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Arrowhead Pharmaceuticals, Inc. (ARWR-NASDAQ)

ARWR: Catalyst-Rich 2023…

Based on our probability adjusted DCF model that takes into account potential future revenues from the company's development products, ARWR is valued at $80/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 (02/08/23)	$33.62
Valuation	**$80.00**

OUTLOOK

On February 6, 2022, Arrowhead Pharmaceuticals, Inc. (ARWR) announced financial results for the first quarter of fiscal year 2023 that ended December 31, 2023 and provided a business update. The company has a large number of catalysts ahead in 2023, including multiple data readouts and trial initiations. In the first quarter of 2023 we anticipate Phase 1 data from JNJ for JNJ-0795; in the second quarter of 2023 we anticipate early P1/2 data for ARO-RAGE, ARO-MUC5AC, and ARO-C3, the disclosure of the company's next cell type and supporting data, and the initiation of the P1/2 study of DUX4; in mid-2023 we anticipate data from the ARCHES and GATEWAY P2 trials of ARO-ANG3; in the second half of 2023 we anticipate data from the SHASTA-2 and MUIR P2 studies of ARO-APOC3 and the initiation of the P2 study of JNJ-0795; in the fourth quarter of 2022 we anticipate early data for ARO-MMP7.

SUMMARY DATA

52-Week High	**$54.66**
52-Week Low	**$27.79**
One-Year Return (%)	**-35.52**
Beta	**1.02**
Average Daily Volume (sh)	**895,856**
Shares Outstanding (mil)	**108**
Market Capitalization ($mil)	**$3,641**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**65**
Insider Ownership (%)	**5**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**60.7**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2020 Estimate	**-31.1**
P/E using 2021 Estimate	**-13.6**

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

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2022	27.4 A	151.8 A	32.4 A	31.6 A	243.2 A
2023	62.5 A	30.0 E	32.0 E	34.0 E	158.5 E
2024					250.0 E
2025					300.0 E

Earnings per Share

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2022	-$0.60 A	$0.42 A	-$0.68 A	-$0.81 A	-$1.67 A
2023	-$0.39 A	-$0.68 E	-$0.69 E	-$0.72 E	-$2.50 E
2024					-$1.64 E
2025					-$1.30 E

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WHAT'S NEW

Business Update

Multiple Catalysts Ahead in 2023

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 that includes 12 drug candidates in clinical trials (six that are wholly owned and six that are partnered) with that number anticipated to increase to 15 or 16 by the end of 2023. We are anticipating a number of catalysts this year that includes data readouts and trial initiations:

- In the first quarter of 2023 we anticipate Phase 1 data for JNJ-0795, which is being developed by Janssen for the treatment of non-alcoholic steatohepatitis (NASH). The collaboration with Janssen for JNJ-0795 was announced in November 2021 and stems from a research collaboration and option agreement entered into with Janssen in October 2018. JNJ-0795 targets phospholipase domain containing 3 (PNPLA3). A polymorphism in PNPLA3 that results in a change from isoleucine (I) to methionine (M) at position 148 of the protein is strongly associated with increased hepatic fat levels and with hepatic inflammation, two hallmarks of NASH and its precursor non-alcoholic fatty liver disease (NAFLD) (Romeo *et al*., 2008).

- In the second quarter of 2023 we anticipate early Phase 1/2 data from normal healthy volunteers (NHVs) for two of the company's pulmonary programs, ARO-RAGE and ARO-MUC5AC. ARO-RAGE 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. ARO-MUC5AC targets the expression of MUC5AC, which is a mucin protein that is upregulated in the airway of asthmatic patients (Bonser *et al*., 2017). ARO-RAGE is being studied in the ARORAGE-1001 trial that will enroll up to 64 NHVs and up to 16 patients with mild-to-moderate asthma (NCT05276570). ARO-MUC5AC is being studied in the AROMUC5AC-1001 trial that will enroll up to 42 NHVs and up to 16 patients with moderate-to-severe asthma (NCT05292950).

- In the second quarter of 2023 we anticipate early data from the Phase 1/2 clinical trial of ARO-C3, which targets 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 Phase 1/2 trial is investigating 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 patients with complement-mediated renal disease (Part 2). We anticipate data from Part 1 of the study in the second quarter of 2023 and the company will likely be selecting doses for Part 2 of the study this month in the hopes of opening patient cohort enrollment in the coming months.

- In the second quarter of 2023 we anticipate the initiation of the ARO-DUX4 Phase 1/2 clinical trial. ARO-DUX4 is the company'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). Arrowhead previously presented preclinical data on the ability of the TRiM platform to be used in muscle and in a mouse model of FSHD with a tamoxifen-inducible human DUX4 gene, ARO-DUX4 prevented the tamoxifen-

induced increase in DUX4, prevented DUX-4 induced body weight loss, prevented and reversed muscle fibrosis, and prevented rotarod performance loss.

- In mid-2023, we anticipate data from the ARCHES-2 and GATEWAY trials of ARO-ANG3, which targets angiopoietin like protein 3 (ANGPTL3). ANGPTL3 loss-of-function mutations lead to low levels of low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (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).

    - **ARCHES-2**: 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-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. Total planned enrollment of 204 patients is complete. Data presented at AHA showed that patients treated with 50, 100, or 200 mg of ARO-ANG3 had reductions in triglycerides of up to 59% and LDL-C up to 32% at Week 16. In addition, ARO-ANG3 was associated with median relative reduction in liver fat at Week 24 of 28% for the 100 and 200 mg dose, with no liver specific adverse events reported to date. ARO-ANG3 has been well tolerated with TEAEs) reflecting the underlying comorbidities of the study population.

    - **GATEWAY**: This is a Phase 2, open-label trial in patients with homozygous familial hypercholesterolemia (HoFH). Sixteen patients were randomized 1:1 to receive two doses of 200 or 300 mg ARO-ANG3 on Day 1 and Day 84 and they are being evaluated over a 36-week period. The study is fully enrolled and data should be available in mid-2023.

- In the second half of 2023, we anticipate data from the SHASTA-2 and MUIR trials of ARO-APOC3, which is targeted to apolipoprotein C-III (APOC3), a component of VLDL and an inhibitor of lipoprotein lipase. In support of targeting APOC3, an APOC3 loss-of-function mutation results in lower TG levels (Jørgensen *et al*., 2014). Arrowhead is also conducting the Phase 3 PALISADE trial of ARO-APOC3 in patients with familial chylomicronemia syndrome (FCS). We anticipate enrollment completing for that trial in the second quarter of 2023 and for topline data to be reported in the second quarter of 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. The trial is fully enrolled with 216 subjects and data from 177 subjects that had entered the study at the time of data cutoff was recently presented at the 2022 American Heart Association Scientific Sessions (Ballantyne *et al*., 2022). Following two doses of ARO-APOC3, data showed patients treated with 10, 25, or 50 mg ARO-APOC3 had decreases in TGs up to 86%, non-HDL-C up to 45%, and increased HDL-C up to 99% through the week 16 timepoint. Safety data was encouraging as ARO-APOC3 was well tolerated with the treatment emergent adverse events (TEAEs) reflecting the underlying comorbidities of the study population.

    - **MUIR**: This is a Phase 2b, double blind, placebo controlled trial in adults with mixed dyslipidemia, which is defined the same as in the ARCHES-2 trial. 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. The total planned enrollment of 320 patients has been reached. Data presented by the company showed patients treated with 10, 25, of 50 mg ARO-APOC3 had decreases of TGs up to 65%, non-HDL-C up to 28%, LDL-C of up to 20%, and increased HDL-C up to 50% through the week 16 timepoint.

- In the fourth quarter of 2023, we anticipate early data from the Phase 1/2 clinical trial of ARO-MMP7, which targets matrix metalloproteinase 7 (MMP7), a secreted endopeptidase that is highly overexpressed in patients with idiopathic pulmonary fibrosis (IPF) (Bauer *et al*., 2017). MMP7 is also useful as a biomarker due to its increased expression being correlated with disease progression. In addition, MMP7 knockout mice are protected from pulmonary fibrosis induced by intratracheal bleomycin (Zuo *et al*., 2002). Unfortunately, MMP7 is a difficult target for drug development as there is substantial domain homology with other MMPs, thus making gene silencing a potentially useful mechanism for downregulating MMP7 expression. The Phase 1/2 clinical trial is a single ascending dose and multiple ascending dose trial designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ARO-MMP7 in up to 56 healthy volunteers and in up to 21 patients with IPF.

Financial Update

On February 6, 2023, Arrowhead announced financial results for the first quarter of fiscal year 2023 that ended December 31, 2022. The company reported revenue of approximately $62.5 million for the first quarter of fiscal year 2023 compared to approximately $27.4 million for the first quarter of fiscal year 2022. This revenue included the recognition of $16.3 million associated with the Takeda License Agreement, a $15 million milestone payment from Horizon due to the first patient being enrolled in the Phase 1 trial of HZN-457, and a $25 million milestone payment from Amgen following enrollment of the first patient in the Phase 3 trial of olpasiran.

R&D expenses for the quarter ending December 31, 2022 were approximately $83.7 million compared to $65.8 million for the quarter ending December 31, 2021. The increase was primarily due to increased salaries, facilities-related expenses, 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 first quarter of fiscal year 2023 were $21.0 million compared to $25.0 million for the first quarter of fiscal year 2022. The decrease was primarily due to lower non-cash, stock-based compensation

Arrowhead exited the first quarter of fiscal year 2023 with approximately $617.6 million in cash, cash equivalents, and investments. As of February 1, 2023, Arrowhead had approximately 108.3 million shares outstanding and, when factoring in stock options and restricted stock units, a fully diluted share count of approximately 114.9 million.

Conclusion

Arrowhead has a large number of important catalysts ahead in 2023. The most important near-term catalyst will be the early data from the ARO-RAGE and ARO-MUC5AC trials. The company has indicated that while there are currently three pulmonary programs in the clinic, the goal will be to eventually have eight or nine pulmonary programs. However, this is contingent upon being able to show that reduced expression of a target gene can be achieved in the proper cell type in a well-tolerated fashion in the lungs. If the early data from the ARO-RAGE and ARO-MUC5AC programs are encouraging, as judged by a favorable tolerability profile and ability to reduce gene expression, it would serve as a significant de-risking event for the entire pulmonary franchise.

There were news reports recently about the fact that Johnson and Johnson (JNJ) will be de-prioritizing its hepatitis B franchise, and at this point we are unsure of what that means for JNJ-3989, which JNJ licensed in 2018 as part of a wide-ranging collaboration. We do know that this does not impact JNJ-0795. However, we will have to await word on the fate of JNJ-3989, which may ultimately be returned to Arrowhead. Given the uncertainty surrounding that program we have removed it from our model, which has lowered our valuation to $80 per share.

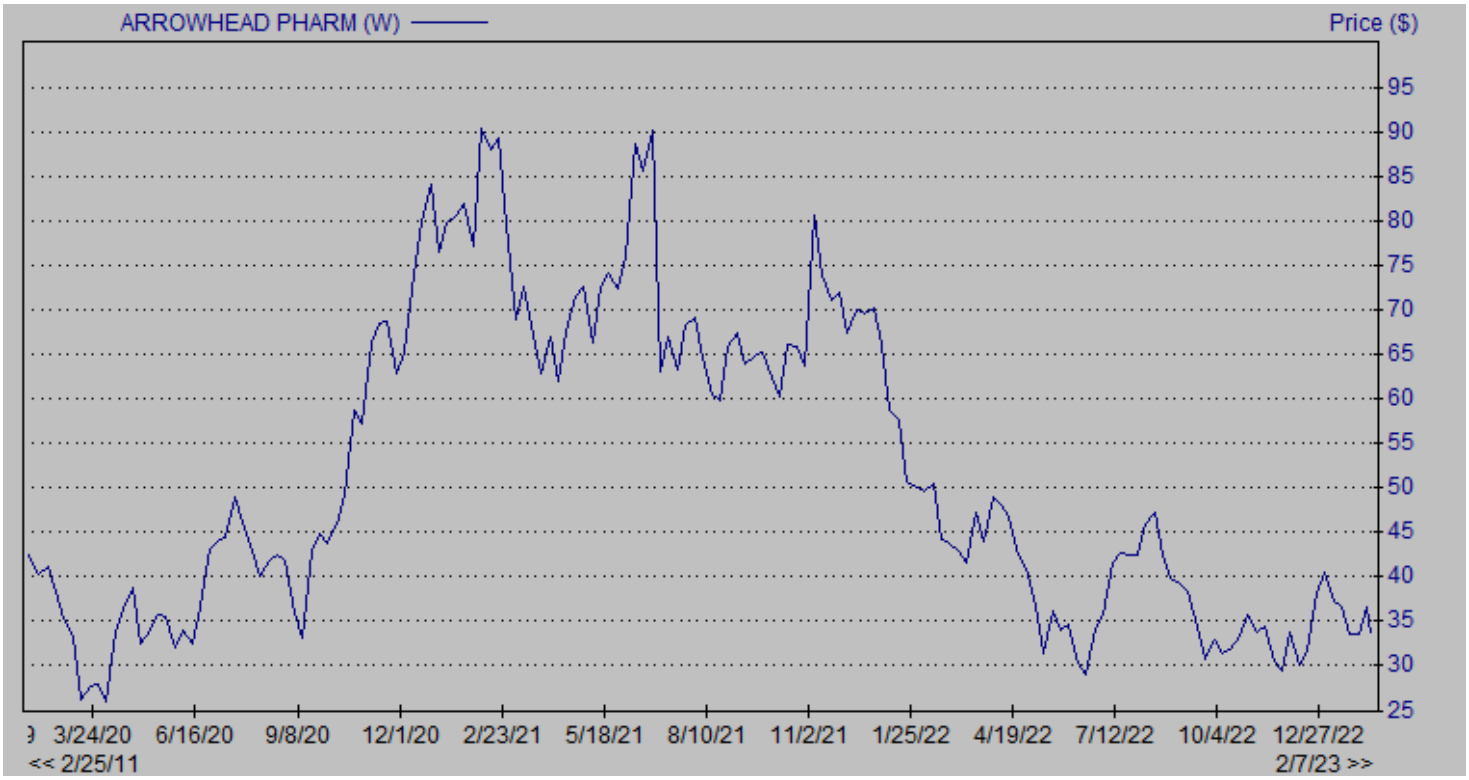
PROJECTED FINANCIALS

Arrowhead Pharmaceuticals, Inc.	FY2022 A	Q1FY23 A	Q2FY23 E	Q3FY23 E	Q4FY23 E	FY2023 E	FY2024 E	FY2025 E
Revenue	$243.23	$62.55	$30.00	$32.00	$34.00	$158.55	$250.00	$300.00
YOY Growth	*469.7%*	*-58.8%*	*-7.4%*	*1.3%*	*-86.0%*	*266.2%*	*48.1%*	*918.5%*
Total Revenues	**$243.2**	**$62.5**	**$30.0**	**$32.0**	**$34.0**	**$158.5**	**$250.0**	**$300.0**
YOY Growth	*469.7%*	*-58.8%*	*-7.4%*	*1.3%*	*-86.0%*	*266.2%*	*48.1%*	*918.5%*
Cost of Revenue	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	**$243.2**	**$62.5**	**$30.0**	**$32.0**	**$34.0**	**$158.5**	**$250.0**	**$300.0**
Gross Margin	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*
R&D	$297.3	$83.7	$75.0	$77.0	$79.0	$314.7	$310.0	$320.0
% R&D	*122.2%*	*133.8%*	*250.0%*	*240.6%*	*232.4%*	*198.5%*	*124.0%*	*106.7%*
Salary and G&A	$124.4	$21.0	$30.0	$32.0	$36.0	$119.0	$130.0	$135.0
% SG&A	*51.2%*	*33.6%*	*100.0%*	*100.0%*	*105.9%*	*75.0%*	*52.0%*	*45.0%*
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	**($178.5)**	**($42.1)**	**($75.0)**	**($77.0)**	**($81.0)**	**($275.1)**	**($190.0)**	**($155.0)**
Operating Margin	*-73.4%*	-	-	-	-	*-173.5%*	*-76.0%*	*-51.7%*
Other Income (Net)	$5.8	$0.3	$1.5	$1.5	$1.5	$4.8	$6.0	$6.0
Pre-Tax Income	**($172.7)**	**($41.8)**	**($73.5)**	**($75.5)**	**($79.5)**	**($270.3)**	**($184.0)**	**($149.0)**
Net Taxes (benefit)	$3.8	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*-2.2%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Reported Net Income	**($176.5)**	**($41.8)**	**($73.5)**	**($75.5)**	**($79.5)**	**($270.3)**	**($184.0)**	**($149.0)**
YOY Growth	-	-	-	-	-	-	-	-
Net Margin	*-72.6%*	-	-	-	-	*-170.5%*	*-73.6%*	*-49.7%*
Reported EPS	**($1.67)**	**($0.39)**	**($0.68)**	**($0.69)**	**($0.72)**	**($2.50)**	**($1.64)**	**($1.30)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	105.4	106.0	108.0	109.0	110.0	108.3	112.0	115.0

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

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