical data presented for ARO-AAT; Balance sheet remains strong;

Relative valuation metrics indicates a fair value at $30/share.

OUTLOOK

After discontinuation of three DPCiv programs, Arrowhead shifted its focus on subcutaneous and extra-hepatic therapeutics.

Two Phase I study are ongoing with positive interim data presented.

New financing will extend its cash runway into 2019.

We remain optimistic about Arrowhead's prospect.

Current Price (09/07/18)	$19.74
Valuation	**$30.00**

SUMMARY DATA

52-Week High	**$19.74**
52-Week Low	**$2.79**
One-Year Return (%)	**534.73**
Beta	**1.91**
Average Daily Volume (sh)	**2,904,775**
Shares Outstanding (mil)	**88**
Market Capitalization ($mil)	**$1,738**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**N/A**
Insider Ownership (%)	**N/A**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**227.8**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2018 Estimate	**-29.6**
P/E using 2019 Estimate	**-33.5**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**Mid-Growth**
Industry	**Med-Drugs**
Zacks Rank in Industry	**N/A**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2016	0.04 A	0.04 A	0.04 A	0.03 A	0.16 A
2017	4.37 A	8.99 A	9.34 A	8.71 A	31.4 A
2018	3.50 A	0.65 A	0.73 A	0.50 E	5.39 E
2019					5.00 E

Price/Sales Ratio (Industry = 2.5x)

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2016	-$0.32 A	-$0.35 A	-$0.32 A	-$0.34 A	-$1.34 A
2017	-$0.21 A	-$0.08 A	-$0.08 A	-$0.14 A	-$0.50 A
2018	-$0.18 A	-$0.18 A	-$0.18 A	-$0.22 E	-$0.76 E
2019					-$0.84 E

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

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WHAT'S NEW

Clinical Data of ARO-HBV Presented

On Sep. 6, 2018, Arrowhead presented initial clinical data for **ARO-HBV** at the 18th World Gastroenterologists Summit in Auckland, New Zealand. ARO-HBV is the company's third generation subcutaneously (SC) administered RNAi therapeutic being developed as a potentially curative therapy for patients with chronic hepatitis B virus (HBV) infection.

Background of the ARO-HBV Program

In Mach 2018, Arrowhead initiated a **Phase I/II** first-in-human study of **ARO-HBV** for the treatment of chronic hepatitis B virus **(HBV)** infection in New Zealand. Dosing began on May 14, 2018.

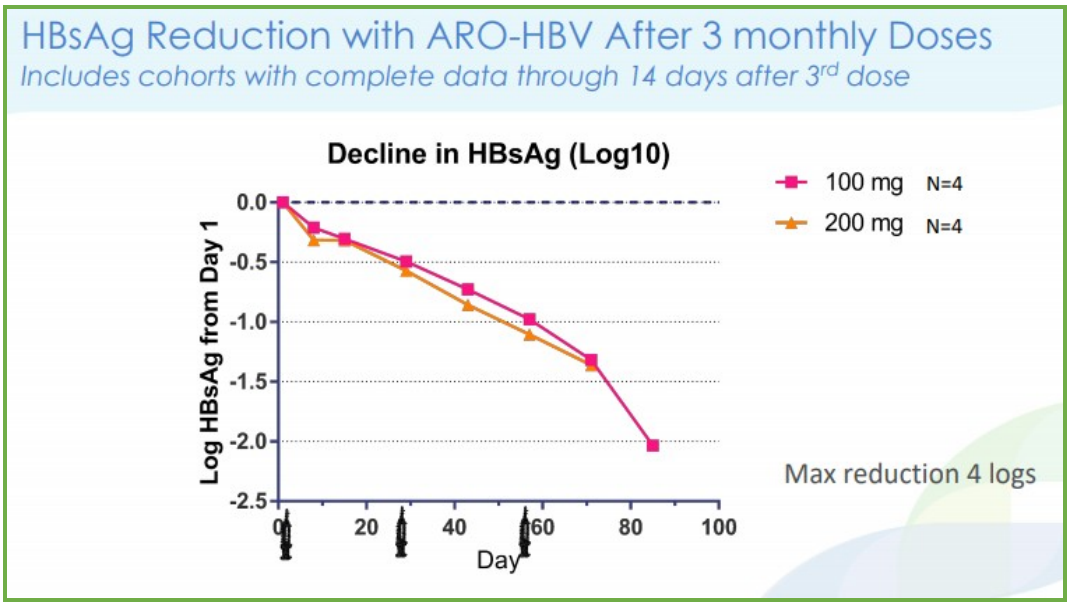
The study, **AROHBV1001** (NCT03365947), is a Phase I/II study to evaluate the safety, tolerability, and pharmacokinetic effects of single-ascending doses (**SAD**) of ARO-HBV in healthy adult volunteers, and to evaluate the safety, tolerability, and pharmacodynamic effects of multiple-ascending doses (**MAD**) of ARO-HBV in patients with chronic HBV.

The SAD portion is designed to include up to 5 cohorts of 6 subjects per cohort. Each SAD subject will receive a single-dose administration of either placebo or ARO-HBV at up to 5 dose levels (35, 100, 200, 300, 400 mg). The MAD portion is designed to include up to 8 cohorts of 4 HBV patients per cohort. Each MAD patient will receive 3 doses of ARO-HBV at up to 4 dose levels (100, 200, 300, 400 mg).

In May 2018, the company completed enrollment and dosing of all 5 planned cohorts of healthy adult volunteers in the SAD portion of the Phase I/II study of ARO-HBV. The first 2 MAD cohorts at doses of 100 mg and 200 mg have been fully enrolled.

The Clinical Data Presented at the Summit

At the Summit, Arrowhead presented initial data of **eight patients** from the first two MAD dose cohorts of the AROHBV1001 clinical study: 100mg and 200mg.



Following is the summary of the key clinical data presented at the Summit:

- Maximum reduction of HBsAg was 4.0 log10 (99.99%) after three monthly doses of ARO-HBV
- Mean reduction of HBsAg was 2.0 log10 (99%) on day 85 in cohort 2b (100 mg) and 1.4 log10 (96%) on day 71 in cohort 3b (200 mg)
- Minimum HBsAg reduction in all patients from cohorts 2b and 3b was 1.2 log10 (93%)
- Activity was demonstrated in all patient types (HBeAg pos/neg, NUC naïve/treated)

ARO-HBV was generally well-tolerated with generally mild and self-limiting injection site adverse events being the most common reported event in chronic HBV patients, occurring in around 10% of injections. The other most commonly reported events included symptoms consistent with upper respiratory tract infection and headache.

These results represent the first clinical data presented on ARO-HBV, which was very encouraging in our view. The data indicated that ARO-HBV is highly active in the treatment of HBV with good safety profile.

The company intends to submit a late-breaking abstract with additional clinical data to the Liver Meeting®, the Annual Meeting of the American Association for the Study of Liver Disease (AASLD), being held in November 2018.

Update on Fiscal Third Quarter Financials

Total revenue was $0.93 million and $9.34 million for the three months ended June 30, 2018 and 2017, respectively.

Revenue for the fiscal third quarter of 2018 was primarily related to the upfront payments received from Amgen in 2016 that was recognized as revenue as performance is completed for the ARO-LPA (AMG-890) and ARO-AMG1 Agreements. The decrease during the three months ended June 30, 2018 was driven by a reduction in the amount of revenue recognized associated with the $30 million upfront payment received from Amgen associated with the ARO-LPA (AMG-890) Agreement.

R&D expenses for the fiscal third quarter of 2018 was $12 million.

G&A expenses for the fiscal third quarter of 2018 was $4.6 million.

Net loss for the fiscal third quarter of 2018 was $15.6 million ($0.18 per share).

As of June 30, 2018, the Company had cash and investments of $78.2 million.

In January 2018, Arrowhead closed an underwritten public offering of 11,500,000 shares of its common stock, which included shares issued upon the exercise in full by the underwriters of their option to purchase 1,500,000 additional shares.

The offering was priced at $5.25 per share, and the company received gross proceeds of approximately $60.4 million.

Current financial resources are sufficient to fund its operations for next two years according to our financial model.

Update on Amgen Collaboration Programs

On August 1, 2018, Arrowhead announced that it has earned a $10 million milestone payment from Amgen following the administration of the first dose of AMG 890, formerly referred to as ARO-LPA, in a clinical study.

Amgen is evaluating **AMG 890** in a **Phase I** clinical study designed to assess its safety in volunteers with elevated levels of lipoprotein (a) (Lp(a)). AMG 890 is an RNAi therapeutic designed to lower Lp(a) for the treatment of cardiovascular disease.

In September 2016, Arrowhead announced two license and collaboration agreements with Amgen to develop and commercialize **two cardiovascular programs** based on Arrowhead's RNAi platform.

These programs will utilize Arrowhead's proprietary **subcutaneous RNAi delivery technology**.

Pursuant to one agreement, Amgen receives a worldwide, exclusive license to Arrowhead's novel, RNAi **ARC-LPA program**, which is designed to reduce production of apolipoprotein A, a key component of lipoprotein(a), which has been genetically linked with increased risk of cardiovascular diseases, independent of cholesterol and LDL levels. ARC-LPA is Arrowhead's first drug candidate to use a subcutaneously administered delivery construct. Elevated lipoprotein(a), or Lp(a), is widely viewed as a key risk factor for cardiovascular diseases, including coronary artery disease, atherosclerosis, thrombosis and stroke.

Under the second agreement, Amgen receives an option to a worldwide, exclusive license for a RNAi therapy for an **undisclosed genetically validated cardiovascular target**.

In both agreements, Amgen will be wholly responsible for clinical development and commercialization.

In connection with the two collaborations, Arrowhead will receive $35 million in upfront payments; $21.5 million in the form of an equity investment by Amgen in Arrowhead common stock (about 3 million shares); and up to $617 million in option payments, and development, regulatory and sales milestone payments. Arrowhead is further eligible to receive single digit royalties for sales of products against the undisclosed target and up to low double-digit royalties for sales of products under the ARC-LPA agreement.



Update on ARO-AAT Phase I Program for Alpha-1 Liver Disease

On June 29, 2018, Arrowhead presented **preclinical and initial clinical data** on **ARO-AAT** for the treatment of alpha-1 antitrypsin **(AAT)** deficiency at the Alpha-1 National Education Conference in San Francisco.

ARO-AAT is the company's second generation subcutaneously administered RNA interference (RNAi) therapeutic, which is developed as a treatment for AAT, a rare genetic liver disease associated with alpha-1 antitrypsin deficiency.

AATD is a rare genetic disorder associated with liver disease in children and adults and pulmonary disease in adults. AAT is primarily synthesized and secreted by liver hepatocytes. Its function is to inhibit enzymes that can break down normal connective tissue.

The most common disease variant, the Z mutant, has a single amino acid substitution that results in improper folding of the protein. The mutant protein cannot be effectively secreted and accumulates in globules inside the hepatocytes. This triggers continuous hepatocyte injury, leading to fibrosis, cirrhosis, and increased risk of hepatocellular carcinoma.

ARO-AAT is designed to knock down the hepatic production of the mutant alpha-1 antitrypsin (Z-AAT) protein. Reducing production of the inflammatory Z-AAT protein is expected to halt the progression of liver disease and potentially allow it to regenerate and repair.

The US FDA has granted **orphan drug designation** to ARO-AAT.

Background of the Phase I Study

In February 2018, Arrowhead received approval from the New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE) and from the local Ethics Committee to proceed with a first-in-human **Phase I** study of **ARO-AAT** for the treatment of **alpha-1 antitrypsin deficiency (AATD)**.

The company began **dosing** patients in March 2018.

The study, which is designated as **AROAAT1001** (NCT03362242), is a Phase I single- and multiple-ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and effect of ARO-AAT on serum alpha-1 antitrypsin levels in healthy adult volunteers. The study has two parts: double blind and unblinded.

DOUBLE BLIND PART

- 4 treatment arms
  - 35, 100, 200 and 300 mg
  - 100, 200, 300 mg receive ***3 monthly doses***
  - 4 active, 4 placebo
- Assessments of safety, tolerability, plasma levels of ARO-AAT, plasma AAT changes

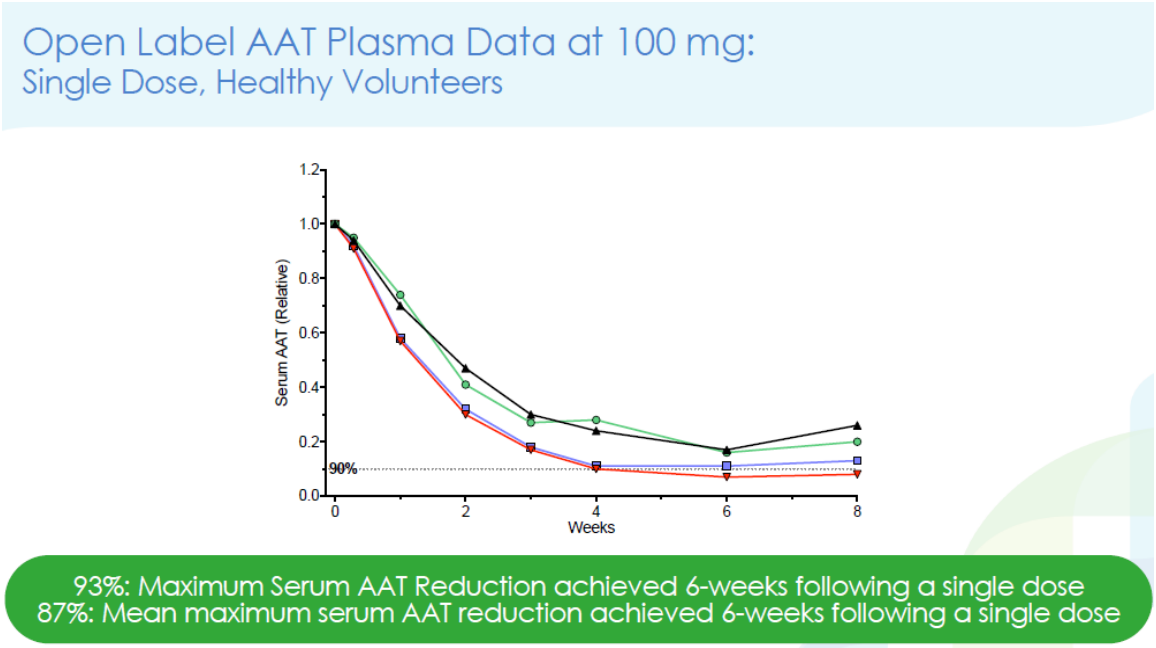
UNBLINDED PART

- No placebo
- 3 groups
  - ***Single doses*** of 100, 200 and 300 mg of ARO-AAT
  - 4 per cohort
- Assessments of safety, tolerability, depth and duration of AAT reductions after a single dose

The enrollment has completed, and 44 total subjects enrolled (28 active, 16 placebo) and have received at least one dose. Multi-dose cohorts dosing is ongoing and still blinded.

Key New Clinical Data Presented at the Alpha-1 National Education Conference

In the AROAAT1001 **Phase I** clinical study, a single, open-label dose of 100 mg of ARO-AAT in four subjects achieved 93% maximum serum AAT knockdown and 87% mean maximum serum AAT knockdown. At 8 weeks post-dose, mean serum AAT knockdown remained at 83%.



The single 100 mg dose of ARO-AAT equates to an average dose of 1.4 mg/kg (range 1.0-1.6 mg/kg) in the subjects studied, who had an average weight of 72.9 kg (range 61.8-98.9 kg).

ARO-AAT appeared to be generally well-tolerated and as of the data cutoff of June 11, 2018, the following safety measures were observed in 40 subjects (24 received ARO-AAT and 16 received placebo):

- No serious or severe adverse events (AEs)
- Most AEs reported were mild (one moderate gastroenteritis)
- Two cases of injection site erythema at 100 mg after 1st dose, both were classified as mild and resolved within 48 hours
- No clinically meaningful adverse changes in BUN, creatinine, ALT, AST or total bilirubin
- No dose-related pattern of adverse laboratory changes seen

On Aug. 31, 2018, Arrowhead announced that it has completed dosing of a **Phase I** clinical study of **ARO-AAT**.

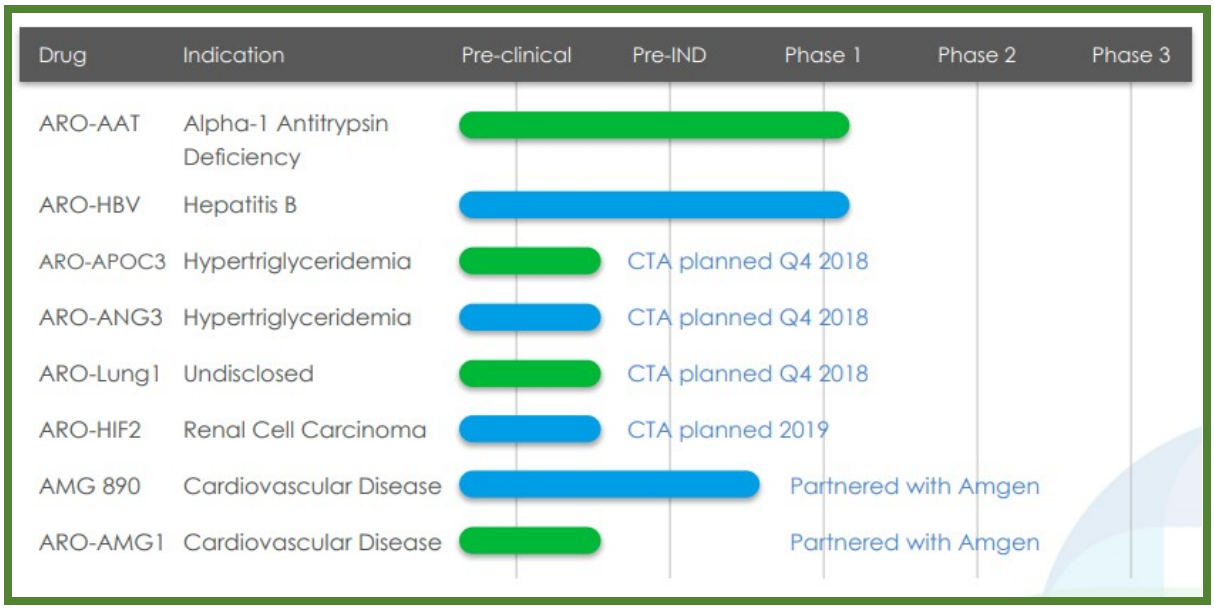
The company intends to submit a late-breaking abstract with initial clinical data on ARO-AAT to the Liver Meeting®, the Annual Meeting of the American Association for the Study of Liver Disease (AASLD), being held in November 2018.

Additional Pipeline Update

In addition to **HBV**, and **AAT,** Arrowhead has expanded its cardiometabolic pipeline, which now includes **ARO-APOC3**, targeting apolipoprotein C-III, and **ARO-ANG3**, targeting angiopoietin-like protein 3 (ANGPTL3); with CTA filings planned around the end of 2018.

Arrowhead has also achieved continued progress with the company's **extra-hepatic platform** and pipeline, including:

- ARO-Lung1, Arrowhead's first candidate against an undisclosed gene target in the lung, which achieved nearly 90% target knockdown following inhaled administration in rodents;
- ARO-HIF2, the Company's candidate targeting renal cell carcinoma, which achieved 85% target gene knockdown in a rodent tumor model.



Update on ARO-HIF2 for Kidney Cancer

In September 2015, Arrowhead nominated **ARO-HIF2** as its first therapeutic candidate delivered using a new Dynamic Polyconjugate™ (DPC™) designed to target tissues outside of the liver. Arrowhead believes that ARO-HIF2, which uses RNA interference to silence transcription factor hypoxia-inducible factor 2α (HIF-2α), is a promising new candidate for the treatment of clear cell renal cell carcinoma **(ccRCC).**

ARO-HIF2 is designed to inhibit the production of HIF-2α, which has been linked to tumor progression and metastasis in ccRCC. Using ARC-HIF2 in a preclinical ccRCC tumor model, mice treated with weekly injections led to greater than 80% knockdown of HIF-2α mRNA in tumors. Furthermore, tumors from treated mice exhibited statistically significant reductions in size and weight, extensive tumor cell death, reduction in the tumor-expressed VEGF-A biomarker, and destruction of the blood vessels feeding the tumors.

The company presented positive **preclinical data** at the European Cancer Congress 2015 (ECC2015) in Vienna on September 27, 2015 in a poster titled "HIF-2α targeting with a novel RNAi delivery platform as therapy for renal cell carcinoma," (abstract #353).

The company further presented positive preclinical data on ARO-HIF2 at AACR2016.

The poster presentation described data from various stages of development of ARO-HIF2, including RNAi trigger selection, HIF2-α target validation, delivery and targeting ligand validation, and multiple RCC tumor models. These data show that important advancements are being made in this program and for Arrowhead's Dynamic Polyconjugate™ (DPCTM) delivery platform generally, including the following key findings:

- Proof-of-concept ligand dependent, functional delivery was demonstrated using the DPC targeted delivery platform
- Silencing HIF2-α expression by RNA interference resulted in reduction of HIF-2α regulated genes
- In two different RCC tumor bearing mouse models, ARO-HIF2 inhibited tumor growth and promoted tumor cell death and structural degeneration

The company is in the process of manufacturing scale up to allow for initiation of IND-enabling studies. Timing for anticipated regulatory submission will be announced in the future.

We Remain Optimistic about the Prospect of Arrowhead

We continue to be optimistic about the prospect of Arrowhead and raise our fair valuation to $30 per share from previous $20 per share based on the recent development within the company.

We believe management decision to focus on the subQ and extra-hepatic programs is prudent.

The discontinuation of the DPCiv programs is not based on the safety or efficacy of the three candidates. Instead, the safety profile of ARC-520, ARC-521, and ARC-AAT in human clinical trials appeared to be favorable, and supported advancing the programs, with a small minority (6%) of infusions being associated with infusion reactions. In addition, across the ARC-520, ARC-521, and ARC-AAT clinical programs, laboratory values have not been deemed indicative of drug induced organ toxicity.

In addition, each candidate was highly active against its respective target. For example, ARC-AAT achieved 90% knockdown of serum AAT, which is believed to be near full suppression of liver production of the protein, in a **Phase I** clinical study. The recent presentation of positive interim clinical data from the ARO-HBV program are very encouraging and represent potential function cure for HBV.

The major reason for discontinuing the DPCiv programs is that it may takes more than 18 months to obtain actionable results to lift the clinical hold on the DPCiv programs. Even after this long delay, the possibility remains that the study could be inconclusive or fall short of satisfying the regulators in some way.

Therefore, management decided to focus entirely on its SubQ and extra-hepatic programs.

We believe it is a natural transition because the company’s SubQ platform is capable of achieving similar results as the EX1 delivery vehicle, with the added benefit of a more convenient mode of administration and expected improved safety margins.

Our price target $30 per share values the company at about $2.64 billion in market capitalization, which we think is appropriate at this time. As long as management remains committed, value will be generated for shareholders in the future.

PROJECTED INCOME STATEMENT

	2017 (Sept)					2018 (Sept)					2019 (Sept)
Cost of Revenue	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	**$4.4**	**$9.0**	**$9.3**	**$8.7**	**$31.4**	**$3.5**	**$0.7**	**$0.7**	**$0.5**	**$5.4**	**$5.0**
Gross Margin	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*
R&D	$9.5	$7.0	$6.9	$8.3	$31.7	$8.4	$12.0	$12.1	$15.0	$47.5	$55.0
% R&D	*218.2%*	*77.6%*	*73.9%*	*95.0%*	*100.9%*	*240.2%*	*1946.2%*	*1657.0%*	*3000.0%*	*881.5%*	*1100.0%*
Salary and G&A	$6.1	$5.2	$5.3	$7.5	$24.1	$5.7	$3.7	$4.6	$5.0	$18.9	$25.0
% SG&A	*140.4%*	*57.9%*	*56.5%*	*86.3%*	*76.8%*	*161.2%*	*566.3%*	*631.6%*	*1000.0%*	*351.5%*	*500.0%*
Other expenses	$3.6	$2.9	$2.9	$3.2	$12.6	$3.2	$0.0	$0.0	$0.0	$3.2	$0.0
% Other	*82.7%*	*32.6%*	*30.6%*	*36.3%*	*40.1%*	*92.1%*	*0.0%*	*0.0%*	*0.0%*	*60.0%*	*0.0%*
Operating Income	**($14.9)**	**($6.1)**	**($5.7)**	**($10.3)**	**($37.0)**	**($13.8)**	**($15.0)**	**($15.9)**	**($19.5)**	**($64.3)**	**($75.0)**
Operating Margin	-	-	-	-	-	-	-	-	-	-	-
Other Income (Net)	$2.8	$0.1	$0.2	($0.5)	$2.6	$0.6	$0.1	$0.0	$0.0	$0.8	($0.5)
Pre-Tax Income	**($12.1)**	**($6.0)**	**($5.5)**	**($10.7)**	**($34.4)**	**($13.2)**	**($14.9)**	**($15.9)**	**($19.5)**	**($63.5)**	**($75.5)**
Net Taxes (benefit)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.3	$0.0	$0.3	$0.0
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*2.0%*	*0.0%*	*0.5%*	*0.0%*
Reported Net Income	**($12.1)**	**($6.0)**	**($5.5)**	**($10.7)**	**($34.4)**	**($13.2)**	**($14.9)**	**($15.6)**	**($19.5)**	**($63.2)**	**($75.5)**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
Net Margin	-	-	-	-	-	-	-	-	-	-	-
Weighted avg. Shares Out	*71.4*	*74.6*	*74.8*	*74.7*	*73.9*	*74.8*	*84.1*	*87.6*	*88.0*	*83.6*	*90.0*
Reported EPS	**($0.17)**	**($0.08)**	**($0.07)**	**($0.14)**	**($0.47)**	**($0.18)**	**($0.18)**	**($0.18)**	**($0.22)**	**($0.76)**	**($0.84)**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
One-time charge	($2.82)	($0.09)	($0.19)	$0.48	($2.62)	($0.61)	($0.15)	$0.00	$0.00	($0.76)	$0.00
Non GAAP Net Income	**($14.9)**	**($6.1)**	**($5.7)**	**($10.3)**	**($37.0)**	**($13.8)**	**($15.0)**	**($15.6)**	**($19.5)**	**($64.0)**	**($75.5)**
Non GAAP EPS	**($0.21)**	**($0.08)**	**($0.08)**	**($0.14)**	**($0.50)**	**($0.18)**	**($0.18)**	**($0.18)**	**($0.22)**	**($0.76)**	**($0.84)**

Source: Company filing and Zacks estimates

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