Zacks Small-Cap Research

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# Arrowhead Pharm (ARWR-NASDAQ)

**ARWR: Zacks Company Report**

**ARWR:** Clinical hold on Heparc-2004 is probably temporary, Collaborations with Amgen announced, Phase I/II ARC-521 initiated

| | |
|---|---|
| Current Price (11/09/16) | $4.20 |
| **Valuation** | **$15.00** |

## 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-520/521 for HBV.

ARC-520/521 are in multiple Phase II trials. The Company also initiated Phase I trial of its second clinical candidate ARC-AAT for liver disease and expanded its pipeline. The acquisition of Novartis' RNAi assets expands and complements its current RNAi estate.

We maintain optimistic about Arrowhead shares.

## SUMMARY DATA

| | |
|---|---|
| **52-Week High** | **$8.08** |
| **52-Week Low** | **$3.18** |
| **One-Year Return (%)** | **-26.96** |
| **Beta** | **2.42** |
| **Average Daily Volume (sh)** | **842,062** |
| **Shares Outstanding (mil)** | **70** |
| **Market Capitalization ($mil)** | **$293** |
| **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 (%)** | **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) |
|---|---|---|---|---|---|
| 2015 | 0.17 A | 0.04 A | 0.12 A | 0.04 A | 0.38 A |
| 2016 | 0.04 A | 0.04 A | 0.04 A | 0.04 E | 0.17 E |
| 2017 | | | | | 0.50 E |
| 2018 | | | | | 5.00 E |

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

| | Q1 (Dec) | Q2 (Mar) | Q3 (Jun) | Q4 (Sep) | Year (Sep) |
|---|---|---|---|---|---|
| 2015 | -$0.37 A | -$0.50 A | -$0.27 A | -$0.51 A | -$1.64 A |
| 2016 | -$0.32 A | -$0.35 A | -$0.32 A | -$0.34 E | -$1.34 E |
| 2017 | | | | | -$1.51 E |
| 2018 | | | | | -$1.23 E |

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

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## WHAT'S NEW

***The Clinical Hold on Heparc-2004 is Probably Temporary***

On November 8, Arrowhead (ARWR) announced that the company was notified verbally by the FDA of its decision to place a **clinical hold** on **Heparc-2004**. The company has not yet received written notice from the FDA.

***The Heparc-2004 Study***

In April 2015, the FDA cleared the multiple-dose **Phase IIb** clinical study of ARC-520 for the treatment of chronic hepatitis B infection.

The clinical study, titled **Heparc-2004**, is a multicenter, randomized, double-blind, placebo-controlled, multi-dose study of ARC-520 administered intravenously to patients with chronic immune active HBV infection maintained on entecavir or tenofovir therapy. The study is planned to enroll up to **12 patients** who will be randomized at a ratio of 2:1 with 8 patients receiving **1 mg/kg** of ARC-520 and 4 patients receiving placebo. Each patient will receive 3 total doses, once every 4 weeks. Patients will be followed through Day 147.

The **primary objective** of Heparc-2004 is to evaluate the depth of hepatitis B surface antigen (HBsAg) decline in response to multiple doses of ARC-520 compared to placebo in patients with chronic, immune active HBV infection as a measure of drug activity. **Secondary objectives** are to measure safety and tolerability and pharmacokinetics of ARC-520, and to evaluate the effect of ARC-520 on entecavir or tenofovir pharmacokinetics, in addition to other exploratory safety and pharmacodynamic objectives.

***The Clinical Hold***

The clinical hold was prompted by deaths at the highest dose of an ongoing **non-human primate** toxicology study. This study involves higher doses of EX1 than those used clinically in humans and higher than those used in the company's previous animal toxicology studies. The cause of these animal deaths is unknown and under investigation. The EX1 delivery vehicle is used in the company's ARC-520, ARC-521, and ARC-AAT programs.

The FDA did not indicate the clinical hold was based on any human findings. To date, EX1 has been administered over 800 times in more than 300 human study subjects and patients. Across this substantial clinical experience, only 3 serious adverse events (SAE) have been observed. Two of these were fevers, treated with acetaminophen, after which the patients continued on the study with no further complications. The other SAE was an instance of hepatic carcinoma in a patient with chronic HBV and cirrhosis, judged by the treating physician to be unrelated to the drug. A small minority (6%) of infusions in ARC-520 studies have been associated with infusion reactions, with 4 patients discontinuing ARC-520 treatment. In addition, across the ARC-520, ARC-521, and ARC-AAT clinical programs, laboratory values have not been deemed indicative of any drug-induced organ toxicity.

***Our Assessment***

We believe the clinical hold is probably temporary based on the current information we have.

The company is working collaboratively with the FDA and is providing responses to questions arising from the nonclinical toxicology. The company has disseminated data from the same animal study to agencies across its development programs and is providing updates as appropriate.

We believe the findings in animal toxicology studies are related to dose level. At this time, we don't have further information on the clinical hold, but will update investors on this when we have further information from the company and the FDA.

### *We Remain Bullish on Arrowhead's Shares*

We continue to be optimistic about the prospect of Arrowhead and maintain our valuation at $15 per share based on the progress the company has made in the past quarter and the recent deal with Amgen for two CV programs.

Arrowhead has been busy recently to move forward with its clinical programs. We believe the company's lead HBV program ARC-520 is a viable drug for chronic HBV patients and the addition of ARC-521 further expands its HBV franchise.

In the area of HBV therapy under development, we think Arrowhead is substantially ahead of its competitors. The company's ARC-520 has the strong advantage of positive data from the long term chimp study and dozens of patients. ARC-520 also has a favorable safety profile. Given the ongoing Phase II studies, we believe that if a breakthrough in HBV is going to occur in the next 12 months it should come from Arrowhead.

The acquisition of Novartis' RNAi development portfolio significantly expands and complements the company's current RNAi assets and will provide the opportunity to rapidly expand its clinical pipeline in the coming years.

We believe current market price of Arrowhead shares does not reflect the intrinsic value of the company.

Based on the current development plan, we expect Arrowhead will be able to initiate **pivotal Phase III** trial of ARC-520 in 2017, and data should be available in late 2017. NDA could be filed in late 2017, and the FDA approval is in late 2018 or early 2019.

We estimate Arrowhead will become profitable in fiscal 2019 with an EPS of $0.68 based on revenue of $210 million. We think a P/E ratio of 38x is appropriate for Arrowhead considering its growth in the next few years. Based on this P/E multiple, we think Arrowhead should be valued at $15.00 per share using 20% discount for 3 years. Our price target values Arrowhead at $1 billion in market cap, which we think is appropriate and fare compared to its peers.

We think ARC-520/ARC-521 is the primary value driver in near- and mid-term for Arrowhead. The successful development of ARC-520/ARC-521 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 initiation of the multiple Phase IIb studies of ARC-520 and the initiation of Phase I/II ARC-521 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 II trials 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.

### *Collaborations with Amgen for Two Cardiovascular Programs*

Earlier today (Sept. 29, 2016), Arrowhead announced two license and collaboration agreements with Amgen to develop and commercialize two cardiovascular programs based on Arrowhead's RNAi platform.

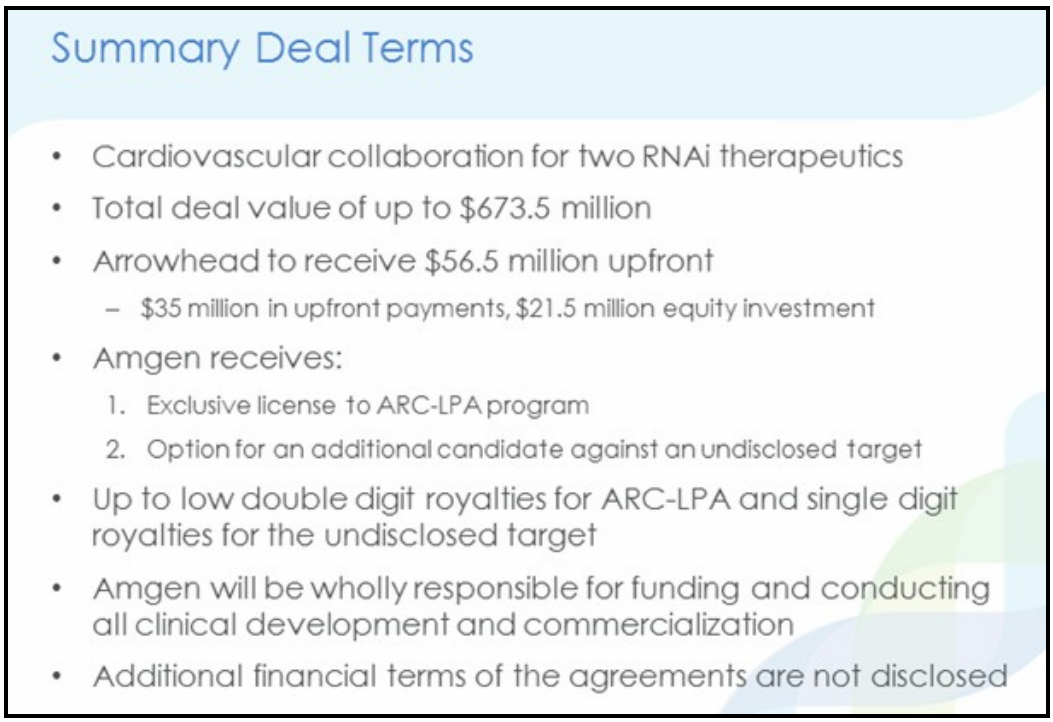
These programs will utilize Arrowhead's proprietary **subcutaneous RNAi delivery technology**.

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.




***Our Takeaways from the Deal***

We welcome this deal and think it's positive to Arrowhead in the following aspects:

**First,** the collaborations immediately boost the company's balance sheet with the $56.5 million upfront payment. In the long run, milestone payment and royalty will further enhance the company's cash position in a non-dilutive way.

As of June 30, 2016, Arrowhead has $44.5 million in cash and investment.

On August 12, Arrowhead closed a private offering with a select group of investors including Orbimed, RA Capital Management, Perceptive Advisors, RTW Investments and certain other institutional investors. Gross proceeds were $45 million. Approximately 7.63 million shares of common stock were issued at a price of $5.90 per share.

Current cash plus the new proceeds can support the company's operations into calendar 2018 according to our financial model.

**Second**, the deal with Amgen further validates Arrowhead's RNAi technology and its clinical application.

**Third,** with a great partner Amgen, this deal could serve as a signal of renewed interest in RNAi technology and similar deal could be signed in the future for Arrowhead.

We will provide further updates on this deal for investors when they are available.

***Phase II of ARC-AAT Initiated***

In early September 2016, Arrowhead initiated a **Phase II** clinical study of **ARC-AAT** for the treatment of liver disease associated with alpha-1 antitrypsin deficiency (AATD). The study is designed to evaluate safety and tolerability and determine the effect of multiple doses of ARC-AAT on levels of circulating and intrahepatic alpha-1 antitrypsin as evidenced by changes in liver biopsy in patients with AATD.

The ARC-AAT Phase II study (**ARCAAT2001)** is a multi-center, open-label, multiple dose-escalation study of ARC-AAT in patients with AATD. In total, the study will consist of at least 8 and a maximum of 12 participants. Two dose levels, 4 mg/kg and 6 mg/kg, will be evaluated in two separate cohorts. All subjects will receive a pre-dose biopsy, seven doses of ARC-AAT (once every 28 days), and a post-dose biopsy completed at Day 183. The study will be conducted at multiple centers in Canada, Ireland, and Sweden. The Company may add additional centers in other countries.

In late February 2015, Arrowhead initiated a **Phase I** clinical trial of ARC-AAT for the treatment of liver disease associated with Alpha-1 Antitrypsin Deficiency (AATD) in **Australia**.

The Phase I trial is a multi-center, randomized, placebo-controlled, double-blind, single dose-escalation study to evaluate the safety, tolerability, pharmacokinetics of ARC-AAT and the effect on circulating alpha-1 antitrypsin (AAT) levels. The study plans to enroll in dose cohorts of six participants each, with participants randomized at a ratio of 2:1 (active:placebo) to receive a single intravenous injection of either ARC-AAT or placebo (normal saline). The study will consist of **two parts**, with **Part A** planned to be conducted in healthy volunteers and **Part B** planned to be conducted in patients with PiZZ genotype AATD. In Part A, dose escalation will proceed until the achievement of certain target knockdown parameters. That target is at least 30% reduction of serum AAT levels in 3 subjects or greater than 60% reduction in a single subject. When these AAT knockdown parameters are achieved, dose escalation in healthy volunteers (Part A) is planned to stop and dosing in patients with AATD (Part B) is planned to begin at the highest dose level used in Part A and then dose escalation will proceed. Participants will be evaluated for 28 days following dosing with additional follow-up every 2 weeks until AAT levels return to baseline.

The company has completed enrollment in Part A of the study in healthy volunteers and will report top-line data from Part A **later in the year.**

ARC-AAT has been granted orphan drug designation (ODD) by both the FDA and the European Medicines Agency.

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.

ARC-AAT is Arrowhead s second clinical candidate, which further de-risks its pipeline. In the absence of specific therapy other than liver transplant for AATD associated liver disease, we believe RNAi holds great potential.

***Arrowhead Initiates Phase I/II Study of ARC-521***

On June 9, Arrowhead announced that it initiated a **Phase I/II** study of **ARC-521**, the company's second RNAi-based candidate for the treatment of chronic hepatitis B virus **(HBV)** infection.

The company dosed the first patient on September 7, 2016 in the multiple ascending dose (MAD) portion of its ongoing Phase I/II study of ARC-521.

To date 24 healthy volunteers have been treated in the study, and the drug safety committee (DSC) approved initiation of the MAD after a planned review of safety data from cohort 3 of the healthy volunteer portion of the study. The MAD is designed to evaluate the safety, tolerability, and antiviral activity of single and multiple doses of ARC-521 in patients with chronic HBV.

The MAD portion of the ARC-521 study (**ARC5211001**) is a multicenter, sequential, multiple dose, open label study in patients with chronic HBV. Up to 24 chronic HBV patients (8 patients per dose level) that are negative for Hepatitis B e-antigen (HBeAg) at screening will enroll sequentially into up to 3 dose levels (2 mg/kg, 4 mg/kg, 6 mg/kg) to receive 3 monthly doses of open label ARC-521.

The study is designed to evaluate the safety, tolerability, and pharmacokinetics of single doses of ARC-521 in healthy volunteers and the safety, tolerability, and antiviral activity of single and multiple doses of ARC-521 in patients with chronic HBV. This study may have multiple readouts, including single dose safety data, single dose antiviral activity data, and multiple dose safety and antiviral activity data.

The study is currently recruiting at a single center in **New Zealand** and the company plans to add additional centers in other countries.

**ARC-521** is being developed to target both cccDNA and also integrated DNA, which appears to be a more significant producer of HBsAg in patients who have been treated with NUCs or who are **e-antigen negative**.

ARC-521 is also derived from the company’s DPC platform; therefore, its safety profile is expected to be similar to ARC-520. While ARC-520 is designed to target cccDNA, ARC-521 is designed to target both cccDNA and integrated DNA. Therefore, ARC-521 is a complement to ARC-520.

In HBeAg-negative chimps predicted to have higher levels of integrated DNA, administration of ARC-521 led to 99% (2 logs) of additional HBsAg reduction.

The initiation of the Phase I/II trial of ARC-521 is a significant milestone for Arrowhead in the development of HBV infection. ARC-521 increases the company’s leadership position in the HBV space and the race to a functional cure.

***Updated Data on ARC-520 Presented at the ILC 2016***

The company made **three presentations** on ARC-520 at The International Liver Congress™ 2016 (ILC 2016), in Barcelona, Spain, April 13-17, 2016.

Collectively, these presentations demonstrated several important findings from Arrowhead's clinical and nonclinical studies of ARC-520, including the following:

- ARC-520 and entecavir produced rapid HBV DNA suppression with all hepatitis B e-antigen (HBeAg) positive, treatment naïve patients achieving serum HBV DNA reductions of up to 5.5 log (99.9997%), and all HBeAg negative, treatment naïve patients achieving reductions that put them below the limit of quantitation;
- ARC-520 effectively inhibited HBV cccDNA-derived mRNA with observed viral protein reduction in HBV patients of up to 2.0 log (99%) after a single dose;
- ARC-520 had a long duration of effect with HBsAg still reduced by 83% after 2 months and 75% after 3 months, which is the final time point of the study, after a single dose;
- Based on HBsAg epitope profile analysis, poster authors and Arrowhead collaborators had previously identified a predictive hepatitis B surface-antigen (HBsAg) Clearance Profile associated with HBsAg clearance in antiviral therapy cohorts;
- There was a significant association between the development of an HBsAg Clearance Profile and ARC-520 therapy in HBV patients;
- Complexed HBsAg antibodies (anti-HBs) were developed and detected in HBV patients treated with ARC-520, which may represent a recovery of the immune system response;
- After monthly administration of 6-11 doses of ARC-520 in chimpanzees chronically infected with HBV, the ARC-520 target site sequences remained virtually unchanged, indicating that no drug resistance developed during the treatment period;

***Update on Phase IIb of ARC-520 for HBV***

Arrowhead already began dosing patients in **three Phase IIb studies**: the Heparc-2008 (MONARCH) study, the Heparc-2007 long-term extension, and the Heparc-2001 open-label extension.

***The Heparc-2008 (Monarch) Study***

The MONARCH study is a multicenter, open-label study to evaluate ARC-520 administered alone and in combination with other therapeutics in patients with chronic hepatitis B virus infection. The primary outcome measure is the percentage of patients achieving a 1-log reduction in hepatitis B surface antigen (HBsAg) compared to baseline. Secondary outcome measures include the percentage of patients achieving HBsAg loss and time to HBsAg loss based on qualitative assay, percentage of patients achieving anti-HBs seroconversion and time to anti-HBs seroconversion (antibody to HBsAg), percentage of patients achieving a 1-log reduction in HBsAg and achieving a HBsAg level less than 100 IU/L, as well as other outcome measures.

The initial **six cohorts** are each planned to consist of up to twelve treatment naïve patients. Patients in cohort 1 will receive ARC-520 as monotherapy once every 4 weeks for 48 weeks (13 doses). Patients in cohorts 2-6 will be stratified by e-antigen status and HBV genotype. They will receive the same regimen of ARC-520 for 48 weeks in combination with daily entecavir for 60 weeks and pegylated interferon alpha 2a (PEG IFN) for 48 weeks. MONARCH is designed to allow for new cohorts to be added that test additional dosing regimens and different combinations as new agents become available for study.

**On Jan 7, 2016**, the company dosed the first patient in the Phase IIb MONARCH combination study of ARC-520 for the treatment of chronic HBV infection. The clinical trial is currently enrolling patients at multiple centers in Australia and New Zealand. This study is intended to identify one or more combinations of ARC-520 and other therapeutic agents that can potentially lead to a functional cure of chronic HBV.

We expect to see deep knockdown of all gene products, especially in HBeAg positive patients.

It is estimated in the U.S. that 95% of people chronically infected with HBV are currently NUC-naïve and at least 50% of them are likely to be HBeAg-positive. In West Europe, 90% of estimated CHB patients are naïve, and about 33% of them are HBeAg positive. The effect on HBsAg in NUC-naïve HBeAg-positive patients makes this group especially attractive to study and a key focus for multi-dose studies going forward.

***Update on ARC-HIF2 for Kidney Cancer***

In September, 2015, Arrowhead nominated **ARC-HIF2** as its first therapeutic candidate delivered using a new Dynamic Polyconjugate™ (DPC™) designed to target tissues outside of the liver. Arrowhead believes that ARC-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).**

ARC-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 ARC-HIF2 at AACR2016.

The poster presentation described data from various stages of development of ARC-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, ARC-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.

***Update on ARC-LPA for Cardiovascular Disease***

Arrowhead's RNAi-based candidate ARC-LPA is in preclinical development as a potential treatment for cardiovascular diseases. ARC-LPA is designed to reduce production of apolipoprotein(a), a key component of lipoprotein(a), or Lp(a). Lp(a) levels in humans are genetically defined and higher levels correlate 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.

In May 2016, Arrowhead presented additional promising preclinical data on ARC-LPA at the Arteriosclerosis, Thrombosis and Vascular Biology | Peripheral Vascular Disease (ATVB|PVD) 2016 Scientific Sessions in Nashville.

The poster presentation described data from **in vitro** screening of RNAi triggers and multiple in vivo models, including transiently transgenic mice, transgenic mice (Tg), and non-human primates (NHPs). Key findings from these studies include the following:

- Screening of RNAi triggers in Tg mice identified those that exhibited substantial and sustained knockdown of serum apo(a) and Lp(a) levels
- RNAi trigger sequences were active in both intravenous and SQ platforms
- Structure activity relationship (SAR) studies looking at chemical modifications to the RNAi trigger identified a lead that demonstrated **greater than 98%** maximum knockdown after a single 3 mg/kg SQ dose in transgenic mice
- Duration of effect gains were also made with greater than 85% knockdown still seen at 6 weeks post dose
- In NHPs, 85-90% reduction of serum Lp(a) levels was observed after three weekly 3 mg/kg SQ doses
- Duration of effect in NHPs was long, with Lp(a) levels still reduced by 75% 6 weeks after the final dose

***Update on ARC-F12 for Hereditary Angioedema***

Arrowhead is also developing a preclinical program **ARC-F12** for hereditary angioedema.
ARC-F12 is in preclinical development as a potential treatment for **factor XII (F12) mediated diseases**. There are clear unmet needs in hereditary angioedema (HAE) and thromboembolic diseases. The biology of factor 12 as part of the coagulation cascade and the kinin-kallikrein system suggest that its reduction through RNAi may present opportunities in both disease areas.

In May 2016, Arrowhead presented promising preclinical data on ARC-F12 at AAAAI 2016.

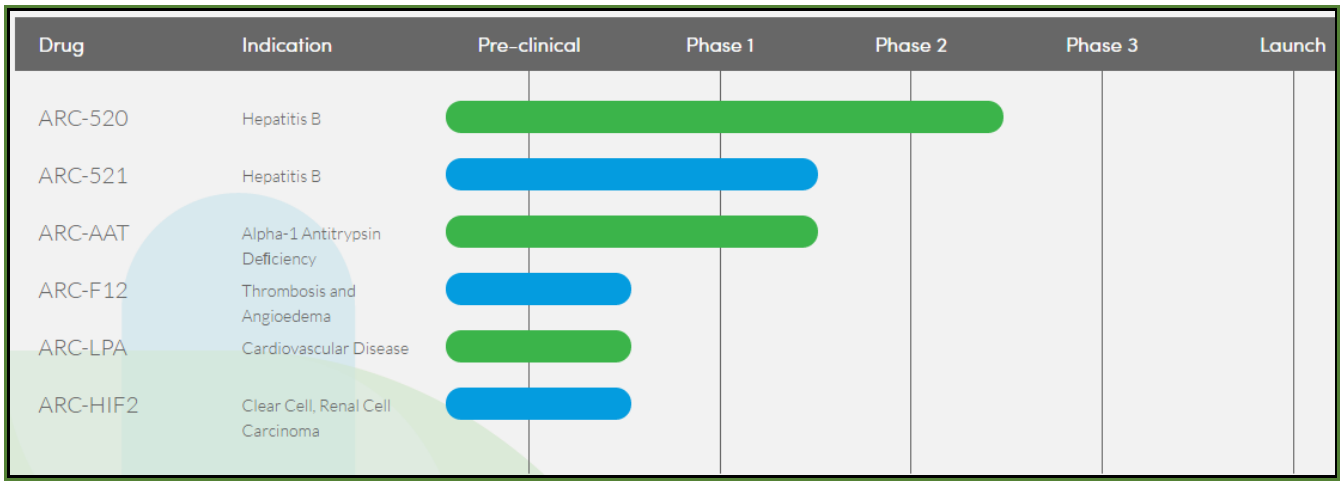
In a carrageenan-induced paw edema model in rats, treatment with ARC-F12 seven days prior to carrageenan challenge led to a significant reduction in edema ($p < 0.001$). The reduction in swelling in ARC-F12 treated rats is similar to that seen in rats treated with a kallikrein-targeted antibody. This supports Arrowhead's position that F12 inhibition could be an attractive target for the rare genetic disorder, hereditary angioedema (HAE).

In a mouse model of **thrombosis**, a dramatic increase in occlusion times was observed in mice receiving ARC-F12. The time to blood flow occlusion is measured as a clinically relevant indicator of physiological response to F12 knockdown and is a measure of the inhibition of thrombus formation. Further, in multiple relevant models of bleeding risk, ARC-F12 did not cause an increase in bleeding times or bleeding risk. Anticoagulants can be used to reduce thrombus formation and thromboembolism occurrence, but also can cause an increase in serious bleeding risk. ARC-F12 may be able to reduce the risk of blood clot formation, without the undesirable bleeding risk caused by anticoagulants.

In vivo studies in wild type mice showed that a single 2 mg/kg dose of ARC-F12 achieved greater than 95% knockdown of F12 levels. In multi-dose primate studies, a 4 mg/kg dose resulted in greater than 90% knockdown with even greater knockdown following subsequent doses. Knockdown was also highly durable with greater than 80% reduction maintained between monthly doses. ARC-F12 appeared to be generally well-tolerated and no drug-related changes in toxicity markers were observed as measured by clinical chemistry and hematologic parameters.

The company is currently conducting studies in order to advance ARC-F12 into **clinical trials**.

With a platform technology, we believe the pipeline can be further expanded with ease.


Drug
Indication
Pre-clinical
Phase 1
Phase 2
Phase 3
Launch
ARC-520
Hepatitis B
ARC-521
Hepatitis B
ARC-AAT
Alpha-1 Antitrypsin Deficiency
ARC-F12
Thrombosis and Angioedema
ARC-LPA
Cardiovascular Disease
ARC-HIF2
Clear Cell, Renal Cell Carcinoma

## PROJECTED INCOME STATEMENT

| | 2015 (Sept) | | | | | 2016 (Sept) | | | | | 2017 (Sept) | 2018 (Sept) | 2019 (Sept) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $ in millions except per share data | Q1 | Q2 | Q3 | Q4 | FYE | Q1 | Q2 | Q3 | Q4 | FYE | FYE | FYE | FYE |
| Revenue | $0.17 | $0.04 | $0.12 | $0.04 | $0.38 | $0.04 | $0.04 | $0.04 | $0.04 | $0.17 | $0.50 | $5.00 | $210.00 |
| *YOY Growth* | | | | | | - | - | - | - | - | *199.3%* | *900.0%* | *4100.0%* |
| **Total Revenues** | **$0.17** | **$0.04** | **$0.12** | **$0.04** | **$0.38** | **$0.04** | **$0.04** | **$0.04** | **$0.04** | **$0.17** | **$0.50** | **$5.00** | **$210.00** |
| *YOY Growth* | *297.1%* | *0.0%* | *182.9%* | *-1.7%* | *118.3%* | *-74.4%* | *0.0%* | *-68.0%* | *-8.6%* | *-56.3%* | *199.3%* | *900.0%* | *4100.0%* |
| *Cost of Revenue* | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.1 | $0.8 | $29.4 |
| **Gross Income** | **$0.2** | **$0.0** | **$0.1** | **$0.0** | **$0.4** | **$0.0** | **$0.0** | **$0.0** | **$0.0** | **$0.2** | **$0.4** | **$4.3** | **$180.6** |
| *Gross Margin* | *100.0%* | *100.0%* | *100.0%* | *100.0%* | *100.0%* | *100.0%* | *100.0%* | *100.0%* | *100.0%* | *100.0%* | *85.0%* | *85.0%* | *86.0%* |
| R&D | $17.7 | $21.8 | $7.5 | $10.4 | $57.4 | $10.3 | $10.0 | $9.4 | $12.0 | $41.8 | $75.0 | $55.0 | $60.0 |
| *% R&D* | *10392.0%* | *49791.0%* | *6052.8%* | *23752.8%* | *15028.8%* | *23631.6%* | *22904.8%* | *23806.2%* | *30000.0%* | *25007.3%* | *15000.0%* | *1100.0%* | *28.6%* |
| Salary and G&A | $5.2 | $5.2 | $5.4 | $8.6 | $24.5 | $5.9 | $8.1 | $6.4 | $7.5 | $27.8 | $30.0 | $37.5 | $50.0 |
| *% SG&A* | *3067.0%* | *11973.2%* | *4363.6%* | *19680.4%* | *6409.7%* | *13420.6%* | *18438.9%* | *16141.4%* | *18750.0%* | *16655.1%* | *6000.0%* | *750.0%* | *23.8%* |
| Other expenses | $2.3 | $2.7 | $3.2 | $4.4 | $12.6 | $3.2 | $3.2 | $3.6 | $3.7 | $13.7 | $8.5 | $10.0 | $12.0 |
| *% Other* | *1349.9%* | *6067.7%* | *2607.8%* | *10017.0%* | *3290.3%* | *7256.4%* | *7361.7%* | *9016.5%* | *9250.0%* | *8178.2%* | *1700.0%* | *200.0%* | *5.7%* |
| **Operating Income** | **($25.1)** | **($29.6)** | **($16.0)** | **($23.3)** | **($94.1)** | **($19.3)** | **($21.3)** | **($19.3)** | **($23.2)** | **($83.1)** | **($113.1)** | **($98.3)** | **$58.6** |
| *Operating Margin* | - | - | - | - | - | - | - | - | - | - | - | - | *27.9%* |
| Other Income (Net) | $2.5 | $0.9 | $0.1 | ($5.4) | ($1.9) | $0.1 | $0.4 | ($0.1) | ($0.1) | $0.3 | ($0.5) | ($0.5) | ($0.5) |
| **Pre-Tax Income** | **($22.6)** | **($28.7)** | **($15.9)** | **($28.8)** | **($96.0)** | **($19.3)** | **($20.8)** | **($19.4)** | **($23.3)** | **($82.8)** | **($113.6)** | **($98.8)** | **$58.1** |
| Net Taxes (benefit) | $0.0 | $0.0 | $0.0 | ($4.0) | ($4.0) | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 |
| *Tax Rate* | *0.0%* | *0.0%* | *0.0%* | *14.0%* | *4.2%* | *0.0%* | *0.0%* | *0.0%* | *0.0%* | *0.0%* | *0.0%* | *0.0%* | *0.0%* |
| **Reported Net Income** | **($22.6)** | **($28.7)** | **($15.9)** | **($24.7)** | **($91.9)** | **($19.3)** | **($20.8)** | **($19.4)** | **($23.3)** | **($82.8)** | **($113.6)** | **($98.8)** | **$58.1** |
| *YOY Growth* | - | - | - | - | - | - | - | - | - | - | - | - | - |
| *Net Margin* | - | - | - | - | - | - | - | - | - | - | - | - | - |
| *Weighted avg. Shares Out* | *54.7* | *55.7* | *59.5* | *59.5* | *57.4* | *59.5* | *59.8* | *60.0* | *68.0* | *61.8* | *75.0* | *80.0* | *85.0* |
| **Reported EPS** | **($0.41)** | **($0.51)** | **($0.27)** | **($0.42)** | **($1.60)** | **($0.32)** | **($0.35)** | **($0.32)** | **($0.34)** | **($1.34)** | **($1.51)** | **($1.23)** | **$0.68** |
| *YOY Growth* | - | - | - | - | - | - | - | - | - | - | - | - | - |
| One-time charge | $2.54 | $0.95 | $0.06 | ($5.44) | ($1.89) | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| **Non GAAP Net Income** | **($20.0)** | **($27.7)** | **($15.9)** | **($30.2)** | **($93.8)** | **($19.3)** | **($20.8)** | **($19.4)** | **($23.3)** | **($82.8)** | **($113.6)** | **($98.8)** | **$58.1** |
| **Non GAAP EPS** | **($0.37)** | **($0.50)** | **($0.27)** | **($0.51)** | **($1.64)** | **($0.32)** | **($0.35)** | **($0.32)** | **($0.34)** | **($1.34)** | **($1.51)** | **($1.23)** | **$0.68** |

*Source: Company filing and Zacks estimates*

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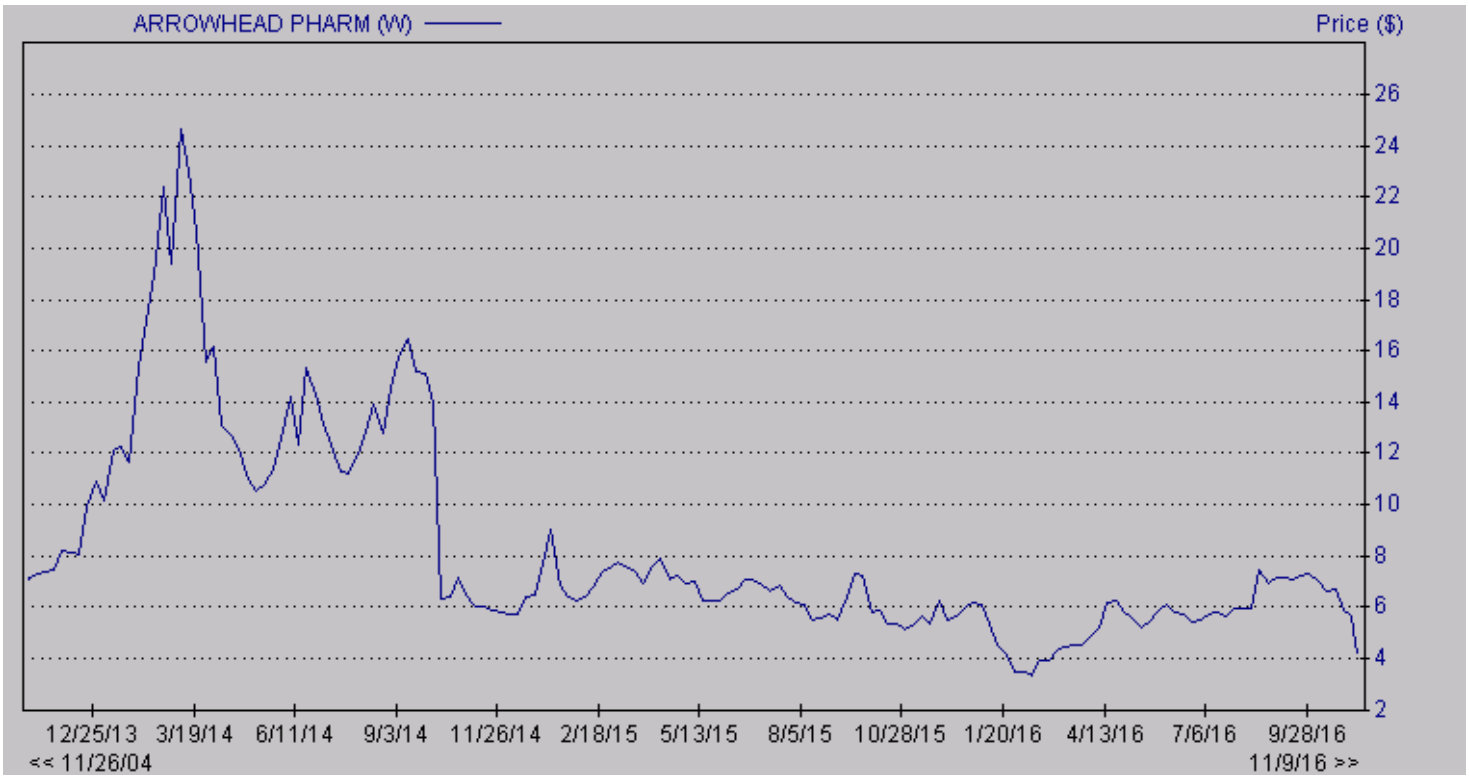


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