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September 10, 2020
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Arrowhead Pharmaceuticals, Inc. (ARWR-NASDAQ)

ARWR: Encouraging Data Presented for Both ARO-APOC3 and ARO-ANG3…

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 (09/10/20)	$36.14
Valuation	**$58.00**

OUTLOOK

On August 31, 2020, Arrowhead Pharmaceuticals, Inc. (ARWR) announced the presentation of positive data from the company's two Phase 1/2 clinical trials of ARO-APOC3 (targeting Apolipoprotein C-III) and ARO-ANG3 (targeting ANGPTL3). Presentations for both compounds were given at the European Society of Cardiology Congress 2020. Data for each compound come from the repeat-dose portion of the ongoing Phase 1/2 clinical trials in healthy volunteers. Both candidates had favorable safety and tolerability profiles with long durations of effect that may lead to dosing once every 4-6 months. Additional data for these compounds from studies in various patient populations will be shared later this year.

SUMMARY DATA

52-Week High	**$73.01**
52-Week Low	**$20.56**
One-Year Return (%)	**17.00**
Beta	**1.67**
Average Daily Volume (sh)	**849,250**
Shares Outstanding (mil)	**102**
Market Capitalization ($mil)	**$3,697**
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 (%)	**362.7**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2020 Estimate	**-86.3**
P/E using 2021 Estimate	**-36.3**

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)
2019	34.7 A	48.2 A	42.7 A	43.3 A	168.8 A
2020	29.5 A	23.5 A	27.4 A	20.6 E	101.0 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	-$0.15 A	-$0.15 E	-$0.51 E
2021					-$0.74 E
2022					-$1.04 E

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WHAT'S NEW

Business Update

Positive Data for ARO-APOC3 and ARO-ANG3 Presented at ESC 2020

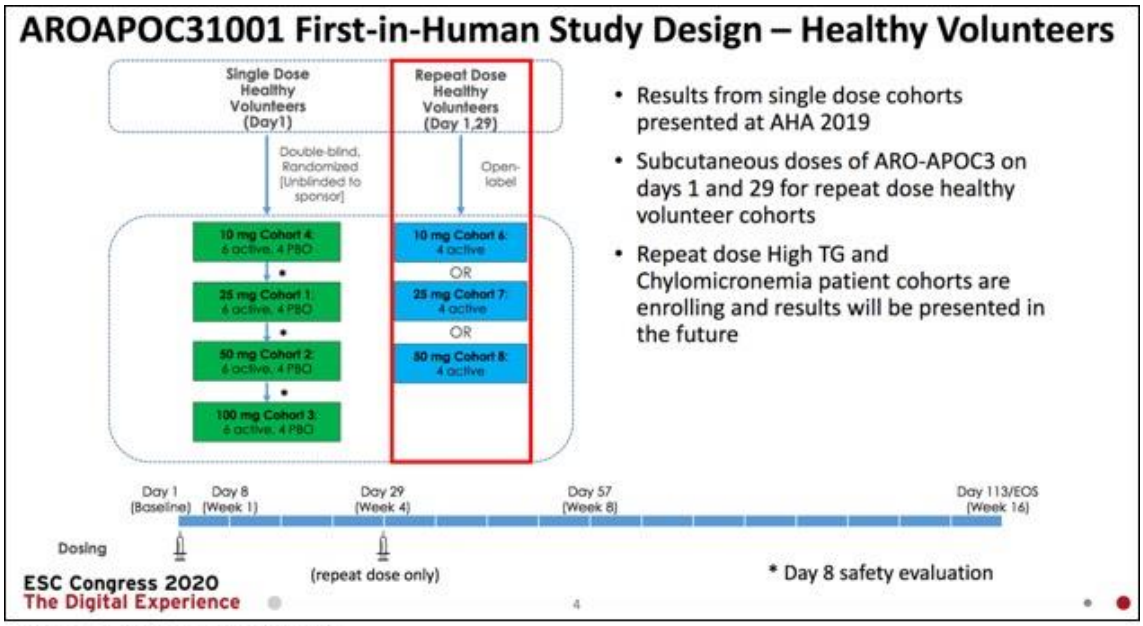
On August 31, 2020, Arrowhead Pharmaceuticals, Inc. (ARWR) announced the presentation of data from ongoing Phase 1/2 clinical trials of ARO-APOC3 and ARO-ANG3 at the European Society of Cardiology (ESC) Congress 2020. Below we present some of the highlights from each presentation.

ARO-APOC3

In a presentation titled "RNA Interference Targeting Apolipoprotein C-3 with ARO-APOC3 in Healthy Volunteers Mimics Lipid and Lipoprotein Findings Seen in Subjects with Inherited Apolipoprotein C-3 Deficiency" the company presented data from repeat doses of ARO-APOC3 in healthy volunteers. A copy of the presentation can be found here.

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 a history or high risk of pancreatitis. In support of targeting APOC3, an APOC3 loss-of-function mutation 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.

The following slide gives an overview of the ongoing Phase 1/2 clinical trial. The company had previously presented results from the single dose portion of the study in healthy volunteers at AHA 2019. For this portion of the study, ARO-APOC3 was administered on Days 1 and 29 at 10 mg, 25 mg, or 50 mg per dose. The primary objective of the study is evaluating the safety and tolerability of multiple doses of ARO-APOC3 with secondary objectives exploring the pharmacokinetics of the drug and exploratory endpoints evaluating fasting lipids along with fasting and 2-hr postpandrial triglycerides.



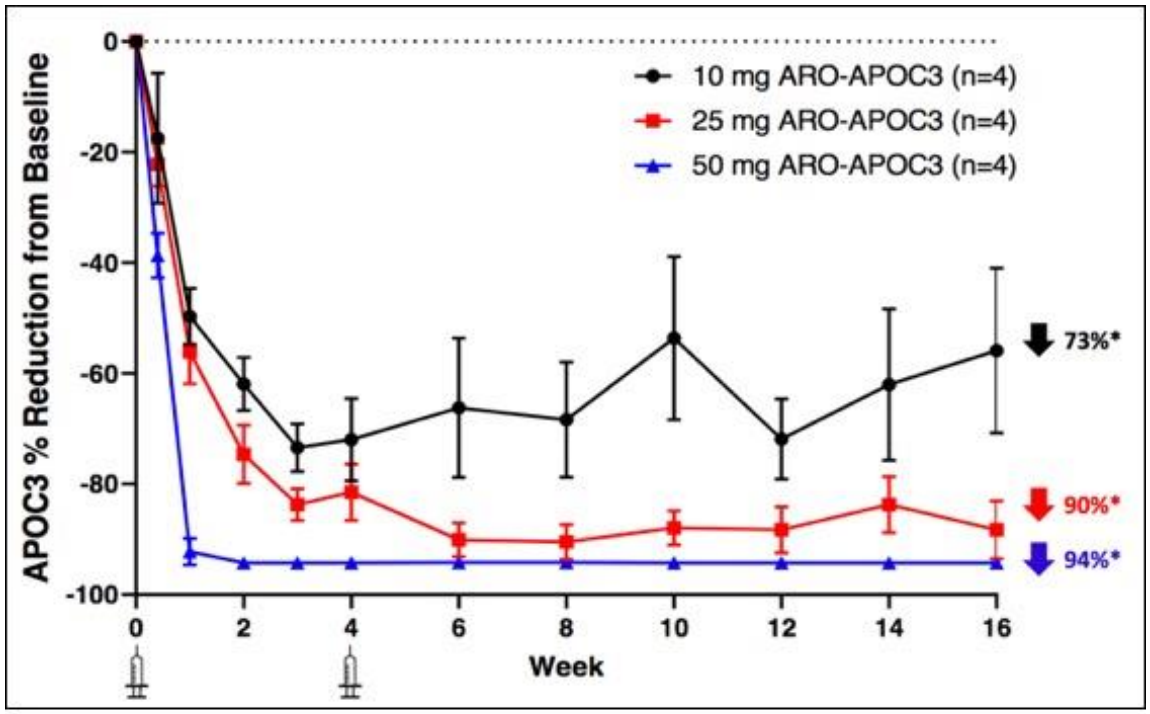
Source: Arrowhead Pharmaceuticals, Inc.

Baseline characteristics for each of the dosing cohorts are shown in the following table. Inclusion criteria included a triglyceride level of >0.903 mmol/L (80 mg/dL) and not currently on statins or other lipid-lowering medications.

	Repeat Dose		
Mean (Range)	10 mg Cohort 6 n = 4 (all active)	25 mg Cohort 7 n = 4 (all active)	50 mg Cohort 8 n = 4 (all active)
Age (years)	50.0 (41-57)	50.5 (46-55)	50.0 (37-61)
% Male	75%	50%	75%
BMI (kg/m²) at screening	27.9 (21.8-32.8)	32.2 (25.1-34.1)	30.0 (25.6-36.2)
APOC3 (g/L)	**0.11 (0.09 – 0.13)**	**0.10 (0.08 – 0.12)**	**0.08 (0.07 – 0.10)**
Triglycerides (mmol/L)	**1.65 (1.14 – 2.20)**	**1.64 (1.14 – 2.11)**	**1.59 (1.14 - 2.24)**
LDL-C (mmol/L) (direct assay)	3.71 (2.95 – 4.38)	5.17 (4.43 – 7.12)	3.00 (2.20 – 3.70)
HDL-C (mmol/L)	1.21 (1.01 - 1.40)	1.25 (1.06 – 1.61)	1.08 (0.93 – 1.19)
TC (mmol/L)	5.68 (4.77 – 6.42)	7.23 (6.27 - 9.17)	4.86 (4.22 - 5.59)
Non-HDL-C (mmol/L)	4.47 (3.37 – 5.41)	5.98 (5.21 – 7.98)	3.78 (3.06 - 4.56)
ApoA1 (g/L)	1.50 (1.47 - 1.58)	1.59 (1.45 - 1.82)	1.27 (1.14 - 1.43)
ApoB (g/L)	1.14 (0.85 - 1.37)	1.45 (1.23 - 1.89)	0.90 (0.74 - 1.06)

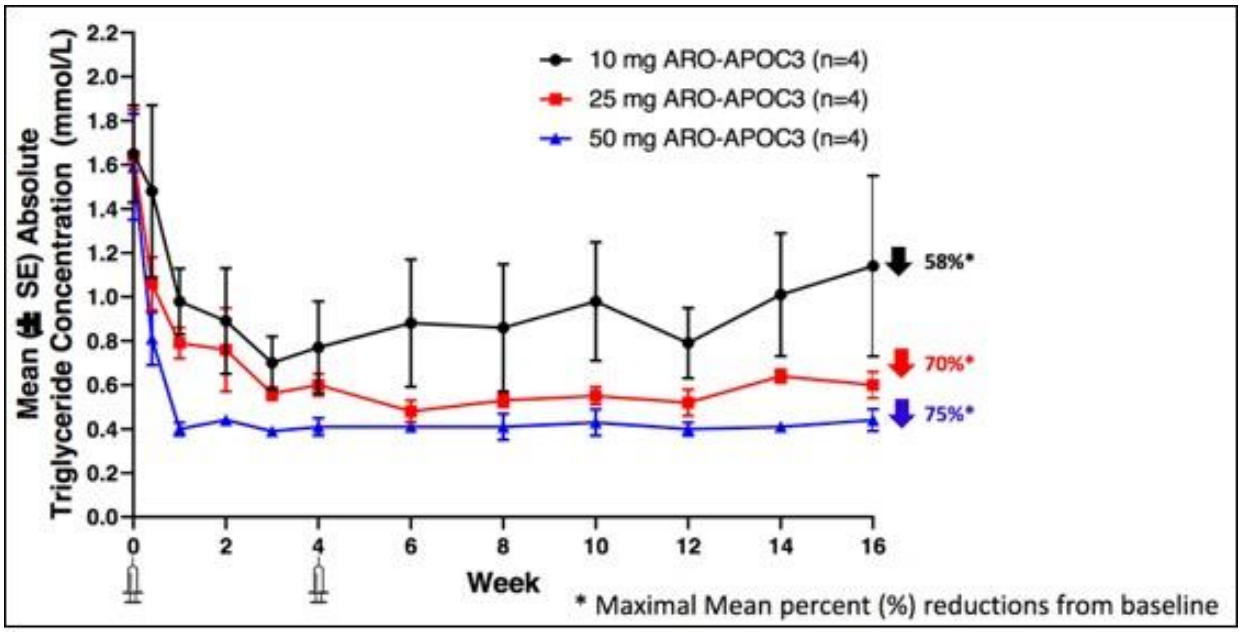
Source: Arrowhead Pharmaceuticals, Inc.

To demonstrate target engagement, the following graph shows a substantial decrease in APOC3 ranging from a peak decrease of 73% at the lowest dose to a peak decrease of 94% at the highest dose. In addition, the reduction in APOC3 is sustained out through 16 weeks following a dose at time 0 and 4 weeks. This suggests that dosing two or three times per year may be feasible.



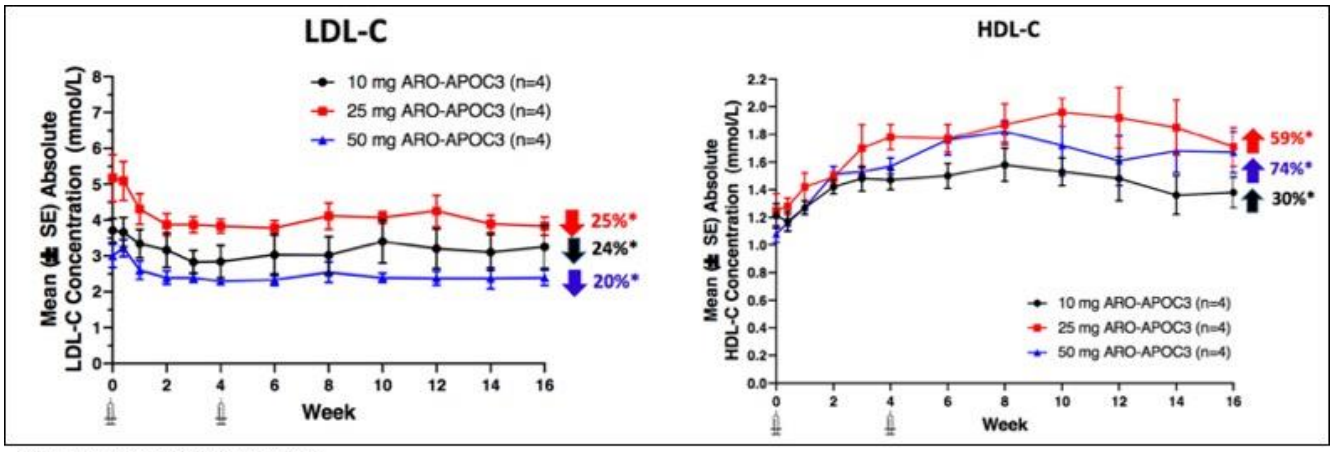
Source: Arrowhead Pharmaceuticals, Inc.

The sustained reduction in APOC3 levels translates to substantial, sustained reductions in triglyceride levels with maximal reductions of 58% at the lowest dose to a maximal reduction of 75% at the highest dose.



Source: Arrowhead Pharmaceuticals, Inc.

In addition to substantial decreases in triglyceride levels, decreases in low-density lipoprotein cholesterol (LDL-C) and increases in high-density lipoprotein cholesterol (HDL-C) were also noted.



Source: Arrowhead Pharmaceuticals, Inc.

Lastly, ARO-APOC3 was generally well tolerated as shown in the following table. The reported adverse events (AEs) were generally mild (including all injection site AEs) and there were no reported serious adverse events (SAEs). In addition, there were no significant adverse changes in platelets, total bilirubin, creatinine, and transaminases.

All AEs Reported in >1 Subject (MedDRA Preferred Terms)	10 mg Cohort 6 n = 4 (all active)	25 mg Cohort 7 n = 4 (all active)	50 mg Cohort 8 n = 4 (all active)	Total n = 12
Any AE at injection site (e.g. injection site reaction, erythema, bruising)	0 (0)	3 (75%)	4 (100%)	7 (58%)
Diarrhea	2 (50%)	1 (25%)	1 (25%)	4 (33%)
Vascular access site bruising	0 (0)	1 (25%)	2 (50%)	3 (25%)
Headache	0 (0)	2 (50%)	1 (25%)	3 (25%)
Upper respiratory tract infection	0 (0)	1 (25%)	1 (25)	2 (17%)
Dermatitis contact	0 (0)	1 (25%)	1 (25%)	2 (17%)

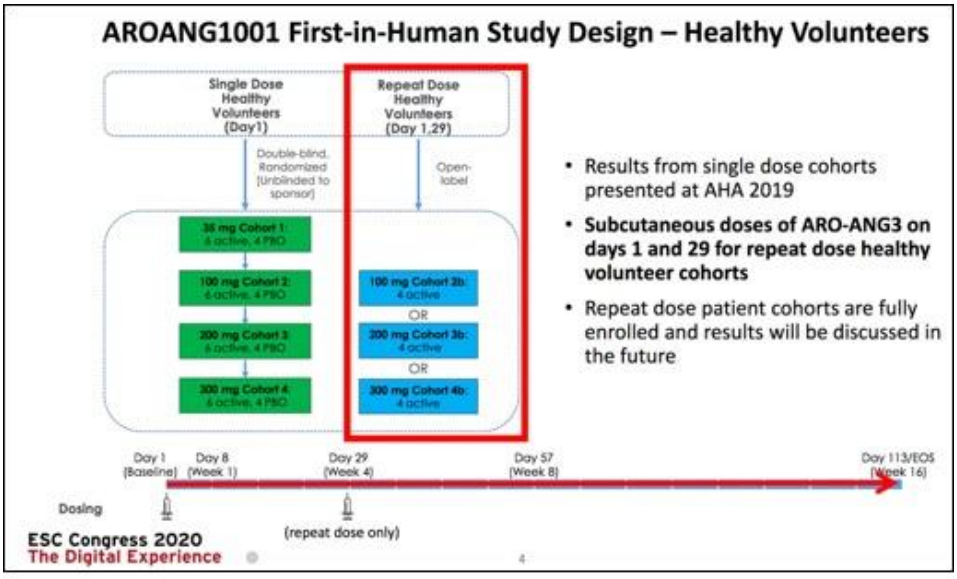
Source: Arrowhead Pharmaceuticals, Inc.

ARO-ANG3

In a presentation titled "RNAi Inhibition of Angiopoietin-like Protein 3 (ANGPTL3) with ARO-ANG3 Mimics the Lipid and Lipoprotein Profile of Familial Combined Hypolipidemia" the company presented data from repeat doses of ARO-ANG3 in healthy volunteers. A copy of the presentation can be found here.

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 ongoing Phase 1/2 clinical trial. The company had previously presented results from the single dose portion of the study in healthy volunteers at AHA 2019. For this portion of the study, ARO-ANG3 was administered on Days 1 and 29 at 100 mg, 200 mg, or 300 mg per dose. The primary objective of the study is evaluating the safety and tolerability of multiple doses of ARO-ANG3 with secondary objectives exploring the pharmacokinetics of the drug and exploratory endpoints evaluating fasting lipids along with fasting and 2-hr postpandrial triglycerides.



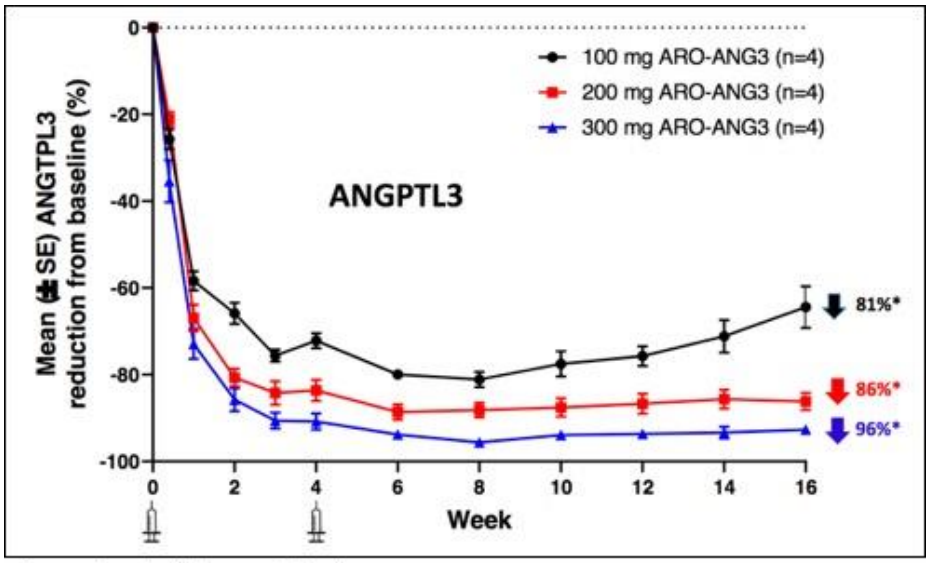
Source: Arrowhead Pharmaceuticals, Inc.

Baseline characteristics for each of the dosing cohorts are shown in the following table. Inclusion criteria included a triglyceride level of >1.13 mmol/L (100 mg/dL), LDL >1.81 mmol/L (70 mg/dL), and not currently on statins or other lipid-lowering medications.

	Repeat Dose		
Mean (Range)	100 mg Cohort 2b n = 4 (all active)	200 mg Cohort 3b n = 4 (all active)	300 mg Cohort 4b n = 4 (all active)
Age (years)	47.0 (20 – 62)	43.3 (29-55)	30.8 (22-42)
% Male	50%	100%	50%
BMI (kg/m²)	25.1 (21.7 – 28.0)	25.3 (22.4 – 28.4)	32.0 (25.6 – 39.9)
ANGPTL3 (ng/mL)	**98 (92 - 112)**	**107 (90 - 119)**	**91 (69 - 107)**
TG (mmol/L)	**1.67 (0.81 – 2.31)**	**1.59 (1.27 – 1.85)**	**1.83 (0.64 - 3.66)**
VLDL-C (mmol/L)	0.76 (0.36 – 1.06)	0.73 (0.57 – 0.85)	0.83 (0.28 – 1.68)
LDL-C (mmol/L) (direct assay)	4.09 (3.29 – 5.00)	3.22 (2.75 – 3.96)	2.88 (2.28 – 3.68)
HDL-C (mmol/L)	1.30 (0.98 - 1.97)	1.02 (0.93 – 1.14)	0.95 (0.67 – 1.42)
TC (mmol/L)	6.39 (5.34 - 7.30)	5.26 (4.90 - 5.88)	4.87 (3.91 - 5.80)
Non-HDL-C (mmol/L)	5.10 (3.94 - 6.11)	4.24(3.76 - 4.90)	3.92 (3.11 - 5.13)
ApoB (mmol/L)	1.16 (0.86 - 1.43)	0.96 (0.81 - 1.09)	0.91 (0.75 - 1.21)

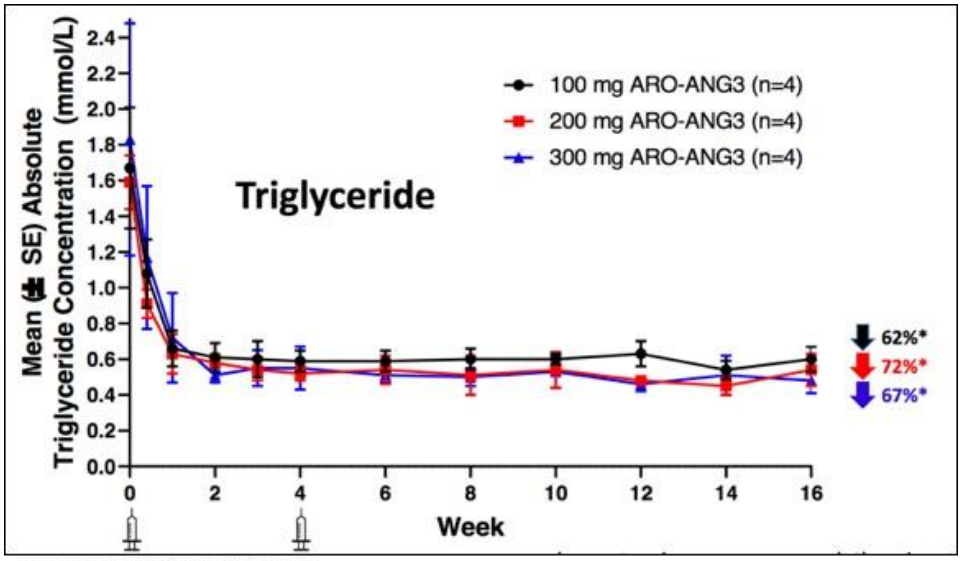
Source: Arrowhead Pharmaceuticals, Inc.

To demonstrate target engagement, the following graph shows a substantial decrease in ANGPTL3 ranging from a maximum of 81% at the lowest dose to a maximum of 96% at the highest dose. In addition, the reduction in ANGPTL3 is sustained out through 16 weeks following a dose at time 0 and 4 weeks. This suggests that dosing two or three times per year may be feasible.



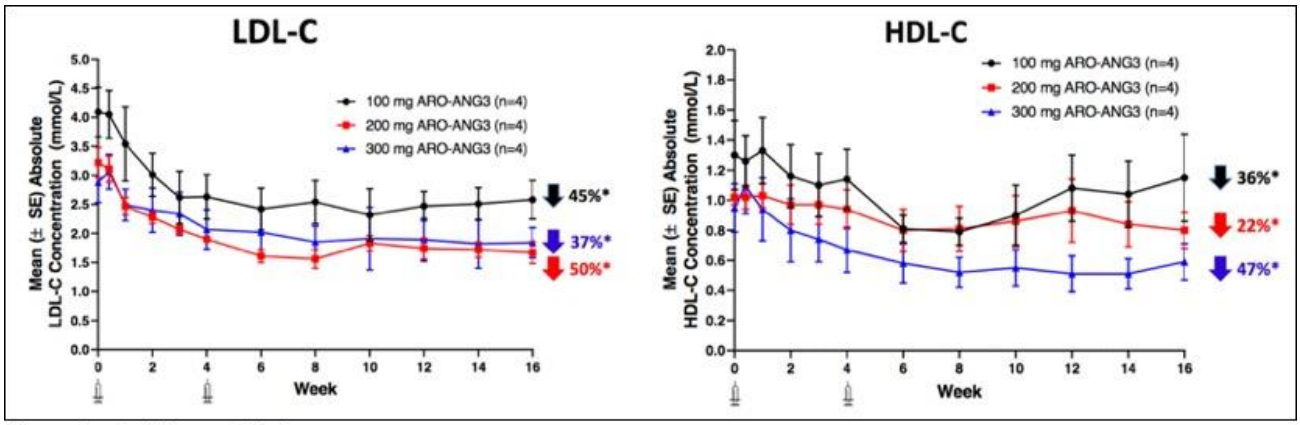
Source: Arrowhead Pharmaceuticals, Inc.

The sustained reduction in ANGPTL3 levels translates to substantial, sustained reductions in triglyceride levels with maximal reductions of 62% for the 100 mg dose, 72% for the 200 mg dose, and 67% for the 300 mg dose.



Source: Arrowhead Pharmaceuticals, Inc.

In addition to substantial decreases in triglyceride levels, substantial decreases in LDL-C, ranging from 37% to 50%, and HDL-C, ranging from 22% to 47%, were also noted.



Source: Arrowhead Pharmaceuticals, Inc.

Lastly, ARO-ANG3 was generally well tolerated as shown in the following table. The reported adverse events (AEs) were generally mild (the most commonly reported was headache) and there were no reported serious adverse events (SAEs). In addition, there were no significant adverse changes in platelets, total bilirubin, creatinine, and transaminases.

AEs Reported in > 1 subject AE Term (MedDRA Preferred Term)	100 mg Cohort 2b n = 4 (all active)	200 mg Cohort 3b n = 4 (all active)	300 mg Cohort 4b n = 4 (all active)	Total n = 12
Headache	1 (25%)	1 (25%)	3 (75%)	5 (42%)
Upper respiratory tract infection	1 (25%)	1 (25%)	2 (50%)	4 (33%)
Vascular access site bruising, Vascular access site swelling	1 (25%)	0 (0)	3 (75%)	4 (33%)
Ligament sprain, Muscle strain, Tendon injury	2 (50%)	0 (0)	1 (25%)	3 (25%)
Diarrhea	0 (0)	0 (0)	2 (50%)	2 (17%)
Injection site bruising, injection site discoloration	0 (0)	0 (0)	2 (50%)	2 (17%)
Lethargy	1 (25%)	1 (25%)	0 (0)	2 (17%)
Abdominal pain, Abdominal pain lower	1 (25%)	0 (0)	1 (25%)	2 (17%)

Source: Arrowhead Pharmaceuticals, Inc.

Conclusion

The data for both ARO-APOC3 and ARO-ANG3 are very impressive and show substantial reductions in triglycerides and other lipoproteins in addition to exhibiting strong on-target effects. Despite advancements in LDL and triglyceride management, there exists a significant population of patients that are not responsive to currently available therapies (e.g., statins, PCSK9s, etc.). In addition, the decrease in triglycerides of 50-75% puts these compounds in a 'league of their own' when compared to currently available therapies such as Vascepa®, which results in average decreases in triglycerides of 25-30% (Vascepa prescribing information).

At this point the company has many different regulatory pathways it could pursue with both drugs. For example, ARO-APOC3 could be used in patient populations ranging from those with an ultra-rare, genetically defined disease such as familial chylomicronemia syndrome (FCS), with a prevalence of approximately 1 in 1 million, all the way to those with simply mildly elevated triglycerides > 150 mg/dL, which has a population measured in the tens of millions. The same holds true for ARO-ANG3, which may be appropriate for patients with both elevated triglycerides and LDL cholesterol. We look forward to updates on these two programs over the next several months, including additional data and the planned regulatory pathway for each. With no changes to our model, our valuation remains at $58.

PROJECTED FINANCIALS

Arrowhead Pharmaceuticals, Inc.	FY2019 A	Q1FY20 A	Q2FY20 A	Q3FY20 A	Q4FY20 E	FY2020 E	FY2021 E	FY2022 E
Revenue	$168.80	$29.45	$23.53	$27.38	$20.62	$100.98	$73.22	$50.00
YOY Growth	*945.7%*	*-38.8%*	*-44.9%*	*-36.8%*	*-87.8%*	*191.4%*	*52.1%*	*17.1%*
Total Revenues	**$168.8**	**$29.5**	**$23.5**	**$27.4**	**$20.6**	**$101.0**	**$73.2**	**$50.0**
YOY Growth	*945.7%*	*-38.8%*	*-44.9%*	*-36.8%*	*-87.8%*	*191.4%*	*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**	**$27.4**	**$20.6**	**$101.0**	**$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	$32.6	$25.3	$110.7	$105.0	$110.0
% R&D	*48.0%*	*79.4%*	*125.1%*	*119.0%*	*122.8%*	*109.6%*	*143.4%*	*220.0%*
Salary and G&A	$26.6	$10.9	$16.3	$10.7	$12.2	$50.2	$52.2	$55.0
% SG&A	*15.7%*	*37.1%*	*69.4%*	*39.3%*	*59.3%*	*49.7%*	*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)**	**($15.9)**	**($16.9)**	**($60.0)**	**($84.0)**	**($115.0)**
Operating Margin	*36.3%*	-	-	-	-	*-59.4%*	*-114.7%*	*-230.0%*
Other Income (Net)	$7.0	$2.2	$2.4	$2.3	$1.7	$8.7	$7.0	$6.0
Pre-Tax Income	**$68.1**	**($2.7)**	**($19.8)**	**($13.6)**	**($15.2)**	**($51.3)**	**($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)**	**($13.6)**	**($15.2)**	**($51.3)**	**($77.0)**	**($109.0)**
YOY Growth	-	-	-	-	-	-	-	-
Net Margin	*40.3%*	-	-	-	-	*-50.8%*	*-105.2%*	*-218.0%*
Reported EPS	**$0.69**	**($0.03)**	**($0.20)**	**($0.13)**	**($0.15)**	**($0.51)**	**($0.74)**	**($1.04)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	98.6	97.1	101.7	101.8	102.0	100.6	104.5	104.5

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

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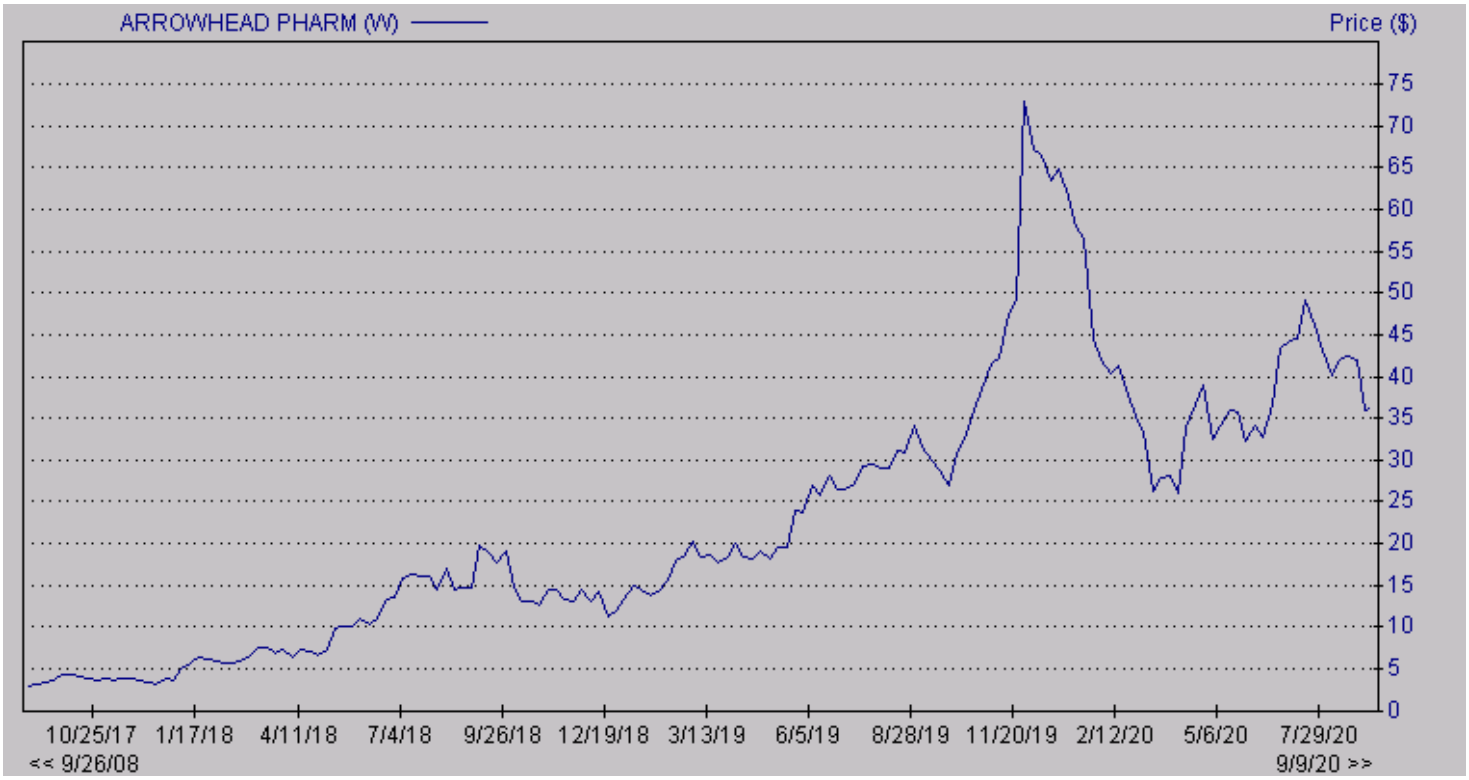
HISTORICAL STOCK PRICE



Source: Zacks SCR

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