Zacks Small-Cap Research
Sponsored – Impartial - Comprehensive

June 16, 2020
David Bautz, PhD
312-265-9471
dbautz@zacks.com

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

Arrowhead Pharmaceuticals, Inc. (ARWR-NASDAQ)

ARWR: Multiple 'Shots on Goal' for RNAi Platform…

Based on our probability adjusted DCF model that takes into account potential future revenues from the company's development products, ARWR is valued at $58/share. This model is highly dependent upon the continued clinical success of those programs and will be adjusted accordingly based upon future clinical outcomes.

Current Price (06/16/20)	$33.22
Valuation	**$58.00**

OUTLOOK

Arrowhead Pharmaceuticals, Inc. (ARWR) is developing medicines that cause gene silencing using RNA interference (RNAi), a specific means of inhibiting the expression of genes and stopping the production of a specific protein. The company currently has six internal programs that are either in clinical testing or will be initiating trials shortly. In addition, Arrowhead has two partnerships with Amgen and Johnson & Johnson. The company is looking to expand to disease targets outside the liver this year with products targeting HIF2α for treating kidney cancer and ENaC in lung tissue for treating cystic fibrosis.

SUMMARY DATA

52-Week High	**$73.01**
52-Week Low	**$20.56**
One-Year Return (%)	**25.59**
Beta	**1.76**
Average Daily Volume (sh)	**1,027,641**
Shares Outstanding (mil)	**102**
Market Capitalization ($mil)	**$3,381**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**64**
Insider Ownership (%)	**4**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**383.0**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**369.1**
P/E using 2020 Estimate	**-87.1**
P/E using 2021 Estimate	**-37.0**

Risk Level	**Average**
Type of Stock	**Mid-Growth**
Industry	**Med-Drugs**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2019	34.7 A	48.2 A	42.7 A	43.3 A	168.8 A
2020	29.5 A	23.5 A	18.5 E	20.6 E	92.1 E
2021					73.2 E
2022					50.0 E

Earnings per Share

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2019	$0.13 A	$0.24 A	$0.21 A	$0.11 A	$0.69 A
2020	-$0.03 A	-$0.20 A	-$0.16 E	-$0.15 E	-$0.53 E
2021					-$0.74 E
2022					-$1.04 E

© Copyright 2020, Zacks Investment Research. All Rights Reserved.

WHAT'S NEW

Business Update

Arrowhead Pharmaceuticals Inc (ARWR) is developing medicines that cause gene silencing using RNA interference (RNAi), a specific means of inhibiting the expression of genes and stopping the production of a specific protein. The company has a deep and diverse pipeline consisting of the following development product candidates, including eight in-house programs and three partnered drugs, two with Johnson and Johnson (JNJ) and one with Amgen (AMGN). Below we provide updates for each of the programs.



Source: Arrowhead Pharmaceuticals, Inc.

ARO-AAT: This is the company's second generation, subcutaneously administered RNAi therapeutic being developed as a treatment for the rare genetic liver disease, alpha-1-antitrypsin (AAT) deficiency. This program was granted Fast Track status by the FDA in June 2019 (which was in addition to Orphan Drug designation in the U.S. and E.U. granted in early 2018). The company is currently conducting the SEQUOIA Phase 2/3 trial and the AROAAT2002 open label study. In March 2020, new patient screening and enrollment for both studies was paused for at least a 4-week period due to the ongoing coronavirus pandemic. The company is in the process of opening the sites and resuming screening and enrollment. Prior to the pause in enrollment, the first cohort of the 2002 study was fully enrolled and we anticipate six-month biopsy data being presented in the Fall of 2020 at a scientific meeting. While there is unlikely to be histological changes at the six-month timepoint, the amount of AAT monomer will be presented along with pre- and post-treatment levels of accumulated AAT polymer.

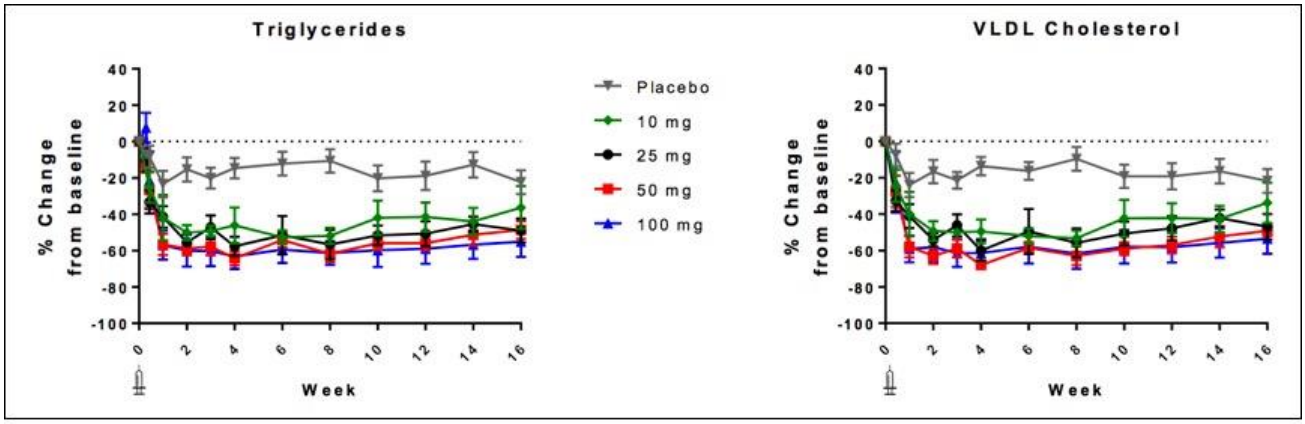
ARO-APOC3: This program is focused on treating patients with severe hypertriglyceridemia and a history or high risk of pancreatitis by targeting apolipoprotein C-III (APOC3). APOC3 is a component of very low density lipoprotein (VLDL) and inhibits lipoprotein lipase. An APOC3 loss-of-function results in lower triglyceride (TG) levels (Jørgensen *et al*., 2014). Approximately 80-90% of APOC3 is produced in hepatocytes, thus making it an ideal target for the TRiM™ platform.

While some patients do have a single genetic cause of the disease, for example familial chylomicronemia syndrome (FCS) is caused by an impaired lipoprotein lipase and results in patients have TG levels >880 mg/dl, many patients have a polygenic disorder (multifactorial chylomicronemia, MCM) that is exacerbated by comorbidities, diet, and lifestyle and greatly increases the risk for pancreatitis. Both conditions are treated with currently available therapies and changes to diet/lifestyle, however adherence

is difficult. While FCS is rare (prevalence is approximately 1 in 1 million [Brahm *et al*., 2015]), MCM is thought to affect up to 3.4 million Americans (Christian *et al*., 2011), although only a small percentage of those patients are currently on medication.

The company presented data from the AROAPOC31001 Phase 1/2 clinical trial at the American Heart Association (AHA) Scientific Sessions meeting in November 2019. The trial consisted of a single dose group and a multiple dose group. The single dose group consisted of four different cohorts of healthy volunteers with fasting TG > 80 mg/dl that received either 25 mg, 50 mg, 100 mg, or 10 mg of ARO-APOC3. Each cohort had 10 participants, six received ARO-APOC3 and four received placebo. Importantly, there were no safety signals as no serious or severe adverse events were reported.

Dose dependent reductions were seen in serum APOC3, with mean maximum reductions between 72% to 94%. The reductions were maintained through the end of the study (16 weeks after dosing), with mean reductions of 70% to 91%. Reductions were also seen in TG and VLDL cholesterol. The mean maximum reductions in TG ranged from 53% to 64% and reductions in VLDL cholesterol ranged from 53% to 68%.



Source: Arrowhead Pharmaceuticals, Inc.

The company is planning to discuss the regulatory path forward with regulators in the second half of 2020 and we believe it is likely that the current trial will lead directly into a Phase 3 trial, likely initiating in the first half of 2021.

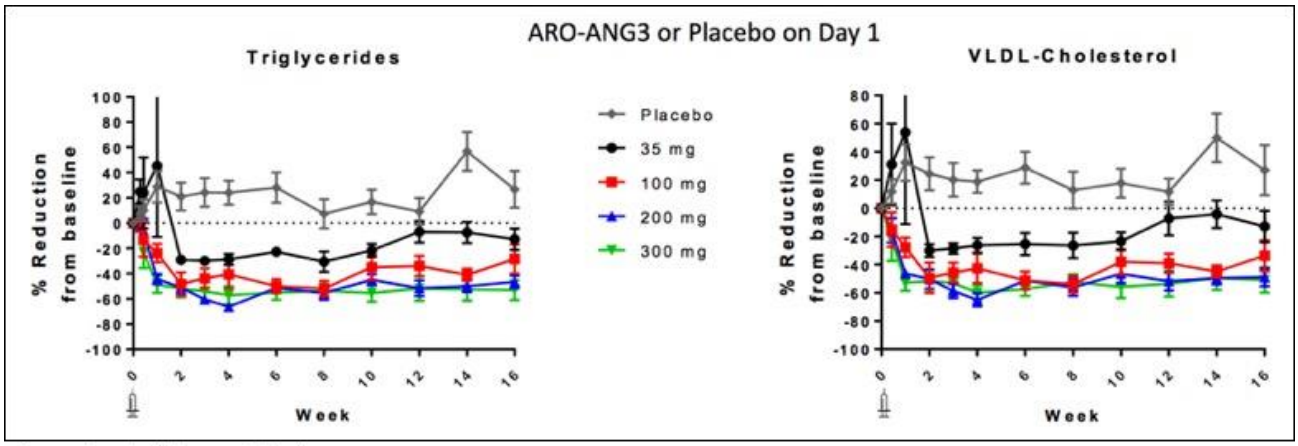
ARO-ANG3: This program is focused on treating patients with mixed dyslipidemia and potentially metabolic diseases through targeting angiopoietin like protein 3 (ANGPTL3). ANGPTL3 loss-of-function mutations lead to low levels of LDL, VLDL, HDL, and TG, with genome-wide association studies (GWAS) showing a reduced risk of cardiovascular disease (CVD). Just like APOC3, the majority of ANGPTL3 is produced in hepatocytes, also making it an ideal target for for the TRiM™ platform.

Mixed dyslipidemia patients have both elevated TG and elevated LDL-cholesterol. There are an estimated 10-15 million mixed dyslipidemia patients in the U.S., making it a very large opportunity. While there are a number of treatments currently available, the ability for ARO-ANG3 to lower both TGs and LDL could lead to a better outcome than statins or PCSK9 inhibitors alone.

The company presented data from the AROANG1001 Phase 1/2 clinical trial at the American Heart Association (AHA) Scientific Sessions meeting in November 2019. The trial consisted of a single dose group and a multiple dose group. The single dose group consisted of four different cohorts of healthy volunteers with fasting TG > 100 mg/dl and LDL-C > 70 mg/dl that received either 35 mg, 100 mg, 200 mg, or 300 mg of ARO-ANG3. Each cohort had 10 participants, six received ARO-ANG3 and four received placebo. Importantly, there were no safety signals as no serious or severe adverse events were reported.

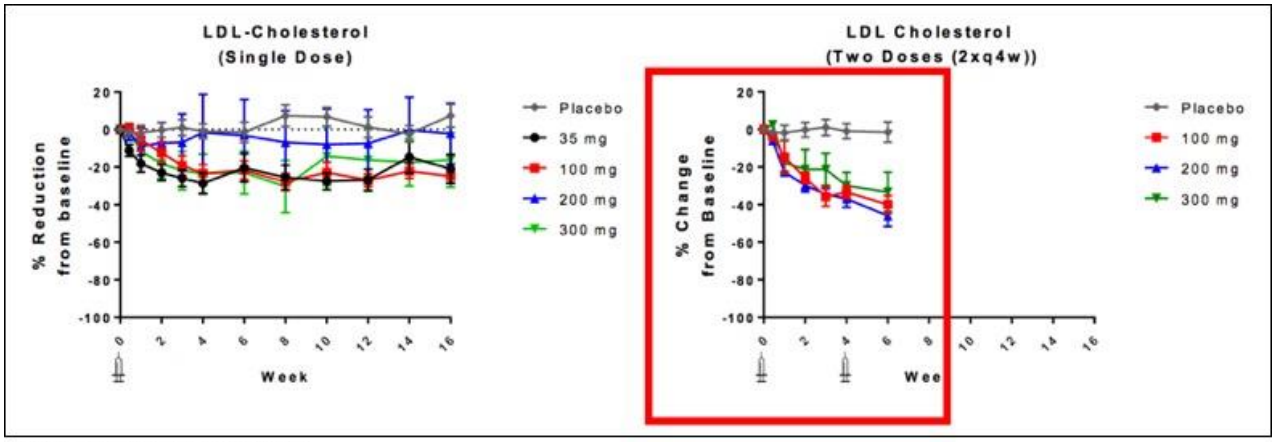
Following a single dose of ARO-ANG3, dose dependent reductions in serum ANGPTL3 were seen ranging from 55% to 83%, and reductions were maintained through week 16 with mean reductions at

week 16 of 43% to 75%. Dose dependent reductions were also seen in TGs and VLDL cholesterol, with mean TG reductions of 31% to 66% and mean VLDL cholesterol reductions of 30% to 65%.



Source: Arrowhead Pharmaceuticals, Inc.

Changes in LDL and HDL were seen with mean maximum HDL reductions of 8% to 26% and LDL reduced by 9% to 30%. Two subjects in the 200 mg single dose cohort showed increased LDL following dosing, which affected the mean maximum reductions for that cohort. However, the multiple dose data at 200 mg showed reductions in LDL that were similar to 100 mg and 300 mg doses of 33% to 46%.

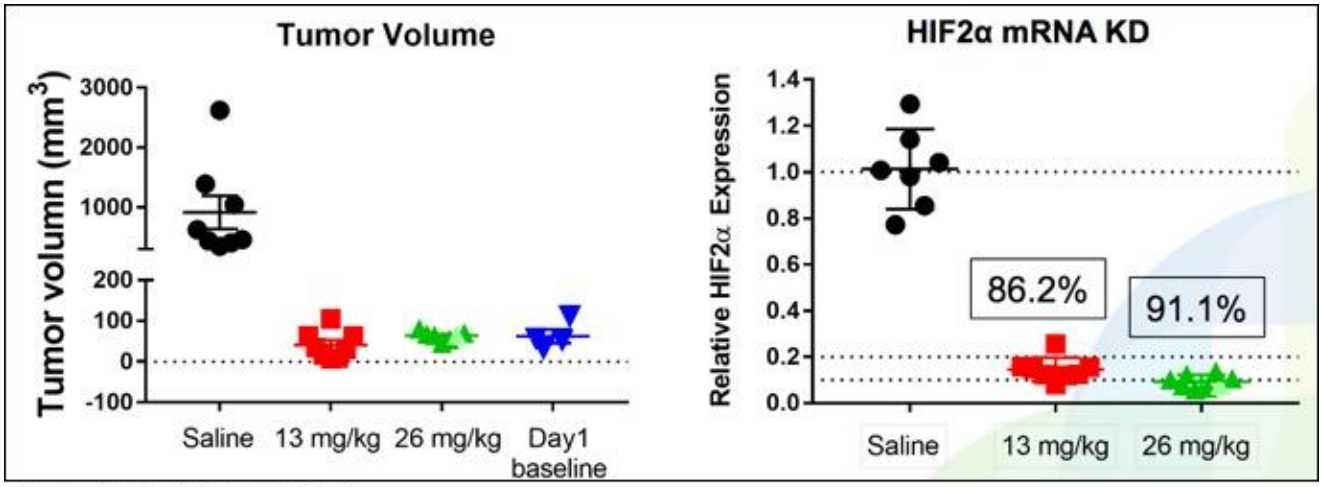


Source: Arrowhead Pharmaceuticals, Inc.

Arrowhead plans on meeting with the FDA later this year to discuss the regulatory path forward for ARO-ANG3. At this point we believe it will be necessary to conduct a Phase 2b study instead of moving straight into a Phase 3 pivotal trial due to the size of the population being targeted.

ARO-HIF2: This is designed to treat clear cell renal cell carcinoma (ccRCC) and targets hypoxia inducible factor 2α (HIF2α). Approximately 74,000 cases of kidney cancer were diagnosed in 2019, with approximately 70-80% of those being ccRCC. The Von Hippel-Lindau (VHL) tumor suppressor gene is inactivated in the majority of ccRCC cases. Phosphorylated VHL controls the degradation of HIFs, and numerous studies have shown that the overexpression of HIF2α is a driver of ccRCC. Thus, suppression of HIF2a may be a good target for treating ccRCC.

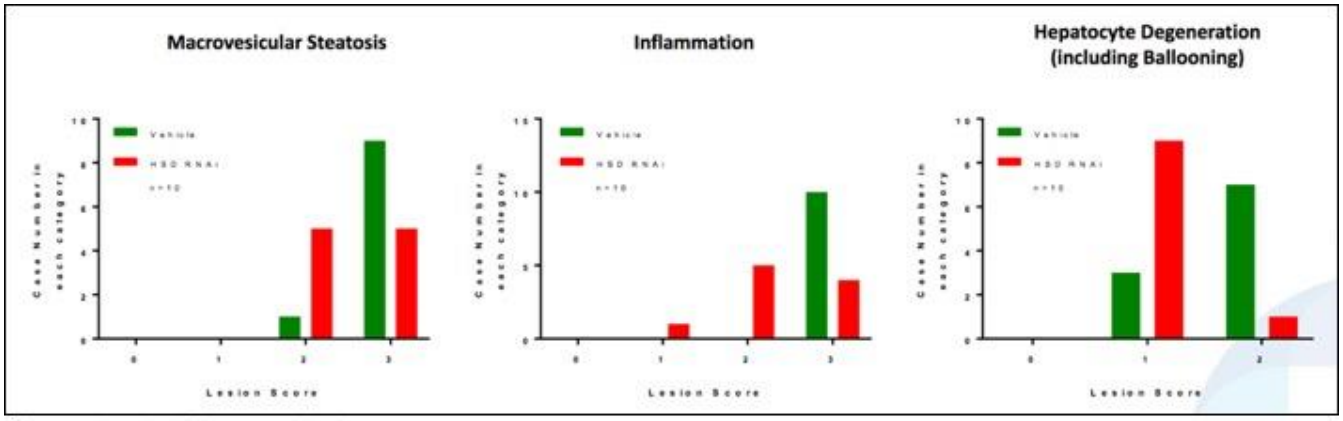
ARO-HIF2 was studied in a mouse model of ccRCC that utilizes the cell line A498, which contains a VHL mutation and overexpresses HIF2α. The following graph shows that both 13 mg/kg and 26 mg/kg ARO-HIF2 controlled tumor growth, with tumor volumes similar to what was seen on Day 1. In addition, levels of HIF2a mRNA were decreased 86.2% and 91.1% compared to vehicle control, showing excellent target engagement.



Source: Arrowhead Pharmaceuticals, Inc.

Arrowhead filed an IND for ARO-HIF2 in December 2019 and we anticipate a Phase 1 trial to initiate enrollment very soon. With the ongoing coronavirus epidemic, enrollment may not be sufficient this year to report any data, however we anticipate updates on patient enrollment as the year goes on. The company will be evaluating biopsy samples to look for HIF2α knockdown, and if good target engagement is noted this would serve as proof-of-principle for additional solid tumor indications where HIF2α is known to drive tumor growth.

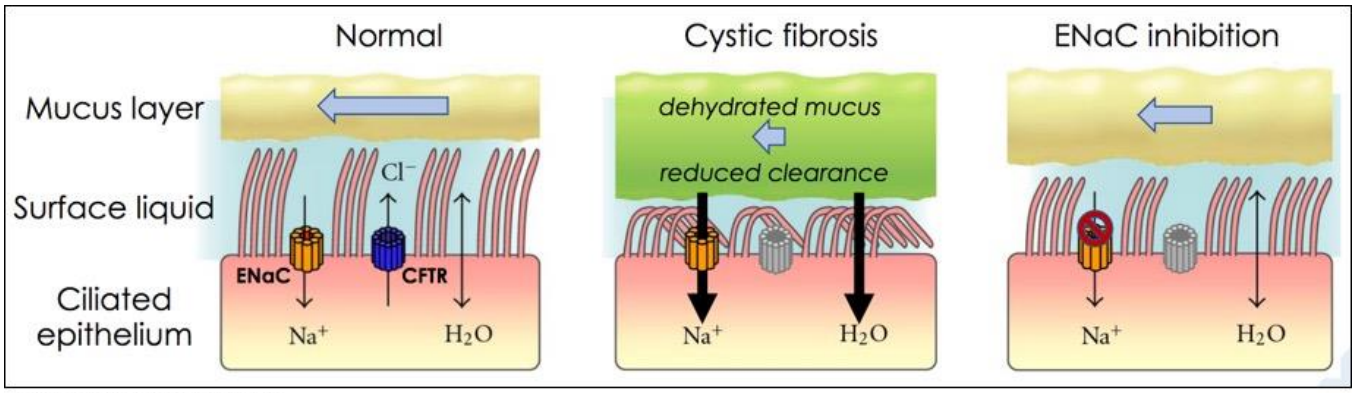
ARO-HSD: This targets hydroxysteroid 17β-dehydrogenase 13 (HSD17B13), a member of the HSD17B family that is markedly upregulated in patients and mice with non-alcoholic fatty liver disease (NAFLD) (Su *et al*, 2019). Loss-of-function mutations in HSD17B13 provide the strongest known protection against NASH cirrhosis, alcoholic hepatitis, and cirrhosis (Abul-Husn *et al*., 2018). In the CDAA (choline-deficient, methionine-reduced, 60% fat) mouse model of non-alcoholic steatohepatitis (NASH), once-weekly treatment with 3 mg/kg ARO-HSD resulted in decreased steatosis, inflammation, and hepatocyte degeneration along with inhibition of liver fibrosis.



Source: Arrowhead Pharmaceuticals, Inc.

The company initiated a Phase 1/2 clinical trial in March 2020 and is through the first dosing cohort, however enrollment in the second cohort was paused due to the coronavirus epidemic. Plans are underway to initiate enrollment soon and it will likely end up being only a minor delay with no lasting effects on timelines. Just as with other trials conducted by the company, the trial is starting with a single dose study in normal volunteers and a multiple dose study in patients with suspected or documented NASH. Biopsies will likely need to be performed in this initial study to determine proper target engagement (knockdown of HSD17B13) and duration of the effect.

ARO-ENaC: This targets the epithelial sodium channel (ENaC) and is being developed for the treatment of cystic fibrosis (CF). CF patients have reduced clearance of dehydrated mucus due to a defect in the CFTR gene that conducts chloride ions across epithelial cell membranes. The lack of Cl^- movement and continued activity of ENaC promotes the dehydration of mucus, however inhibiting the activity of ENaC improves this condition.



Source: Arrowhead Pharmaceuticals, Inc.

Multiple studies validate ENaC as a target in CF. A mutation that increases ENaC activity in patients with a mutation in only one CFTR allele ($CFTR^{+/-}$) causes atypical CF, thus suggesting that decreased ENaC activity could decrease CF pathophysiology (Rauh *et al*., 2010). A loss-of-function mutation in ENaC in pseudohypoaldosteronism (PAH) results in no sodium absorption from airway surfaces, a volume of airway surface liquid that is more than twice the normal value, and an increase in mucociliary clearance compared to healthy individuals (Kerem *et al*., 1999). Lastly, CF patients with a homozygous F508del mutation who lives into their fifth or sixth decade of life were identified and found to have mutations in ENaC genes (Agrawal *et al*., 2017).

Thus far, Arrowhead has shown in preclinical models that ARO-ENaC can durably silence pulmonary αENaC expression in a dose dependent manner in rats and preserves lung clearance in a sheep mucostatic model of CF. While there have been many advancements in the treatment of CF patients, opportunities still exist to help those patients that either a) don't respond to treatment, and/or b) to enhance the response for those on standard of care therapies. Importantly, treatment targeting ENaC can be used in all CF patients, regardless of genotype.

The company has initiated a Phase 1/2 clinical trial in healthy volunteers and CF patients, however it is too early to tell what, if any, effect the coronavirus pandemic will have on the trial in terms of timeline delays. Thus, it is still uncertain if the company will have enough data to present at scientific conferences this year. Assuming the treatment is safe and effective, we believe a Phase 3 study could be initiated in 2021 in CF along with other trials in additional indications (COPD, asthma, pulmonary fibrosis).

Valuation

We value Arrowhead using a probability adjusted DCF model that takes into account potential revenues from the company's development pipeline. We use an 8% discount rate and for all partnerships we model for a 15% royalty rate.

ARO-AAT: We model for an NDA filing in 2023 and approval in 2024 with the company commercializing the drug in the U.S. and partnering in the E.U. We estimate peak sales of $600 million in the U.S. and $500 mililon in the E.U. Using a 60% probability of approval leads to an NPV of approximately $580 million.

ARO-APOC3: We model for an NDA filing in 2022 and approval in 2023 with the company commercializing the drug in the U.S. and partnering in the E.U. We estimate peak sales of $300 million in

the U.S. and $400 million in the E.U. Using a 50% probability of approval leads to an NPV of approximately $290 million.

ARO-ANG3: We model for an NDA filing in 2026 and approval in 2027 with the company commercializing the drug in the U.S. and partnering in the E.U. We estimate peak sales of $1.3 billion in the U.S. and $1.5 billion in the E.U. Using a 30% probability of approval leads to an NPV of approximately $360 million.

ARO-ENaC: We model for an NDA filing in 2024 and approval in 2025 with the company commercializing the drug in the U.S. and partnering in the E.U. We estimate peak sales of $1.0 billion in the U.S. and $1.0 billion in the E.U. Using a 30% probability of approval leads to an NPV of approximately $430 million.

ARO-HIF2: We model for an NDA filing for kidney cancer in 2025 and approval in 2026 with the company commercializing the drug in the U.S. and partnering in the E.U. We estimate peak sales of $1.0 billion in the U.S. and $600 million in the E.U. Using a 30% probability of approval leads to an NPV of approximately $340 million. In addition, we value the extension of the HIF2 program into other solid tumor indications at $1 billion.

ARO-HSD: We model for an NDA filing in 2025 and approval in 2026 with the company commercializing the drug in the U.S. and partnering in the E.U. We estimate peak sales of $1.0 billion in the U.S. and $1.3 billion in the E.U. Using a 30% probability of approval leads to an NPV of approximately $350 million.

Combining the NPVs for each of the company's programs, assigning a value of $100 million for the Amgen partnership, $1 billion for the JNJ partnership, and $1.5 billion for the TRiM™ platform, and adding in the current cash position leads to a total NPV of approximately $6.4 billion. Dividing this by the fully diluted share count of approximately 109.9 million shares leads to a valuation of $58 per share.

PROJECTED FINANCIALS

Arrowhead Pharmaceuticals, Inc.	FY2019 A	Q1FY20 A	Q2FY20 A	Q3FY20 E	Q4FY20 E	FY2020 E	FY2021 E	FY2022 E
Revenue	$168.80	$29.45	$23.53	$18.52	$20.62	$92.12	$73.22	$50.00
YOY Growth	*945.7%*	*-38.8%*	*-44.9%*	*-57.2%*	*-87.8%*	*165.8%*	*52.1%*	*17.1%*
Total Revenues	**$168.8**	**$29.5**	**$23.5**	**$18.5**	**$20.6**	**$92.1**	**$73.2**	**$50.0**
YOY Growth	*945.7%*	*-38.8%*	*-44.9%*	*-57.2%*	*-87.8%*	*165.8%*	*52.1%*	*17.1%*
Cost of Revenue	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	**$168.8**	**$29.5**	**$23.5**	**$18.5**	**$20.6**	**$92.1**	**$73.2**	**$50.0**
Gross Margin	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*
R&D	$81.0	$23.4	$29.4	$24.7	$25.3	$102.8	$105.0	$110.0
% R&D	*48.0%*	*79.4%*	*125.1%*	*133.2%*	*122.8%*	*111.6%*	*143.4%*	*220.0%*
Salary and G&A	$26.6	$10.9	$16.3	$11.7	$12.2	$51.2	$52.2	$55.0
% SG&A	*15.7%*	*37.1%*	*69.4%*	*63.4%*	*59.3%*	*55.6%*	*71.3%*	*110.0%*
Other expenses	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
% Other	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Operating Income	**$61.2**	**($4.9)**	**($22.2)**	**($17.9)**	**($16.9)**	**($61.9)**	**($84.0)**	**($115.0)**
Operating Margin	*36.3%*	-	-	-	-	*-67.2%*	*-114.7%*	*-230.0%*
Other Income (Net)	$7.0	$2.2	$2.4	$2.0	$1.7	$8.3	$7.0	$6.0
Pre-Tax Income	**$68.1**	**($2.7)**	**($19.8)**	**($15.9)**	**($15.2)**	**($53.6)**	**($77.0)**	**($109.0)**
Net Taxes (benefit)	$0.2	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0.3%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Reported Net Income	**$68.0**	**($2.7)**	**($19.8)**	**($15.9)**	**($15.2)**	**($53.6)**	**($77.0)**	**($109.0)**
YOY Growth	-	-	-	-	-	-	-	-
Net Margin	*40.3%*	-	-	-	-	*-58.2%*	*-105.2%*	*-218.0%*
Reported EPS	**$0.69**	**($0.03)**	**($0.20)**	**($0.16)**	**($0.15)**	**($0.53)**	**($0.74)**	**($1.04)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	98.6	97.1	101.7	101.9	102.0	100.7	104.5	104.5

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

© Copyright 2020, Zacks Investment Research. All Rights Reserved.

HISTORICAL STOCK PRICE



© Copyright 2020, Zacks Investment Research. All Rights Reserved.

DISCLOSURES

The following disclosures relate to relationships between Zacks Small-Cap Research ("Zacks SCR"), a division of Zacks Investment Research ("ZIR"), and the issuers covered by the Zacks SCR Analysts in the Small-Cap Universe.

ANALYST DISCLOSURES

I, David Bautz, PhD, hereby certify that the view expressed in this research report accurately reflect my personal views about the subject securities and issuers. I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the recommendations or views expressed in this research report. I believe the information used for the creation of this report has been obtained from sources I considered to be reliable, but I can neither guarantee nor represent the completeness or accuracy of the information herewith. Such information and the opinions expressed are subject to change without notice.

INVESTMENT BANKING AND FEES FOR SERVICES

Zacks SCR does not provide investment banking services nor has it received compensation for investment banking services from the issuers of the securities covered in this report or article.
Zacks SCR has received compensation from the issuer directly, from an investment manager, or from an investor relations consulting firm engaged by the issuer for providing non-investment banking services to this issuer and expects to receive additional compensation for such non-investment banking services provided to this issuer. The non-investment banking services provided to the issuer includes the preparation of this report, investor relations services, investment software, financial database analysis, organization of non-deal road shows, and attendance fees for conferences sponsored or co-sponsored by Zacks SCR. The fees for these services vary on a per-client basis and are subject to the number and types of services contracted. Fees typically range between ten thousand and fifty thousand dollars per annum. Details of fees paid by this issuer are available upon request.

POLICY DISCLOSURES

This report provides an objective valuation of the issuer today and expected valuations of the issuer at various future dates based on applying standard investment valuation methodologies to the revenue and EPS forecasts made by the SCR Analyst of the issuer's business.
SCR Analysts are restricted from holding or trading securities in the issuers that they cover. ZIR and Zacks SCR do not make a market in any security followed by SCR nor do they act as dealers in these securities. Each Zacks SCR Analyst has full discretion over the valuation of the issuer included in this report based on his or her own due diligence. SCR Analysts are paid based on the number of companies they cover. SCR Analyst compensation is not, was not, nor will be, directly or indirectly, related to the specific valuations or views expressed in any report or article.

ADDITIONAL INFORMATION

Additional information is available upon request. Zacks SCR reports and articles are based on data obtained from sources that it believes to be reliable, but are not guaranteed to be accurate nor do they purport to be complete. Because of individual financial or investment objectives and/or financial circumstances, this report or article should not be construed as advice designed to meet the particular investment needs of any investor. Investing involves risk. Any opinions expressed by Zacks SCR Analysts are subject to change without notice. Reports or articles or tweets are not to be construed as an offer or solicitation of an offer to buy or sell the securities herein mentioned.

CANADIAN COVERAGE

This research report is a product of Zacks SCR and prepared by a research analyst who is employed by or is a consultant to Zacks SCR. The research analyst preparing the research report is resident outside of Canada, and is not an associated person of any Canadian registered adviser and/or dealer. Therefore, the analyst is not subject to supervision by a Canadian registered adviser and/or dealer, and is not required to satisfy the regulatory licensing requirements of any Canadian provincial securities regulators, the Investment Industry Regulatory Organization of Canada and is not required to otherwise comply with Canadian rules or regulations.