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Arrowhead Pharmaceuticals, Inc. (ARWR-NASDAQ)

ARWR: Phase 3 PALISADE Study of ARO-APOC3 Underway…

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 (05/16/22)	$31.64
Valuation	**$100.00**

OUTLOOK

On May 10, 2022, Arrowhead Pharmaceuticals, Inc. (ARWR) announced financial results for the second quarter of fiscal year 2022 and provided a business update. Arrowhead recently initiated the company's first Phase 3 clinical trial, the PALISADE study, of ARO-APOC3 in patients with familial chylomicronemia syndrome (FCS). Two additional Phase 2b studies of ARO-APOC3, SHASTA-2 and MUIR, are approximately 50% enrolled with full enrollment expected in the fourth quarter of 2022. Enrollment has also completed in the Phase 2b ARCHES study of ARO-ANG3 in patients with mixed dyslipidemia. Data should be available in the first half of 2023. The GATEWAY study of ARO-ANG3 will enroll up to 16 patients with Homozygous Familial Hypercholesterolemia (HoFH) and the trial should be fully enrolled by the end of 2022.

SUMMARY DATA

52-Week High	**$90.32**
52-Week Low	**$28.95**
One-Year Return (%)	**-56.56**
Beta	**1.41**
Average Daily Volume (sh)	**891,236**
Shares Outstanding (mil)	**106**
Market Capitalization ($mil)	**$3,345**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**65**
Insider Ownership (%)	**3**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**60.1**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2020 Estimate	**-28.9**
P/E using 2021 Estimate	**-16.2**

Risk Level	**Above Avg.**
Type of Stock	**Mid-Growth**
Industry	**Med-Drugs**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2021	21.3 A	32.8 A	45.9 A	38.3 A	138.3 A
2022	27.4 A	151.8 A	45.0 E	40.0 E	262.4 E
2023					200.0 E
2024					250.0 E

Earnings per Share

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2021	-$0.20 A	-$0.26 A	-$0.29 A	-$0.61 A	-$1.36 A
2022	-$0.60 A	$0.42 A	-$0.45 E	-$0.51 E	$1.14 E
2023					-$1.66 E
2024					-$1.45 E

WHAT'S NEW

Business Update

Cardiometabolic Programs Progressing

Arrowhead Pharmaceuticals, Inc (ARWR) has two late-stage cardiometabolic programs, ARO-APOC3 and ARO-ANG3. ARO-APOC3 is targeted to apolipoprotein C-III (APOC3), a component of very low-density lipoprotein (VLDL) and an inhibitor of lipoprotein lipase. This program is currently focused on treating patients with severe hypertriglyceridemia and dyslipidemia. In support of targeting APOC3, an APOC3 loss-of-function mutation results in lower triglyceride (TG) levels (Jørgensen *et al*., 2014). Arrowhead is currently testing ARO-APOC3 in the following clinical trials as part of the SUMMIT program:

PALISADE: This is a Phase 3, double blind, placebo controlled trial in patients with familial chylomicronemia syndrome (FCS). These patients have fasting triglyceride levels >880 mg/dL. Approximately 72 patients are expected to be enrolled and assigned to one of four dose cohorts in a 2:1:2:1 manner (ARO-APOC3 25 mg, volume-matching placebo, ARO-APOC3 50 mg, volume-matching placebo). The primary endpoint of the trial is the percent change from baseline at month 10 in fasting triglycerides. Secondary and exploratory endpoints will include the change in lipid parameters, incidence of acute pancreatitis, and other measures. The goal is to have the trial fully enrolled by mid-2023 and complete it in 2024.

SHASTA-2: This is a Phase 2b, double blind, placebo controlled trial in patients with severe hypertriglyceridemia (SHTG; TG > 500 mg/dL). The primary endpoint of the trial is the safety and efficacy of ARO-APOC3 and to select a dosing regimen for later-stage patients in this population. We anticipate approximately 216 patients being enrolled. This trial is approximately 50% enrolled and full enrollment should be completed in the fourth quarter of 2022.

MUIR: This is a Phase 2b, double blind, placebo controlled trial in adults with mixed dyslipidemia, which is defined as having TG between 150 and 500 mg/dL and non-HDL cholesterol > 100 mg/dL or LDL cholesterol >70 mg/dL. The primary objective is to evaluate the safety and efficacy of ARO-APOC3 and to select a dosing regimen for later stage trials in this patient population. We anticipate a total of approximately 320 patients being enrolled. This trial is approximately 50% enrolled and full enrollment should be completed in the fourth quarter of 2022.

ARO-ANG3 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 (Musunuru *et al*., 2010), with one study showing an ANGPTL3 loss of function associated with a 34% reduction in odds of coronary artery disease (CAD) (Stitziel *et al*., 2017). Arrowhead is currently testing ARO-APOC3 in the following clinical trials under the VISTA program:

ARCHES-2: This is a Phase 2b, double blind, placebo controlled trial in adults with mixed dyslipidemia (patients are defined just as those in the MUIR trial). The primary objective is to evaluate the safety and efficacy of ARO-ANG3 and to select a dosing regimen for later stage trials in this patient population. Three dose levels of ARO-ANG3 (50 mg, 100 mg, 200 mg) are being tested. Patients will receive a subcutaneous injection on day 1 and week 12. Following the 36-week end-of-study visit, patients will be eligible to continue in an open label extension period. The trial should complete by the end of 2022 and topline data should be available in the first half of 2023.

GATEWAY: This will be a Phase 2, open-label trial in patients with homozygous familial hypercholesterolemia (HoFH). Approximately 16 patients will be randomized 1:1 to receive two doses of 200 or 300 mg ARO-ANG3 on Day 1 and Day 84 and they will be evaluated over a 36-week period. The

company is hoping to have the study fully enrolled or at least have a meaningful number of patients enrolled by the end of 2022.

Update on Earlier Stage Programs

During the recent quarterly update call, management provided the following updates on the company's earlier stage assets:

ARO-C3: This program is targeting complement component 3 (C3). The complement pathway is a part of the innate immune system and C3 activation is required for the classical complement pathway, the alternative complement pathway, and the lectin pathway. The company recently dosed the first subjects in a Phase 1/2, placebo controlled, dose-escalating trial to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics in up to 24 healthy volunteers (Part 1) and up to 24 adult patients with paroxysmal nocturnal hemoglobinuria (PNH) and up to 14 adult patients with complement-mediated renal disease (Part 2). Dosing has completed in three of four planned cohorts in Part 1 and Part 2 will initiate when the dose has been selected following the completion of Part 1.

ARO-DUX4: This is Arrowhead's first muscle targeted program and is being developed for the treatment of facioscapulohumeral muscular dystrophy (FSHD). FSHD is a rare genetic disorder characterized by progressive muscle weakness and degeneration most notably in the face, shoulders, and upper arms, however it usually causes weakness in multiple muscle groups all over the body. The disease is caused by the inappropriate expression of the transcription factor double homeobox protein 4 gene (*DUX4*) (Gabriëls *et al*., 1999). Thus far, it has been difficult for those working in the field to identify a reliable biomarker of DUX4 expression or of disease activity in patients with FSDH. For this reason, the Phase 1 results are likely only going to be informative in terms of initial safety, with longer studies likely being required to see any changes in clinical endpoints. With this in mind, Arrowhead is going to hold off on Phase 2 studies until after the results of chronic toxicology studies are known to de-risk those trials. Once the results of the chronic toxicology results are known the company will provide an update on timelines for further studies.

ARO-JNJ1 (JNJ-75220795): This is a collaboration with Janssen that is developing an siRNA therapeutic designed to reduce the expression of patatin-like phospholipase domain containing 3 (PNPLA3) in liver as a treatment for non-alcoholic steatohepatitis (NASH). It is currently being tested in a Phase 1 clinical trial.

ARO-MUC5AC: This targets expression of MUC5AC in bronchial epithelium. MUC5AC is a mucin protein that is upregulated in the airway of asthmatic patients (Bonser *et al*., 2017). As shown in MUC5AC knockout mice, it is not required for normal mucociliary transport or anti-bacterial defense (Roy *et al*., 2014). The protein plays a role in asthma pathogenesis based on results from ovalbumin sensitization and challenge studies (Evans *et al*., 2015). A clinical trial application has been filed and it has now received regulatory clearance to begin clinical trials, which we anticipate initiating in mid-2022.

ARO-RAGE: This targets the receptor for advanced glycation end-products (RAGE). Single nucleotide polymorphisms in the human gene for RAGE are associated with an increased incidence of asthma. RAGE is required for an allergic airway inflammatory response through release of IL-33 into the airway and it acts upstream of IL-5 and IL-13 (Oczypok *et al*., 2015). A soluble form of the protein (S-RAGE) found in the serum can be utilized as an easily measured biomarker to monitor for target knockdown. A clinical trial application has been filed and it has now received regulatory clearance to begin clinical trials, which we anticipate initiating in mid-2022.

Financial Update

On May 10, 2022, Arrowhead announced financial results for the second quarter of fiscal year 2022 that ended March 31, 2022. The company reported revenue of approximately $151.8 million for the second quarter of fiscal year 2022 compared to approximately $32.8 million for the second quarter of fiscal year

2021. This revenue consisted primarily from the recognition of the $120 million associated with the upfront payment from GSK from the GSK license agreement.

R&D expenses for the quarter ending March 31, 2022 were approximately $76.0 million compared to $44.7 million for the quarter ending March 31, 2021. The increase was primarily due to increased salaries, the progression of pipeline candidates into and through clinical trials, R&D discovery expenses, and non-cash stock-based compensation. G&A expenses for the second quarter of fiscal year 2022 were $34.3 million compared to $16.3 million for the second quarter of fiscal year 2021. The increase was primarily due to increased non-cash, stock-based compensation.

Arrowhead exited the second quarter of fiscal year 2022 with approximately $603.5 million in cash, cash equivalents, and investments. As of May 5, 2022, Arrowhead had approximately 105.7 million shares outstanding and, when factoring in stock options and restricted stock units, a fully diluted share count of approximately 113.2 million.

Conclusion

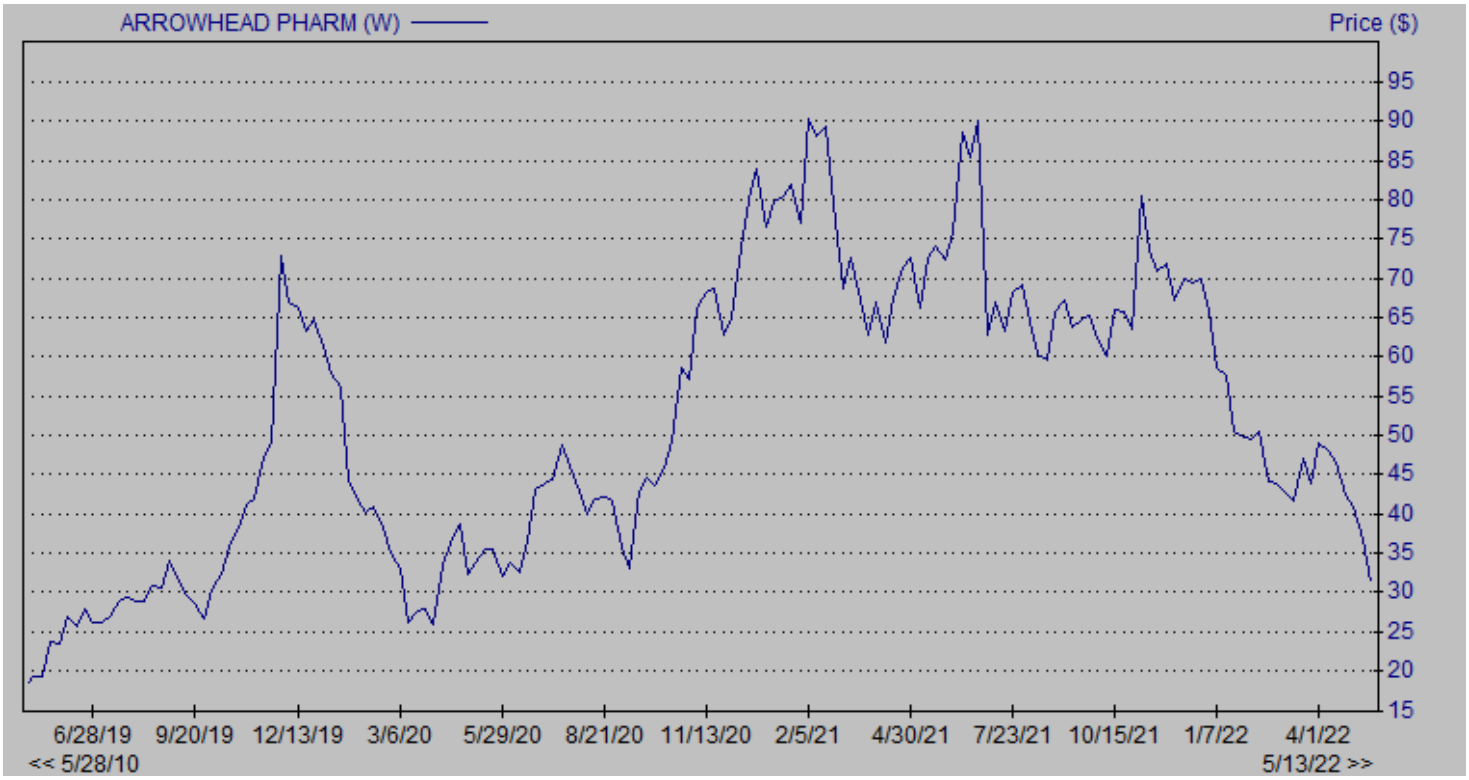
Arrowhead is continuing to advance a large number of products through the clinic. The company did announce that ARO-HIF2 is being discontinued based on the changing competitive landscape and the data acquired thus far. While disappointing that the program won't continue, the company did learn a lot of important lessons regarding target engagement and siRNA-mediated knockdown in solid tumors, which should be applicable to future oncology programs. We have removed ARO-HIF2 from our DCF model, which has resulted in our valuation decreasing to $92 per share, however we still view Arrowhead as a top pick among small/mid cap bios.

PROJECTED FINANCIALS

Arrowhead Pharmaceuticals, Inc.	FY2021 A	Q1FY22 A	Q2FY22 A	Q3FY22 E	Q4FY22 E	FY2022 E	FY2023 E	FY2024 E
Revenue	$138.29	$27.44	$151.81	$45.00	$40.00	$264.24	$200.00	$250.00
YOY Growth	*187.2%*	*-16.4%*	*230.8%*	*17.5%*	*-71.1%*	*518.9%*	*362.0%*	*48.1%*
Total Revenues	**$138.3**	**$27.4**	**$151.8**	**$45.0**	**$40.0**	**$264.2**	**$200.0**	**$250.0**
YOY Growth	*187.2%*	*-16.4%*	*230.8%*	*17.5%*	*-71.1%*	*518.9%*	*362.0%*	*48.1%*
Cost of Revenue	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	**$138.3**	**$27.4**	**$151.8**	**$45.0**	**$40.0**	**$264.2**	**$200.0**	**$250.0**
Gross Margin	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*
R&D	$206.3	$65.8	$76.0	$68.0	$70.0	$279.8	$275.0	$300.0
% R&D	*149.2%*	*239.7%*	*50.1%*	*151.1%*	*175.0%*	*105.9%*	*137.5%*	*120.0%*
Salary and G&A	$81.0	$25.0	$34.3	$26.0	$26.0	$111.3	$110.0	$115.0
% SG&A	*58.6%*	*91.1%*	*22.6%*	*57.8%*	*65.0%*	*42.1%*	*55.0%*	*46.0%*
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	**($149.0)**	**($63.3)**	**$41.6**	**($49.0)**	**($56.0)**	**($126.8)**	**($185.0)**	**($165.0)**
Operating Margin	*-107.8%*	-	-	-	-	*-48.0%*	*-92.5%*	*-66.0%*
Other Income (Net)	$8.2	$0.4	$2.8	$1.5	$1.5	$6.3	$6.0	$6.0
Pre-Tax Income	**($140.8)**	**($62.9)**	**$44.4**	**($47.5)**	**($54.5)**	**($120.5)**	**($179.0)**	**($159.0)**
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	**($140.8)**	**($62.9)**	**$44.4**	**($47.5)**	**($54.5)**	**($120.5)**	**($179.0)**	**($159.0)**
YOY Growth	-	-	-	-	-	-	-	-
Net Margin	*-101.9%*	-	-	-	-	*-45.6%*	*-89.5%*	*-63.6%*
Reported EPS	**($1.36)**	**($0.60)**	**$0.42**	**($0.45)**	**($0.51)**	**($1.14)**	**($1.66)**	**($1.45)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	103.7	104.5	105.5	105.5	106.0	105.4	108.0	110.0

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

HISTORICAL STOCK PRICE



Source: Zacks SCR

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