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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 Data Readouts in 2021…

Based on our probability adjusted DCF model that takes into account potential future revenues from the company's development products, ARWR is valued at $100/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 (02/09/21)	$88.41
Valuation	**$100.00**

OUTLOOK

On February 4, 2021, Arrowhead Pharmaceuticals, Inc. (ARWR) announced financial results for the first quarter of fiscal year 2021 and provided a business update. Twelve-month biopsy data for ARO-AAT is expected in the next month or two, with mid-2021 data readouts for ARO-ENaC (FEV1 data for first dosing cohorts), ARO-HIF2 (preliminary knockdown data), and ARO-HSD (biopsy data). The company will also be initiating multiple clinical trials for ARO-ANG3 and ARO-APOC3 in the first half of 2021. Lastly, we anticipate initiation of the company's first skeletal muscle-targeted program and two additional pulmonary programs during 2021. Following modifications to our model, we have increased our valuation to $100.

SUMMARY DATA

52-Week High	**$90.47**
52-Week Low	**$20.56**
One-Year Return (%)	**106.32**
Beta	**1.39**
Average Daily Volume (sh)	**722,655**
Shares Outstanding (mil)	**104**
Market Capitalization ($mil)	**$9,176**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**66**
Insider Ownership (%)	**4**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**257.5**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2020 Estimate	**-315.8**
P/E using 2021 Estimate	**-151.3**

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

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2020	29.5 A	23.5 A	27.4 A	7.6 A	88.0 A
2021	21.3 A	43.0 E	37.0 E	38.0 E	139.3 E
2022					150.0 E
2023					150.0 E

Earnings per Share

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2019	-$0.03 A	-$0.20 A	-$0.15 A	-$0.47 A	-$0.84 A
2020	-$0.20 A	-$0.05 E	-$0.12 E	-$0.15 E	-$0.52 E
2021					-$0.48 E
2022					-$0.52 E

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WHAT'S NEW

Business Update

Multiple Catalysts in 2021

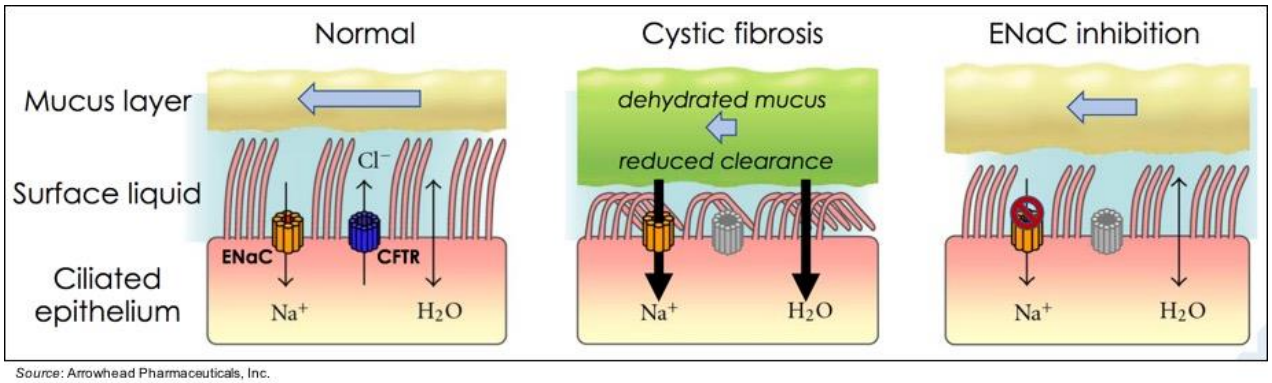
Arrowhead Pharmaceuticals Inc (ARWR) is developing medicines that cause gene silencing using RNA interference (RNAi), a specific means of inhibiting the expression of genes and stopping the production of a specific protein. The company has a deep and diverse pipeline consisting of the following development product candidates, including eight in-house programs and five partnered drugs, four with Johnson and Johnson (JNJ) and one with Amgen (AMGN). In addition, we anticipate the initiation of a skeletal muscle-targeted program and two additional pulmonary programs in 2021.



Source: Arrowhead Pharmaceuticals, Inc.

ARO-ENaC

ARO-ENaC 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 live 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 standard of care therapies 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.

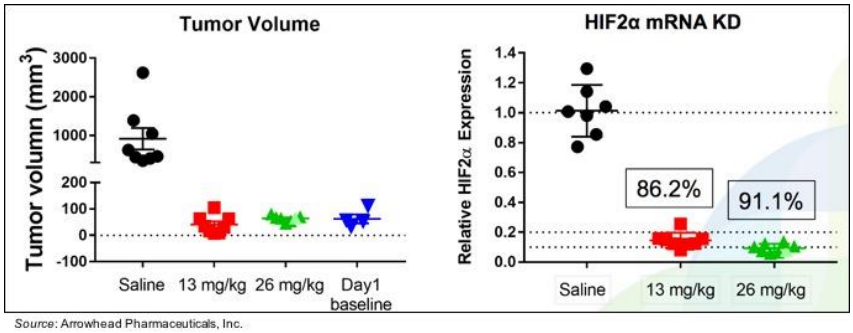
The company is currently conducting a Phase 1/2 clinical trial in 24 healthy volunteers and up to 24 CF patients. Thus far, dosing has completed in all single-dose healthy volunteers and the company is pleased with the safety and tolerability seen thus far. This is important as previous ENaC small molecule inhibitors have been dose limited by toxicity.

We anticipate FEV1 and lung clearance index (LCI) data from the first dosing levels in CF patients and ENaC knockdown data in healthy volunteers in mid-2021. Results will only be available for a small number of CF patients, thus interpreting FEV1 and LCI data may be difficult from this early readout based on the high level of variability typical for those outcomes. However, ENaC knockdown in healthy volunteers should be easier to interpret. The company is hoping to see 50% knockdown, but at this point it is difficult to determine what type of knockdown will translate to a clinically meaningful outcome.

ARO-HIF2

ARO-HIF2 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 HIF2α 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 HIF2α mRNA were decreased 86.2% and 91.1% compared to vehicle control, showing excellent target engagement.



Source: Arrowhead Pharmaceuticals, Inc.

Arrowhead is currently conducting a Phase 1b dose-finding trial in three cohorts with at least six patients per cohort. The second dose cohort is currently enrolling. We anticipate HIF2α knockdown data based on pre- and post-treatment biopsies in mid-2021, and just as with ARO-ENaC, management believes that 50% knockdown would be a positive signal for the program. The company is also evaluating preliminary efficacy data, but it is likely too soon to derive anything meaningful on PFS or ORR outcomes.

ARO-HSD

ARO-HSD 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 non-alcoholic steatohepatitis (NASH) cirrhosis, alcoholic hepatitis, and cirrhosis (Abul-Husn *et al*., 2018). In the CDAA (choline-deficient, methionine-reduced, 60% fat) mouse model of NASH, once-weekly treatment with 3 mg/kg ARO-HSD resulted in decreased steatosis, inflammation, and hepatocyte degeneration along with inhibition of liver fibrosis.

Arrowhead is conducting a Phase 1/2 single and multiple dose-escalating study and have completed the single dose portion in healthy volunteers' cohorts and are currently enrolling and dosing the multi-dose patient portion of the study in those with NASH or suspected NASH. Due to the fact that HSD17B13 is not a secreted protein the only way to assess proper target engagement is through liver biopsies and we anticipate biopsy data in mid-2021. In contrast to other agents in development for NASH, we don't anticipate any effect on liver fat, but at this point will instead be interested in the depth and duration of knockdown of HSD17B13.

ARO-AAT

ARO-AAT is 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).

Arrowhead is currently conducting the SEQUOIA Phase 2/3 trial and the AROAAT2002 open label study. The company previously announced interim 24-week biopsy data for four patients from AROAAT2002. Those results showed that three of four patients experienced a decline in intra-hepatic mutant AAT protein (Z-AAT) polymer and one patient showed a reduction of 97%. Management had previously indicated that they did not anticipate seeing a reduction in Z-AAT polymer this early in the trial, and with a reduction of up to 97% in one patient these results clearly exceeded those expectations and could lead to a significant positive effect for AATD patients.

We anticipate 12-month biopsy data for the AROAAT2002 study in the next month or two and the company plans to meet with the FDA to discuss changes to the study design and endpoints to streamline and accelerate the timeline for that program.

ARO-APOC3 and ARO-ANG3

ARO-APOC3 and ARO-ANG3 are Arrowhead's two wholly-owned cardiometabolic candidates. Please see our previous report for a discussion of the clinical trial data generated thus far for each of those programs.

Upcoming catalysts for these programs include:
- Initiate a Phase 2b dose-finding clinical trial for ARO-ANG3
- File an IND for ARO-APOC3
- Initiate two Phase 2b trials for ARO-APOC3
- Potentially initiate a Phase 3 trial in patients with familial chylomicronemia syndrome (FCS)

Financial Update

On February 4, 2021, Arrowhead announced financial results for the first quarter of fiscal year 2021 that ended Dec. 31, 2020. The company reported revenue of approximately $21.3 million for the first quarter of fiscal year 2021 compared to approximately $29.5 million for the first quarter of fiscal year 2020. This revenue consists of the recognition of a portion of the $252.6 million initial transaction associated with the agreements with Janssen and $8.2 million of revenue associated with the Takeda collaboration.

R&D expenses for the three-month period ending December 31, 2020 were $36.6 million compared to $23.4 million for the three-month period ending December 31, 2019. The increase was primarily due to increased salaries, candidate costs, discovery costs, and non-cash stock-based compensation. G&A expenses for the first quarter of fiscal year 2021 were $8.8 million compared to $10.9 million for the first quarter of fiscal year 2020. The decrease was primarily due to decreased salary expenses, facilities-related expenses, and non-cash stock-based compensation.

Arrowhead exited the first quarter of fiscal year 2021 with approximately $416.2 million in cash, cash equivalents, and investments. In January 2021, the company received the $300 million upfront payment from Takeda associated with the ARO-AAT collaboration, thus we estimate that the company currently has approximately $700 million in cash, cash equivalents, and investments. As of February 1, 2021, Arrowhead had approximately 103.8 million shares outstanding and, when factoring in stock options and restricted stock units, a fully diluted share count of approximately 111.9 millon.

Conclusion

Arrowhead is shaping up to have a very exciting 2021 with multiple data readouts in the next 6 months for the ARO-AAT, ARO-ENaC, ARO-HIF2, and ARO-HSD programs. In addition, the company will be initiating multiple clinical trials for ARO-ANG3 and ARO-APOC3. Lastly, we anticipate the initiation of a new skeletal-muscle targeted program and two more pulmonary programs before the end of 2021. By the end of the year, the company could have at least 11 clinical programs targeting four different cell types, which could result in enormous value creation for shareholders. We have moved our DCF model up a year and increased the probability of approval for ARO-AAT, ARO-APOC3, and ARO-ANG3. This has resulted in an increase to our valuation to $100, with the potential for further upside if there are positive results later this year from ARO-ENaC, ARO-HIF2, and/or ARO-HSD.

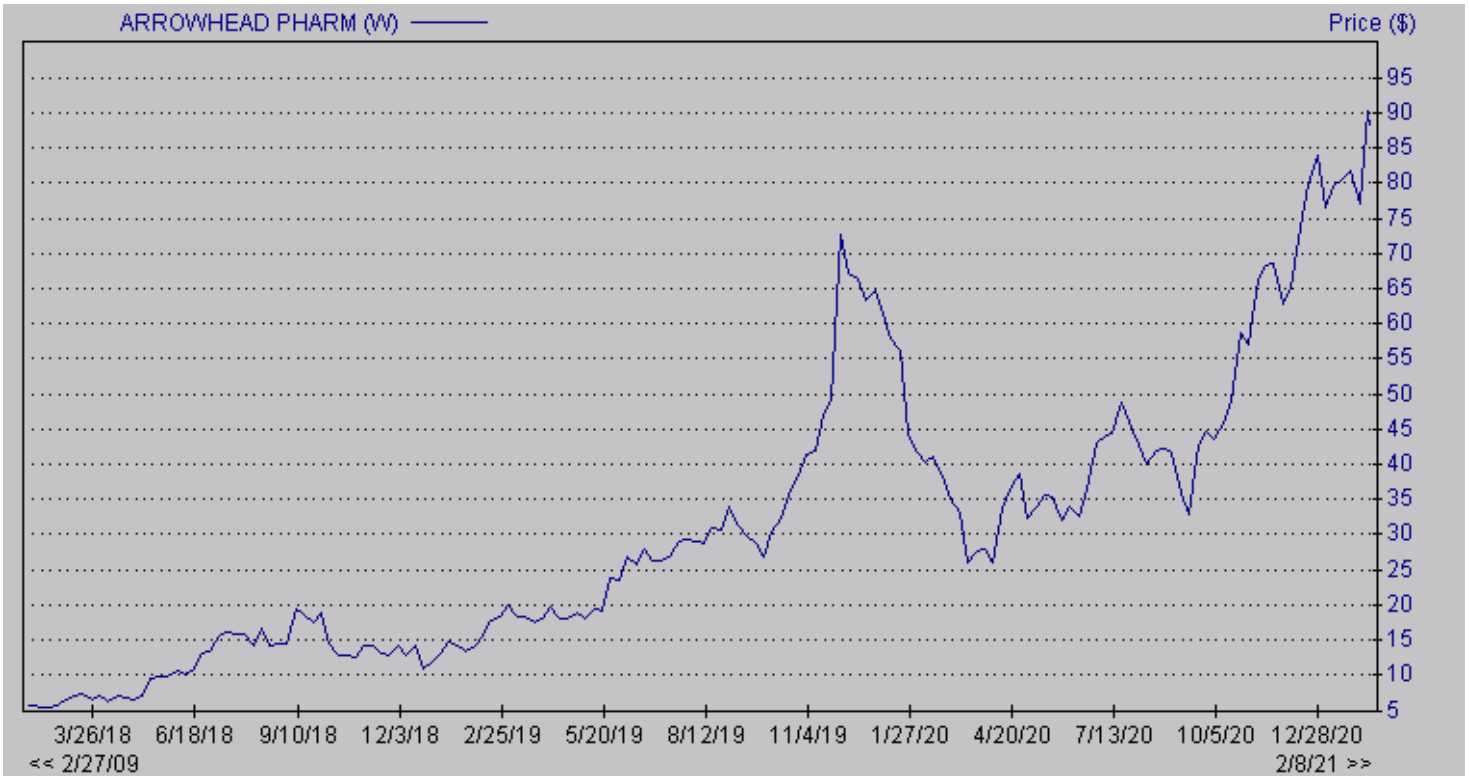
PROJECTED FINANCIALS

Arrowhead Pharmaceuticals, Inc.	FY2020 E	Q1FY21 A	Q2FY21 E	Q3FY21 E	Q4FY21 E	FY2021 E	FY2022 E	FY2023 E
Revenue	$87.99	$21.30	$43.00	$37.00	$38.00	$139.30	$150.00	$150.00
YOY Growth	*153.9%*	*-9.5%*	*57.1%*	*384.7%*	*-56.8%*	*189.3%*	*251.3%*	*246.5%*
Total Revenues	**$88.0**	**$21.3**	**$43.0**	**$37.0**	**$38.0**	**$139.3**	**$150.0**	**$150.0**
YOY Growth	*-47.9%*	*-9.5%*	*57.1%*	*384.7%*	*-56.8%*	*189.3%*	*251.3%*	*246.5%*
Cost of Revenue	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	**$88.0**	**$21.3**	**$43.0**	**$37.0**	**$38.0**	**$139.3**	**$150.0**	**$150.0**
Gross Margin	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*
R&D	$128.9	$36.6	$37.0	$38.0	$41.0	$152.6	$155.0	$160.0
% R&D	*146.5%*	*171.6%*	*86.0%*	*102.7%*	*107.9%*	*109.5%*	*103.3%*	*106.7%*
Salary and G&A	$52.3	$8.8	$13.0	$14.0	$15.0	$50.8	$55.0	$56.0
% SG&A	*59.4%*	*41.3%*	*30.2%*	*37.8%*	*39.5%*	*36.5%*	*36.7%*	*37.3%*
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	**($93.2)**	**($24.1)**	**($7.0)**	**($15.0)**	**($18.0)**	**($64.1)**	**($60.0)**	**($66.0)**
Operating Margin	*-105.9%*	-	-	-	-	*-46.0%*	*-40.0%*	*-44.0%*
Other Income (Net)	$8.6	$3.3	$2.1	$2.2	$2.4	$10.0	$8.9	$9.0
Pre-Tax Income	**($84.6)**	**($20.7)**	**($4.9)**	**($12.8)**	**($15.6)**	**($54.0)**	**($51.1)**	**($57.0)**
Net Taxes (benefit)	$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%*
Reported Net Income	**($84.6)**	**($20.7)**	**($4.9)**	**($12.8)**	**($15.6)**	**($54.0)**	**($51.1)**	**($57.0)**
YOY Growth	-	-	-	-	-	-	-	-
Net Margin	*-96.1%*	-	-	-	-	*-38.8%*	*-34.1%*	*-38.0%*
Reported EPS	**($0.84)**	**($0.20)**	**($0.05)**	**($0.12)**	**($0.15)**	**($0.52)**	**($0.48)**	**($0.52)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	100.7	102.8	104.0	104.5	105.0	104.1	107.0	110.0

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

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