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Arrowhead Pharmaceuticals, Inc. (ARWR-NASDAQ)

ARWR: Update on Cardiometabolic Candidates…

Based on our probability adjusted DCF model that takes into account potential future revenues from the company's development products, ARWR is valued at $75/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 (12/07/20)	$65.29
Valuation	**$75.00**

OUTLOOK

On November 23, 2020, Arrowhead Pharmaceuticals, Inc. (ARWR) announced financial results for fiscal year 2020 and provided a business update. The company recently presented new clinical data for its lead cardiometabolic programs, ARO-APOC3 and ARO-ANG3 and hosted KOL events for each of those programs. In the first half of 2021, we anticipate a Phase 3 trial initiating for ARO-APOC3 in patients with familial chylomicronemia syndrome (FCS) and Phase 2 trials in patients with hypertriglyceridemia (HTG) and severe HTG. For ARO-ANG3, we anticipate a Phase 2 trial initiating in individuals with triglyceride levels >150 mg/dl in the first half of 2021.

SUMMARY DATA

52-Week High	**$70.86**
52-Week Low	**$20.56**
One-Year Return (%)	**-2.94**
Beta	**1.61**
Average Daily Volume (sh)	**1,071,029**
Shares Outstanding (mil)	**103**
Market Capitalization ($mil)	**$6,709**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**62**
Insider Ownership (%)	**4**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**319.9**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2020 Estimate	**142.6**
P/E using 2021 Estimate	**-151.3**

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)
2020	29.5 A	23.5 A	27.4 A	7.6 A	88.0 A
2021	27.0 E	28.0 E	29.0 E	30.0 E	114.0 E
2022					120.0 E
2023					125.0 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	-$0.15 E	-$0.17 E	-$0.20 E	-$0.23 E	-$0.75 E
2021					-$0.73 E
2022					-$0.74 E

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WHAT'S NEW

Business Update

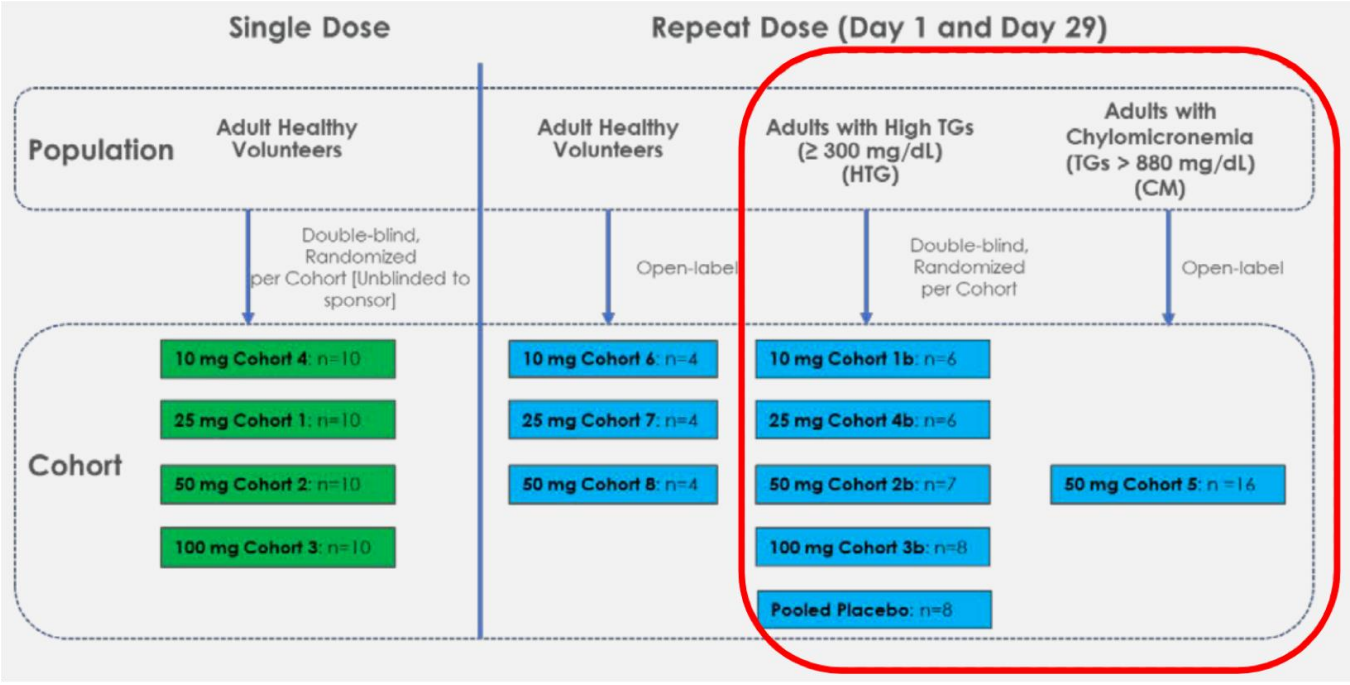
Cardiometabolic Programs Offer Enormous Potential

In November 2020, Arrowhead Pharmaceuticals, Inc. (ARWR) hosted KOL events for its lead cardiometabolic programs, ARO-APOC3 and ARO-ANG3. The company had previously announced encouraging results for each of those programs (see our previous update here) and provided a further update at the 2020 American Heart Association Scientific Sessions. The presentation for ARO-APOC3 can be found here and for ARO-ANG3 here.

ARO-APOC3

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 (SHTG), which is characterized by a triglyceride (TG) level >500 mg/dL, and a history or high risk of pancreatitis. The goal of therapy is to reduce TGs to below 500 mg/dL in order to reduce the risk of acute pancreatitis (NCEP, 2002). In support of targeting APOC3, an APOC3 loss-of-function mutation results in lower 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.

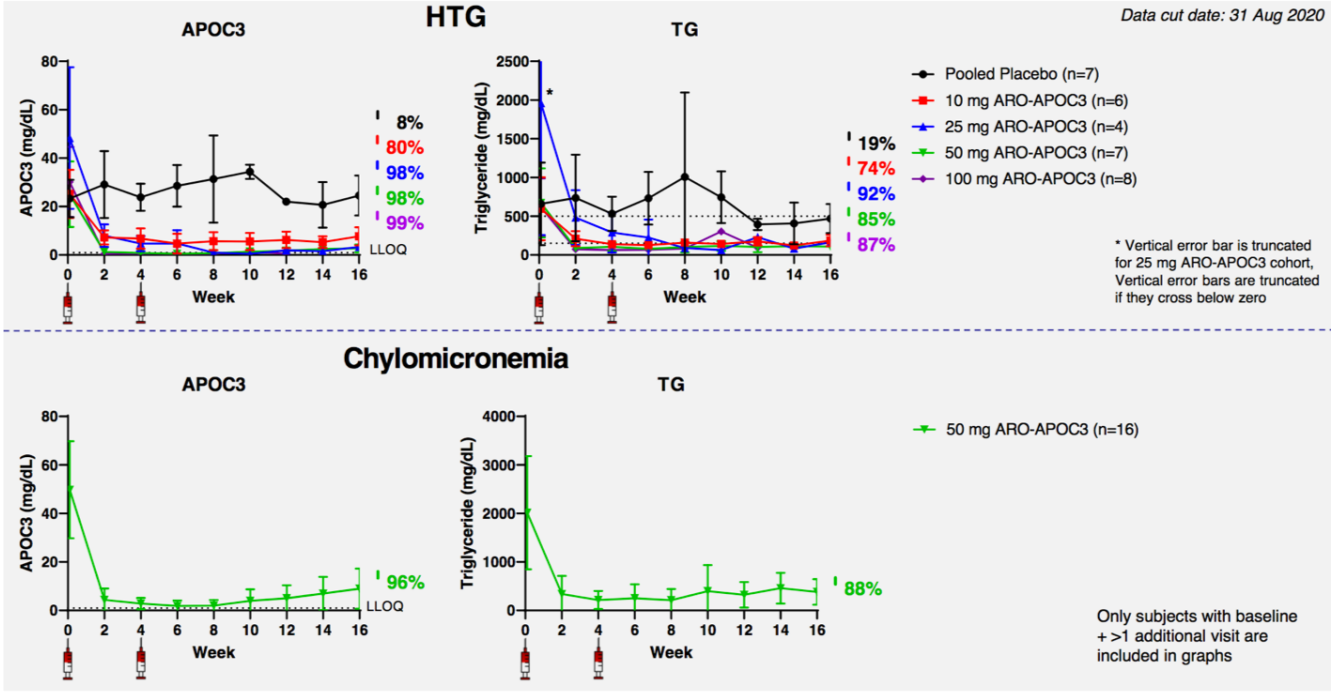
The following slide gives an overview of the Phase 1 trial of ARO-APOC3. Dosing occurred on Day 1 and Day 29 with follow-up to Day 113 (Week 16). Results from treatment of healthy volunteers was previously presented and this update concerned treatment of adults with high TGs (≥300 mg/dL) as well as those with chylomicronemia (TGs > 880 mg/dL). Results focused on changes in APOC3 as well as TGs, high-density lipoprotein (HDL) cholesterol, and non-HDL-C.



Source: Arrowhead Pharmaceuticals, Inc.

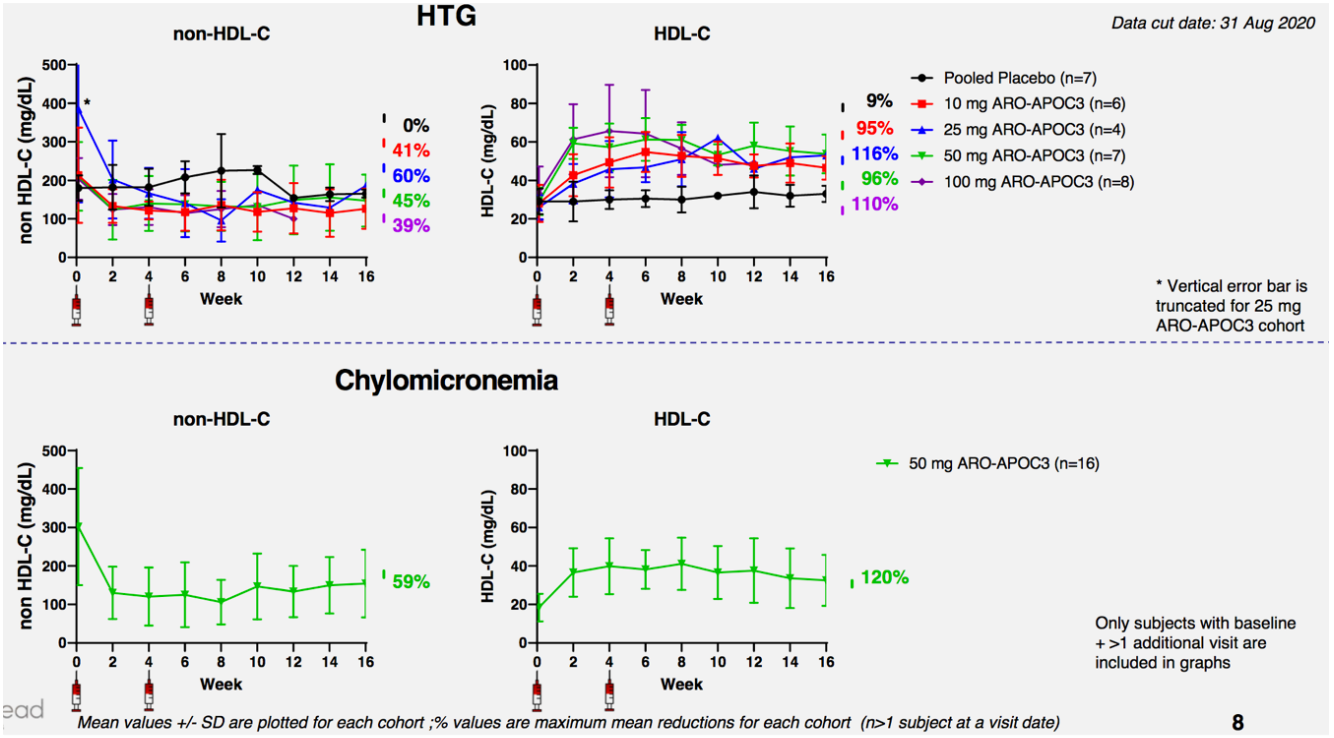
The following slide shows the percent change from baseline for APOC3 and TGs in patients with high TG and chylomicronemia. The % values to the side of each graph are maximal reductions for each cohort.

Similar to what was shown previously in healthy volunteers, treatment with ARO-APOC3 resulted in maximum decreases in APOC3 levels of 80-99% and maximal decreased TG levels by 74-92% in high TG patients. Similar results were seen in chylomicronemia patients. With a target of getting TGs below 500 mg/dL these results far surpass that and could provide meaningful improvement for patient health.



Source: Arrowhead Pharmaceuticals, Inc.

In addition to showing robust decreases in APOC3 and TG, treatment with ARO-APOC3 also results in maximal decreases in non-HDL-C of between 40-60% and maximal increases in HDL-C of >95%. Similar results are seen in both high TG and chylomicronemia patients.



Source: Arrowhead Pharmaceuticals, Inc.

We anticipate Arrowhead initiating a Phase 3 clinical trial of ARO-APOC3 in FCS patients in the first half of 2021. In addition, we anticipate a Phase 2 clinical trial in patients with severe hypertriglyceridemia (>500 mg/dL) and a Phase 2 trial in patients with high TGs (>150 mg/dL) initiating in the first half of 2021.

ARO-APOC3 Competition

To put these results into perspective, the following table shows the results from a randomized, double blind, placebo controlled, study of patients with severe hypertriglyceridemia (>500 mg/dL) who were administered Vascepa® 4 grams per day for 12 weeks (Vascepa Prescribing Information). This is not a direct comparison between the results for ARO-APOC3 and Vascepa, but merely to show what current treatment options are able to accomplish in a high triglyceride patient population. The data for Vascepa shows that following 12 weeks of treatment with 4 g daily leads to a median 27% reduction in TG, a median 8% reduction in Non-HDL-C, and a median 4% reduction in HDL-C. We believe the data for ARO-APOC3 are far and away superior, particularly when it may only require a single dose every few months to achieve the desired results while Vascepa requires two doses daily.

	VASCEPA 4 g/day N=76		Placebo N=75		Difference (95% Confidence
Parameter	**Baseline**	**% Change**	**Baseline**	**% Change**	**Interval)**
TG (mg/dL)	680	-27	703	+10	-33* (-47, -22)
LDL-C (mg/dL)	91	-5	86	-3	-2 (-13, +8)
Non-HDL-C (mg/dL)	225	-8	229	+8	-18 (-25, -11)
TC (mg/dL)	254	-7	256	+8	-16 (-22, -11)
HDL-C (mg/dL)	27	-4	27	0	-4 (-9, +2)
VLDL-C (mg/dL)	123	-20	124	+14	-29** (-43, -14)
Apo B (mg/dL)	121	-4	118	+4	-9**(-14, -3)

% Change= Median Percent Change from Baseline
Difference= Median of [VASCEPA % Change – Placebo % Change] (Hodges-Lehmann Estimate)
p-values from Wilcoxon rank-sum test

*p-value < 0.001 (primary efficacy endpoint)

**p-value < 0.05 (key secondary efficacy endpoints determined to be statistically significant according to the pre-specified multiple comparison procedure)

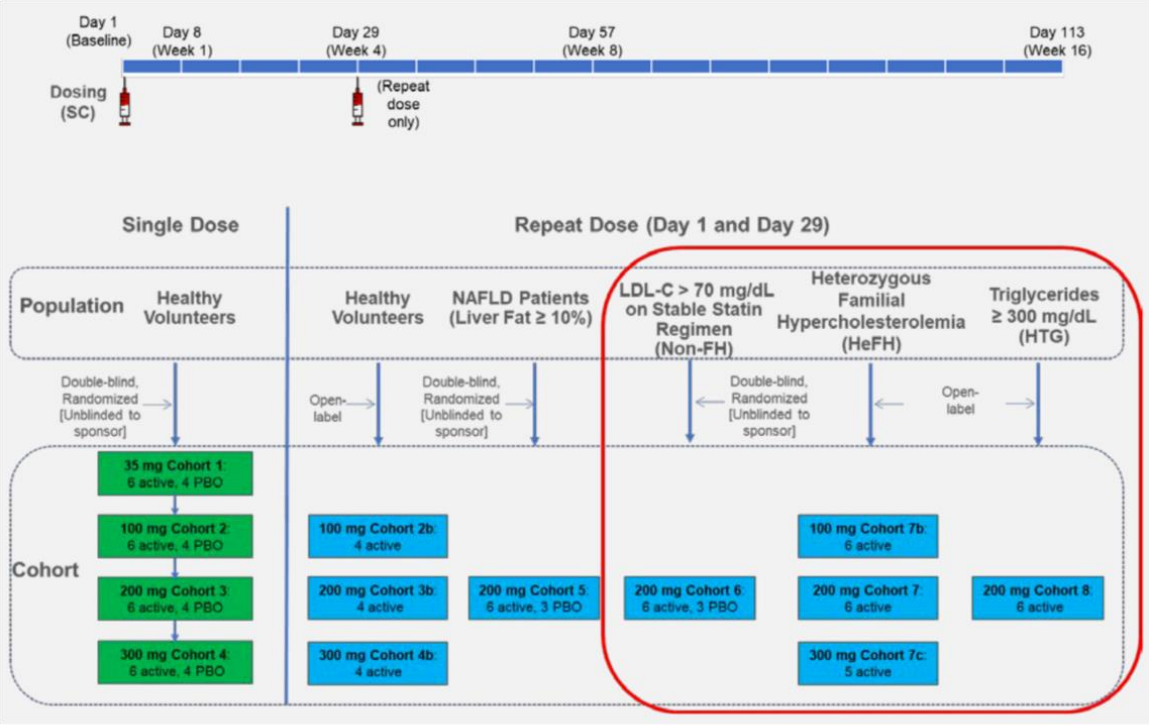
Source: Vascepa® prescribing information

An additional comparison can be made to AKCEA-APOCIII-L_{RX}, which is being developed by Ionis Pharmaceuticals in partnership with Pfizer. Positive Phase 2 results were presented at the European Society of Cardiology (ESC) Congress 2020 in August 2020. Treatment of patients with hypertriglyceridemia showed a significant decrease in TG (mean change of -60% for 50 mg dose administered every 4 weeks) and APOC3 levels (approximately 70% decrease for 50 mg dose administered every 4 weeks). While these results are impressive, the fact that ARO-APOC3 has similar if not better results and may only need to be dosed once every 3 months (or longer) puts it at an advantage to the monthly dosing required for AKCEA-APOCIII-L_{RX}. One advantage for Ionis' drug is that it is further along in development with a Phase 3 clinical trial in FCS patients having just recently initiated.

ARO-ANGPTL3

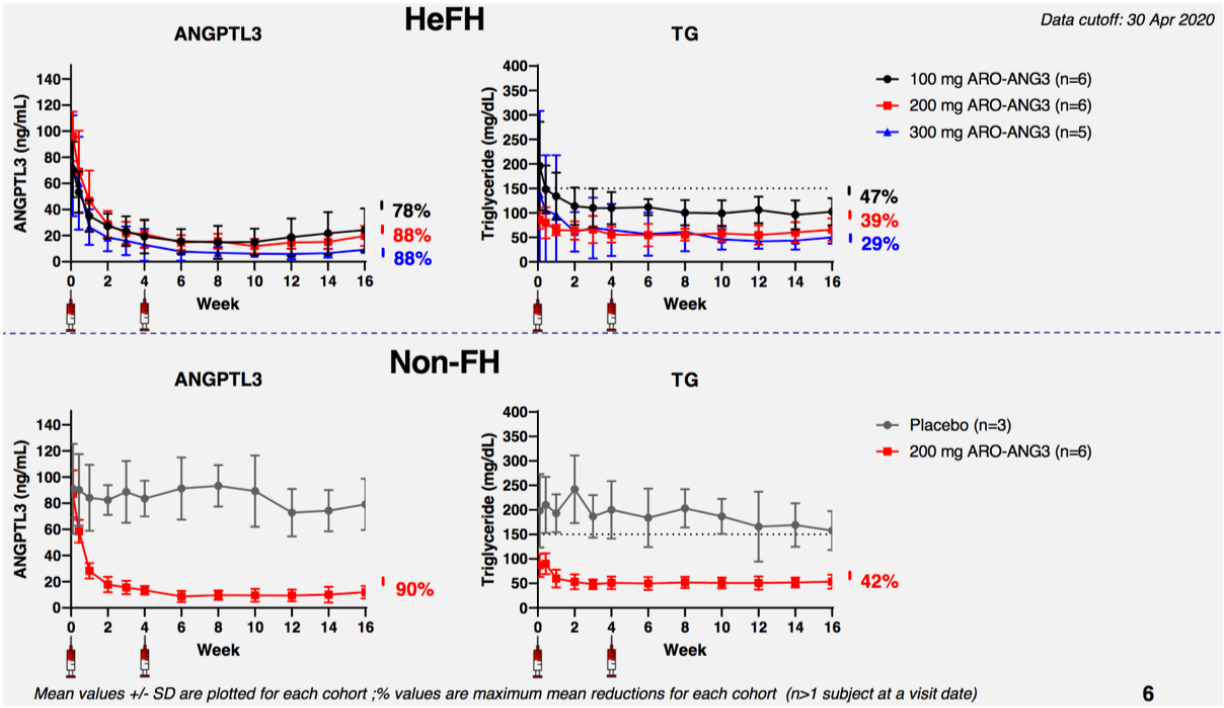
ARO-ANG3 is focused on treating patients with mixed dyslipidemia and potentially metabolic diseases through targeting angiopoietin like protein 3 (ANGPTL3). ANGPTL3 loss-of-function mutations lead to low levels of LDL, VLDL, HDL, and TG (Musunuru *et al.*, 2010), with one study showing an ANGPTL3 loss of function associated with a 34% reduction in odds of coronary artery disease (CAD) (Stitziel *et al.*, 2017). Just like APOC3, the majority of ANGPTL3 is produced in hepatocytes, also making it an ideal target for the TRiM™ platform.

The following slide gives an overview of the Phase 1 trial of ARO-ANG3. The data recently presented focused on patient populations with heterozygous familial hypercholesterolemia (HeFH), patients on stable statin therapy that continue to have LDL-C > 70 mg/dL, and patients with hypertriglyceridemia (>300 mg/dL).



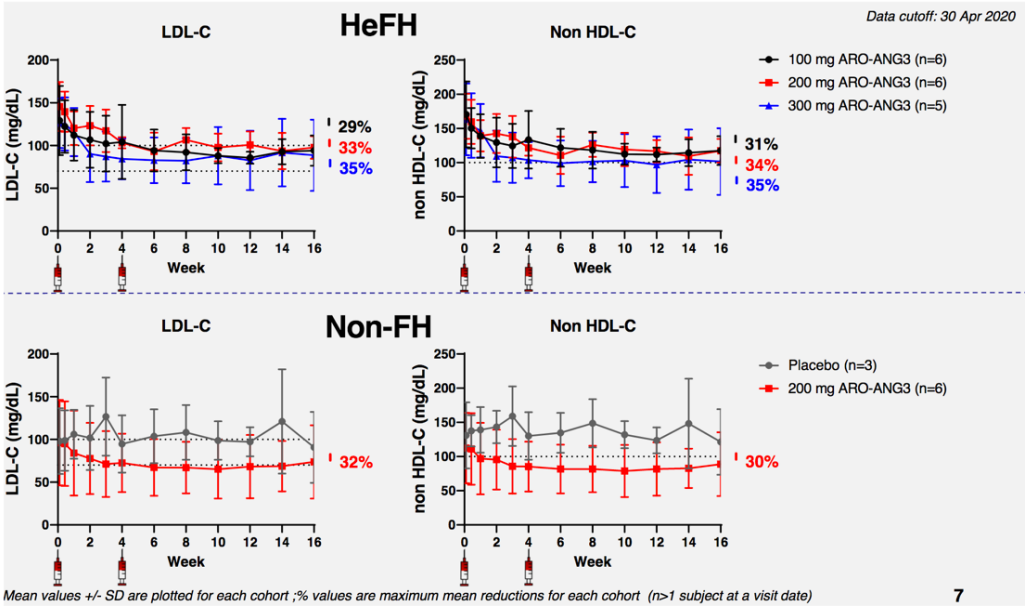
Source: Arrowhead Pharmaceuticals, Inc.

The following figure shows that ARO-ANG shows similar activity in both HeFH and non-FH patients, with average decreases of approximately 80-90% in ANGPTL3 and average decreases from baseline in TG of approximately 30-40%.



Source: Arrowhead Pharmaceuticals, Inc.

In addition, ARO-ANG3 lowered both LDL and Non HDL-C by an average of approximately 30-35% in FH and non-FH patients.



Source: Arrowhead Pharmaceuticals, Inc.

We anticipate Arrowhead initiating a Phase 2 dose finding study of ARO-ANG3 in patients with TGs >150 mg/dL in the first half of 2021 that could lead to a Phase 3 trial in mixed dyslipidemia patients (N =1500) along with a Phase 3 CV outcomes trial (N = 15,000) initiating in the second half of 2023.

ARO-ANG3 Competition

Ionis Pharmaceuticals is developing vupanorsen (formerly AKCEA-ANGPTL3-L_{Rx}), a drug that targets ANGPTL3, for the reduction of cardiovascular disease risk. Earlier in 2020, the company announced positive Phase 2 results for the drug showing an approximately 50% reduction in least squares mean triglycerides from baseline. In addition, there was an approximate 40% reduction in VLDL-C and an approximately 10% reduction in LDL-C. Pfizer recently initiated a Phase 2b study of vupanorsen in statin-treated patients with elevated non-HDL-C and TGs.

In August 2020, Regeneron Pharmaceuticals, Inc. (REGN) submitted a BLA for evinacumab as an adjunct to other lipid-lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH). The PDUFA date for evinacumab is Feb. 11, 2021.. Evinacumab is a monoclonal antibody that targets ANGPTL3. In the Phase 3 ELIPSE HoFH trial, HoFH patients (with a mean baseline LDL of 255.1 mg/dL even on maximum doses of lipid-lowering therapy) had a relative reduction from baseline in LDL cholesterol of 47.1% (Raal *et al.*, 2020). Regeneron is also evaluating evinacumab in a Phase 2 clinical trial in patients with primary hypercholesterolemia (HeFH) or non-HeFH patients with a history of clinical CVD (NCT03175367).

Positive Interim Results for ARO-AAT

On November 13, 2020, Arrowhead announced positive interim results from the company's Phase 2 AROAAT2022 open label clinical trial of ARO-AAT in patients with alpha-1-antitrypsin deficiency (AATD). A copy of the poster that was presented at AASLD can be found here.

A total of four patients with homozygous PiZZ AATD and evidence of fibrosis at screening were administered three doses of ARO-AAT at weeks 0, 4, and 16. Liver biopsies were performed at baseline and at week 24. Results showed reductions in serum Z-AAT of 86-93% and total intra-hepatic Z-AAT

reductions of 72-95%. Importantly, three out of four of the patients had reductions in Z-AAT polymer of 68-97%. The reductions in Z-AAT were accompanied by reduction of ALT (36-66%) and GGT (43-58%) in all patients. In addition, three out of four patients showed a reduction of >20% in FibroScan® values and a reduction of >30% in serum Pro-C3, a marker of fibrogenesis.

These data are very encouraging and point to ARO-AAT having a clear, positive impact on AATD. Arrowhead is also conducting the Phase 2/3 SEQUOIA trial in AATD patients in which treatment will continue for approximately two years. Given the unexpectedly positive results seen at the six-month timepoint in AROAAT2002, the company may consider approaching regulators to streamline and accelerate the SEQUOIA study.

As a reminder, in October 2020 Arrowhead announced a collaboration with Takeda Pharmaceutical Company Ltd. for the co-development and co-commercialization of ARO-AAT for the treatment of AATD. The company announced the closing of that agreement on Nov. 25, 2020. Arrowhead will receive an upfront payment of $300 million and is eligible to receive up to $740 million in development, regulatory, and commercial milestones. The agreement calls for the companies to co-develop ARO-AAT in the U.S. under a 50/50 profit-sharing structure and for Takeda to receive an exclusive license to commercialize ARO-AAT outside the U.S. with Arrowhead receiving a tiered royalty of 20-25% on net ex-U.S. sales.

Financial Update

On November 23, 2020, Arrowhead announced financial results for the fourth quarter and fiscal year (FY) 2020 that ended Sep. 30, 2020. Total revenue recorded for FY 2020 was $88.0 million, compared to $168.8 million for FY 2019. Revenue in FY2020 is related to the recognition of a portion of the $252.6 million initial transaction associated with the agreement with Janssen. In addition, in the current period the company recognized a $20 million payment from Amgen for the initiation of a Phase 2 clinical trial for AMG 890. Revenues in FY2019 were related to the recognition of a portion of the $252.6 million initial transaction associated with the agreement with Janssen.

R&D expenses for FY2020 were $128.9 million compared to $81.0 million in FY2019. The increase was primarily due to increased salaries, clinical trial costs, and increased discovery efforts. G&A expenses for FY2020 were $52.3 million compared to $26.6 million for FY2019. The increase was primarily due to increased salaries, professional services, facility costs, and stock-based compensation.

Arrowhead exited FY2020 with approximately $453 million in cash, cash equivalents, short-term investments, and long-term investments. In October 2020, Arrowhead signed a collaboration with Takeda for the co-development and co-commercialization of ARO-AAT for the treatment of AATD, which included an upfront payment of $300 million.

As of November 16, 2020, Arrowhead had approximately 102.8 million shares and, when factoring in stock options and restricted stock units, a fully diluted share count of approximately 110.8 million.

Conclusion

Arrowhead continues to produce positive data for its lead development candidates. ARO-APOC3 and ARO-ANG3 both show very impressive reductions in triglycerides and other lipoproteins in addition to exhibiting strong on-target effects with benign safety profiles. The development pathways are becoming a bit clearer now for those two candidates, with ARO-APOC3 set to enter a Phase 3 clinical trial for FCS and Phase 2 dose finding studies in different patient cohorts with elevated TGs in the first half of 2021. For ARO-ANG3 we anticipate a Phase 2 dose finding study to initiate in the first half of 2021 that could lead to a larger CV outcomes trial in 2023. Based on the outstanding clinical results seen thus far for both programs, we are increasing our estimated peak worldwide sales estimates for ARO-APOC3 to $3 billion and for ARO-ANG3 to $4.5 billion. This has increased our valuation to $75 per share.

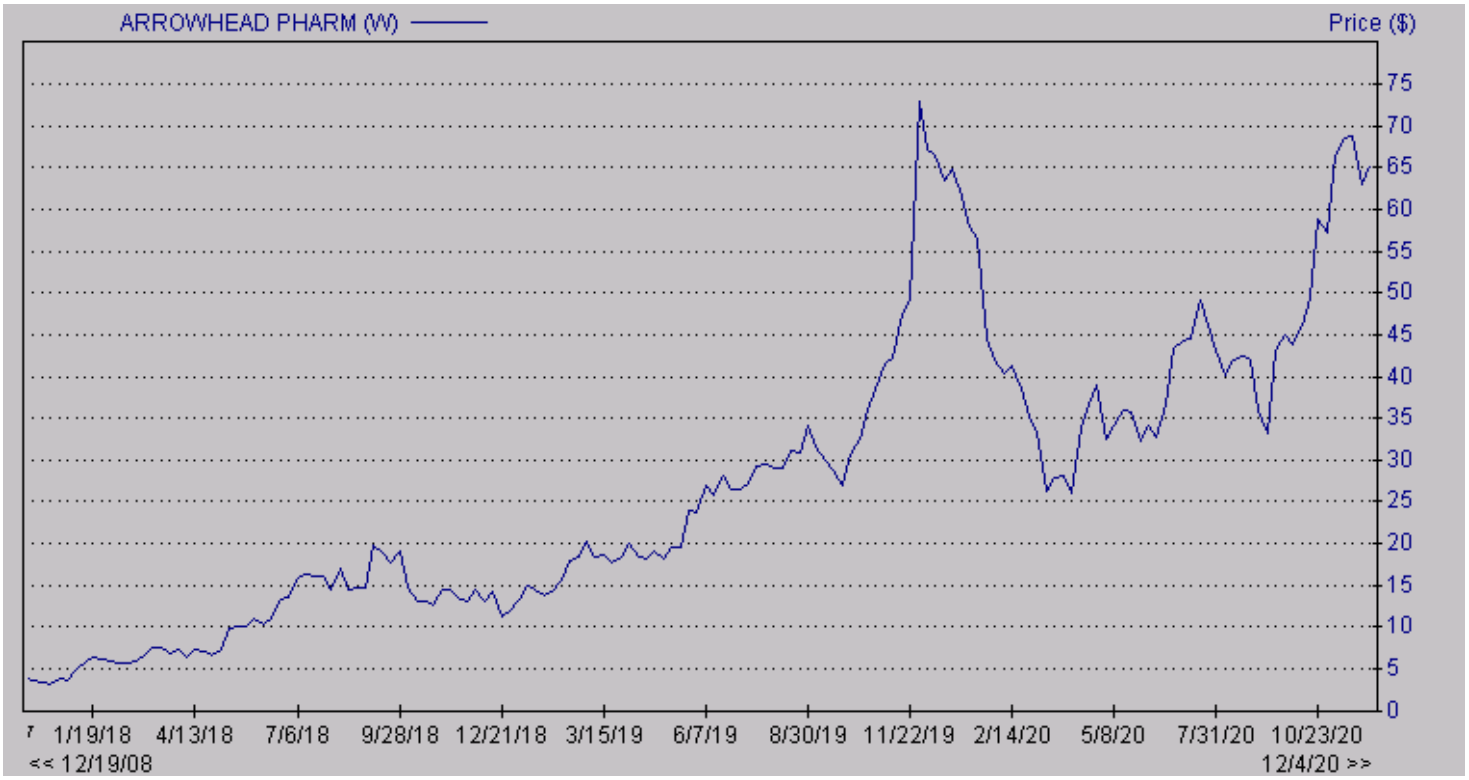
PROJECTED FINANCIALS

Arrowhead Pharmaceuticals, Inc.	FY2020 E	Q1FY21 E	Q2FY21 E	Q3FY21 E	Q4FY21 E	FY2021 E	FY2022 E	FY2023 E
Revenue	$87.99	$27.00	$28.00	$29.00	$30.00	$114.00	$120.00	$125.00
YOY Growth	*153.9%*	*14.8%*	*2.3%*	*279.9%*	*-65.9%*	*136.8%*	*181.1%*	*188.7%*
Total Revenues	**$88.0**	**$27.0**	**$28.0**	**$29.0**	**$30.0**	**$114.0**	**$120.0**	**$125.0**
YOY Growth	*-47.9%*	*14.8%*	*2.3%*	*279.9%*	*-65.9%*	*136.8%*	*181.1%*	*188.7%*
Cost of Revenue	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	**$88.0**	**$27.0**	**$28.0**	**$29.0**	**$30.0**	**$114.0**	**$120.0**	**$125.0**
Gross Margin	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*
R&D	$128.9	$32.0	$35.0	$38.0	$41.0	$146.0	$150.0	$155.0
% R&D	*146.5%*	*118.5%*	*125.0%*	*131.0%*	*136.7%*	*128.1%*	*125.0%*	*124.0%*
Salary and G&A	$52.3	$12.0	$13.0	$14.0	$15.0	$54.0	$55.0	$56.0
% SG&A	*59.4%*	*44.4%*	*46.4%*	*48.3%*	*50.0%*	*47.4%*	*45.8%*	*44.8%*
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)**	**($17.0)**	**($20.0)**	**($23.0)**	**($26.0)**	**($86.0)**	**($85.0)**	**($86.0)**
Operating Margin	*-105.9%*	-	-	-	-	*-75.4%*	*-70.8%*	*-68.8%*
Other Income (Net)	$8.6	$2.0	$2.1	$2.2	$2.4	$8.7	$8.9	$9.0
Pre-Tax Income	**($84.6)**	**($15.0)**	**($17.9)**	**($20.8)**	**($23.6)**	**($77.3)**	**($76.1)**	**($77.0)**
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)**	**($15.0)**	**($17.9)**	**($20.8)**	**($23.6)**	**($77.3)**	**($76.1)**	**($77.0)**
YOY Growth	-	-	-	-	-	-	-	-
Net Margin	*-96.1%*	-	-	-	-	*-67.8%*	*-63.4%*	*-61.6%*
Reported EPS	**($0.84)**	**($0.15)**	**($0.17)**	**($0.20)**	**($0.23)**	**($0.75)**	**($0.73)**	**($0.74)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	100.7	102.8	103.0	103.2	103.5	103.1	104.0	104.5

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

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