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Arrowhead Pharm (ARWR-NASDAQ)

ARWR: ARO-AAT Ph 2/3 Detailed, Could Serve as FDA Pivotal Study. Continued Broad-Based Pipeline Progress

Relative valuation metrics indicates a fair value at $30/share.

Current Price (05/20/19)	$19.20
Valuation	**$30.00**

OUTLOOK

Arrowhead continues to make rapid progress across most of their pipeline with the last few months including several substantive highlights. This includes presentations at the EASL International Liver Congress in April from preclinical long-term data from the previous-generation AAT as well as interim results of JNJ-3989 (ARO-HBV) among 40 patients at 24+ weeks follow-up in their ongoing Phase 1/2 study.

The JNJ-3989 Phase 1/2 study (chronic hepatitis B) continues and was recently expanded to include a triple combination cohort (cohort 12), which along with JNJ-3989, will include additional undisclosed agents chosen by Janssen. Management indicated that this triple combination cohort could generate data relatively quickly – which will be one of several near-term development-related announcements that we anticipate.

Meanwhile, in April ARWR received U.S. regulatory approval to commence a Phase 2/3 study of ARO-AAT in alpha-1 antitrypsin deficiency that could serve as a pivotal FDA registration study. The study ("SEQUOIA") could represent the first U.S. pivotal study of ARWR's TRiM platform. Given that this program potentially represents the most near-term commercialization opportunity, we will be particularly eager to hear related updates.

SUMMARY DATA

52-Week High	**$22.39**
52-Week Low	**$9.56**
One-Year Return (%)	**94.60**
Beta	**2.15**
Average Daily Volume (sh)	**1,380,443**
Shares Outstanding (mil)	**95**
Market Capitalization ($mil)	**$1,826**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**63**
Insider Ownership (%)	**5**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**321.8**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2019 Estimate	**24.9**
P/E using 2020 Estimate	**N/A**
Zacks Rank	**N/A**

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)
2017	4.37 A	8.99 A	9.34 A	8.71 A	31.4 A
2018	3.50 A	0.65 A	0.73 A	11.26 A	16.14 A
2019	34.66 A	48.15 A	60.20 E	35.87 E	178.88E
2020					88.70 E

Price/Sales Ratio (Industry = 2.5x)

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2017	-$0.21 A	-$0.08 A	-$0.08 A	-$0.14 A	-$0.50 A
2018	-$0.18 A	-$0.18 A	-$0.18 A	-$0.12 A	-$0.65 A
2019	$0.13 A	$0.24 A	$0.34 E	$0.06 E	$0.77 E
2020					-$0.31 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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WHAT'S NEW

Pipeline Highlights: AAT Ph2/3 Trial Design, AAT and HBV EASL Presentations, Dosing Starts in ARO-ANG3/APOC3 Ph 1s

Arrowhead continues to make rapid progress across most of their pipeline with the last few months including several substantive highlights. This includes presentations at the EASL International Liver Congress in April from preclinical long-term data from the previous-generation AAT as well as interim results of JNJ-3989 (ARO-HBV) among 40 patients at 24+ weeks follow-up in their ongoing Phase 1/2 study.

The JNJ-3989 Phase 1/2 study (chronic hepatitis B) continues and was recently expanded to include a triple combination cohort (cohort 12), which along with JNJ-3989, will include additional undisclosed agents chosen by Janssen. Management indicated that this triple combination cohort could generate data relatively quickly – which will be one of several near-term development-related announcements that we anticipate. In April ARWR earned a $25M milestone from Janssen related to the initiation of dosing of this new triple combination cohort. Another $25M is expected once Janssen commences the Phase 2 study.

Meanwhile, in April ARWR received U.S. regulatory approval to commence a Phase 2/3 study of ARO-AAT in alpha-1 antitrypsin deficiency that could serve as a pivotal FDA registration study. The study ("SEQUOIA"), the design of which we detail below, could represent the first U.S. pivotal study of ARWR's TRiM platform. Given that this program potentially represents the most near-term commercialization opportunity, we will be particularly eager to hear related updates.

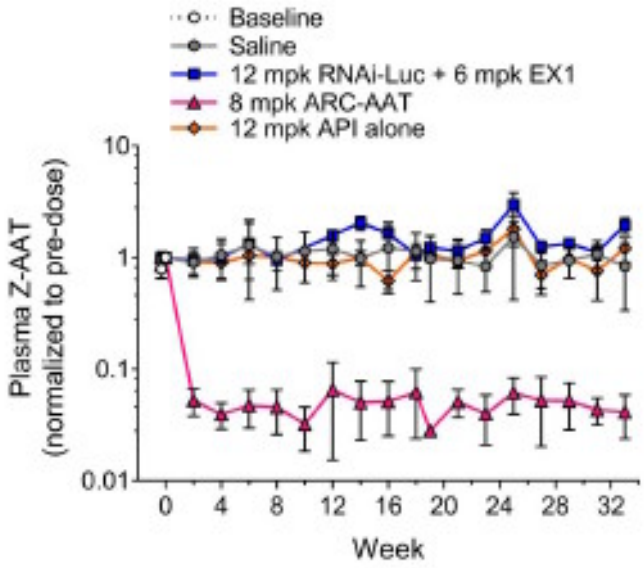
Dosing commenced in the Phase 1 studies of ARO-ANG3 (targeting ANGPTL3) and ARO-APOC3 (targeting apoC-III), the company's two newest clinical candidates which target cardio metabolic diseases. ARWR continues to expect to report data (safety, tolerability, PK and initial duration of effect) from both of these studies later this year. Management believes these programs have the potential to move fairly rapidly as well – and, depending on the data, could provide optionality in terms of addressing both orphan (which could be the initial pursuit) as well as more prevalent diseases (which could be a secondary pursuit). If all goes well, ARWR thinks that pivotal studies for these compounds could begin as soon as next year.

It's not yet mid-year and ARWR has already made significant progress across the majority of their pipeline. And based on management's comments, they expect no slowing down. They now expect to have seven TRiM candidates either in or about to start clinical trials, including five of which they own outright. Moreover, they are targeting the filing of two to three new clinical trial applications per year, targeting a new cell type with their TRiM technology every 18 months and have 10 TRiM candidates in clinical trials by the end of next year.

AAT EASL Presentation

In April ARWR presented long-term preclinical data from their prior generation AAT compound at the EASL International Liver Congress. Results demonstrated that adult PiZ mice treated with ARC-AAT showed sustained RNAi reduction of the mutant Z-AAT protein. After 33 weeks of treatment with ARC-AAT, the PiZ mice showed substantial reversal of disease phenotype including deeply reduced monomeric Z-AAT protein in the liver, reduced polymeric Z-AAT in the liver, up to 98% plasma Z-ATT reduction from baseline and restoration of normal endoplasmic reticulum. While this was a prior generation, we think this lends further support for potential efficacy of AAT in the treatment of alpha-1 antitrypsin deficiency.

AAT sustained reduction of mutant Z-AAT protein[1]



JNJ-3989 EASL Presentation

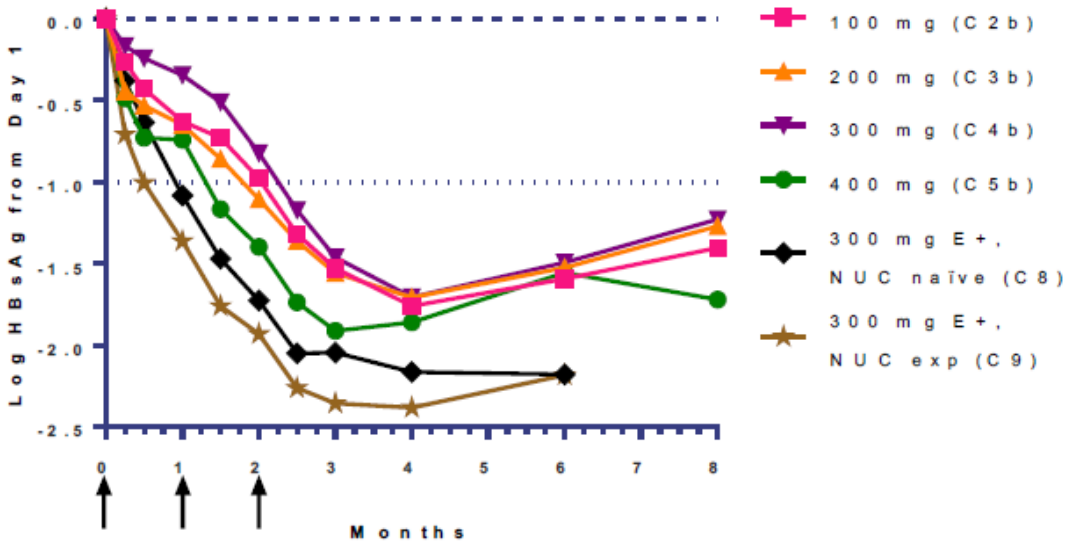
Also at EASL ILC ARWR presented interim results of JNJ-3989 (ARO-HBV) among 40 patients at 24+ weeks follow-up in their ongoing AROHBV1001 study. As a reminder, this is a Phase 1/2 study to evaluate the safety, tolerability, and pharmacokinetic effects of single-ascending doses (SAD) of ARO-HBV in healthy adult volunteers, and to evaluate the safety, tolerability, and pharmacodynamic effects of multiple-ascending doses (MAD) of ARO-HBV in patients with chronic HBV.

Results showed JNJ-3989 rapidly reduced hepatitis B surface antigen (HBsAg) in patients that had 24 weeks or more HBsAg assay results. The reductions were to thresholds potentially associated with improved chance of HBsAg clearance after just three doses.

Specifically, all 40 patients achieved $\geq$ 1.0 log10 IU/mL HBsAg reduction, while 88% (35/40) achieved HBsAg < 100 IU/mL. In terms of safety, there were no drug-related serious adverse events reported while there were 17 mild adverse events at the injection site (such as tenderness and bruising).

[1] Reduction of hepatic Z alpha1 antitrypsin by RNA interference prevents and reverses liver disease including hepatic mitochondrial injury in the PiZ mouse model. Christine I. Wooddell at al. April 2019 EASL Poster

Mean HbsAg reductions from baseline[2]



ARO-AAT Phase 2/3 Trial Design

In April ARWR received IND approval to proceed with a Phase 2/3 study of ARO-AAT in alpha-1 antitrypsin deficiency. Management laid out details of the trial design on the fiscal Q2 call and noted that they believe it could potentially serve as a pivotal FDA registration study. Along with the Phase 2/3 study, called SEQUOIA, a separate open label study, called ARO-AAT 2002, will be conducted in parallel.

The purpose of ARO-AAT 2002, which ARWR anticipates commencing in Q3 of this year (i.e. slightly after SEQUOIA begins), is to essentially have insight into patient response and safety without having to unblind SEQUOIA (and therefore be susceptible to potential bias) – this, they hope, will provide them with ongoing and current data for planning purposes (it should also, we think, provide investors with potential proxy insight into safety and response of SEQUOIA).

SEQUOIA is a multiple dose, multicenter (hope to have up to 40 sites WW), placebo-controlled, adaptive Phase 2/3 study to evaluate the safety, efficacy, and tolerability of ARO-AAT administered subcutaneously to patients with alpha-1 antitrypsin deficiency. Patient, treating physician and Arrowhead will be blinded. SEQUOIA has two parts, A and B. The goal of (multi-dose) Part A is to select a single dose to be used in the two-arm, placebo controlled Part B portion. The following, taken from ARWR's Q2 2019 conference call, describes the SEQUOIA study and below that, the ARO-AAT 2002 study;

- **SEQUOIA Part A:**
    - The primary objective of Part A is to select a single dose level for use in Part B based on a combined evaluation of safety and pharmacodynamic dose response in each Part A cohort using change from baseline in soluble liver Z-AAT and serum AAT levels as pharmacodynamic metrics.
    - Participants in Part A will require a pre-dose biopsy and those who meet the inclusion criteria will be randomized to receive ARO-AAT or placebo on days 1, 29, 113, and then every 84 days thereafter.
    - There are three cohorts each using a different dose level (25mg, 100mg and 200mg). All three cohorts will be randomized in parallel.

[2] Locarnini S. et al Short term RNA interference (RNAi) therapy in chronic hepatitis B (CHB) using JNJ-3989 brings majority of patients to HBsAg <100 IU/ml threshold. April 2019

- Once 36 subjects, 12 in each cohort have completed a Day-113 biopsy, the Part A analysis to select a single dose for Part B will occur.
- Enrollment will continue into all cohorts until the Part B dose is chosen.

- **SEQUOIA Part B:**
  - The primary objective for Part B is to evaluate efficacy as assessed by the proportion of ARO-AAT patients relative to placebo achieving a two-point improvement on a histological grading scale of alpha-1 antitrypsin deficiency associated liver disease and no worsening of liver fibrosis on end-of-study biopsy.
  - Patients enrolled during Part A will continue on study and roll over to the Part B dose level or continue to receive placebo.
  - These patients are intended to receive a minimum of six Part B doses and a minimum of nine doses overall.
  - Remaining patients needed to achieve a total enrollment of 120 will be randomized to the selected Part B dose level or placebo and will receive doses on days 1, 29 and then every three months thereafter for a total of nine doses.

- **ARO-AAT 2002 study** (conducted in parallel to SEQUOIA)
  - Open label, multi-dose, Phase 2 study to assess changes in a novel histological activity scale in response to ARO-AAT over time in patients with alpha-1 antitrypsin deficiency associated liver disease.
    - Primary objective is to evaluate effective ARO-AAT on a histologic liver disease activity scale will be assessed at 24 weeks for cohort one and week 48 for cohort two.
    - Multiple secondary 'exploratory objectives' will also be assessed.
    - Expected to include 12 subjects in two sequential cohorts
      - Cohort one consists of four patients and cohort two consists of eight patients.
        - All eligible patients will require a pre-dose biopsy completed as part of the study. Patients that had been enrolled are expected to receive a minimum of three doses of ARO-AAT in cohort one and five doses in cohort two with repeat biopsies approximately one month after the third or fifth dose, respectively.
        - Doses will be administered on days 129, 113 and approximately every 84 days thereafter. Patients who complete cohorts one or two may elect to participate in an extension cohort which would include an additional four doses, again given quarterly followed by repeat liver biopsy.

Q2 2019 Financial Results

Total revenue for the period ending March 31, 2019 was $48.2M (versus our $43.1M estimate), representing recognition of another portion of the $197.8M transaction price of the Janssen / JJDC collaboration agreement, which closed in late October 2018. To-date, approximately $82.6M of this total has been recognized as revenue. In April (i.e. subsequent to fiscal Q2 quarter-end), ARWR earned a $25M milestone from Janssen related to the initiation of dosing of the aforementioned (new) triple combination cohort in the JNJ-3989 Phase 1/2 study and another $25M will be earned when Janssen begins the Phase 2 portion.

As a reminder, ARWR received $250M upfront and is eligible for another $3.5B in potential additional milestones and for royalties on eventual commercial sales. The collaboration is expected to speed development of ARWR's hepatitis B therapeutic candidate, ARO-HBV (which subsequently changed names to JNJ 3989). The upfront payment consists of $175M cash from Janssen plus a $75M equity investment (@ $23.00/share) from Johnson & Johnson Innovation – JJDC, Inc.

In return, Janssen receives worldwide exclusive license to ARO-HBV and an option to collaborate with ARWR on up to three additional RNAi therapeutics for new targets (to be selected by Janssen). Janssen

will be solely responsible for development and commercialization beyond ARWR's ongoing Phase 1/2 study. The other optional targets will leverage ARWR's TRIM platform technology but will not include any of the company's current pipeline. For these optioned targets, Janssen will fund initial discovery and preclinical work by ARWR and will take over each program following an IND filing by ARWR.

Specifically, as it relates to potential milestone payments, ARWR is eligible to receive $1.6B for the HBV license, which is inclusive of $50M worth of milestones for a Phase 2 study. Up to another $1.9B could be received for the agreement related to other three targets. Commercial sales royalties would be tiered and at a rate of up to the mid-teens percentage.

Q2 operating expenses were $26.1M (versus our $28.0M estimate), which includes $20.8M ($22.2M E) of R&D expense and $5.3M ($5.8M E) in salary/G&A expense. We continue to expect OpEx, and in particular R&D expense, to increase as ARWR's various studies progress to later stages and as new clinical candidates enter the pipeline.

EPS was $0.24, compared to our and average consensus estimates of $0.17 and $0.19, respectively.

Cash
ARWR exited fiscal Q2 with $286M in cash and investments. The company used $19.6M of cash for operations in Q2 but, excluding changes in working capital, the company generated $28.2M of cash from operations in the same period. During the first half of fiscal 2019 ARWR generated $148.7M (or $43.9M ex-changes in working capital) of cash from operations.

Clinical Programs Refresher

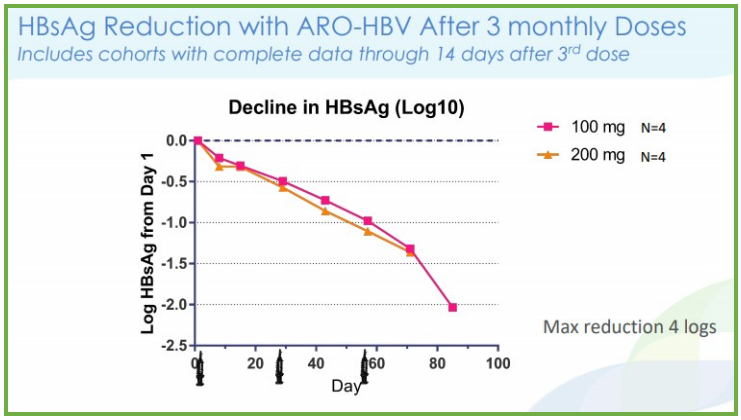
Clinical Data of ARO-HBV (JNJ 3989) Presented
In November 2018 preliminary data from ARWR's Phase 1/2 study of ARO-HBV for the treatment of HBV was presented as a late-breaking poster at the Liver Meeting of the Annual Meeting of the American Association for the Study of Liver Disease (AASLD).

Background of the ARO-HBV Program
In March 2018, Arrowhead initiated a **Phase 1/2** first-in-human study of **ARO-HBV** for the treatment of chronic hepatitis B virus **(HBV)** infection in New Zealand. Dosing began in May 2018.

The study, **AROHBV1001** (NCT03365947), is a Phase 1/2 study to evaluate the safety, tolerability, and pharmacokinetic effects of single-ascending doses (**SAD**) of ARO-HBV in healthy adult volunteers, and to evaluate the safety, tolerability, and pharmacodynamic effects of multiple-ascending doses (**MAD**) of ARO-HBV in patients with chronic HBV.

The SAD portion is designed to include up to 5 cohorts of 6 subjects per cohort. Each SAD subject will receive a single-dose administration of either placebo or ARO-HBV at up to 5 dose levels (35, 100, 200, 300, 400 mg). The MAD portion is designed to include up to 8 cohorts of 4 HBV patients per cohort. Each MAD patient will receive 3 doses of ARO-HBV at up to 4 dose levels (100, 200, 300, 400 mg).

The Clinical Data Presented at the Summit
On Sep. 6, 2018, Arrowhead presented initial clinical data for **ARO-HBV** at the 18th World Gastroenterologists Summit in Auckland, New Zealand, which included initial data of **eight patients** from the first two MAD dose cohorts of the AROHBV1001 clinical study: 100mg and 200mg.



Following is the summary of the key clinical data presented at the Summit:

- Maximum reduction of HBsAg was 4.0 log10 (99.99%) after three monthly doses of ARO-HBV
- Mean reduction of HBsAg was 2.0 log10 (99%) on day 85 in cohort 2b (100 mg) and 1.4 log10 (96%) on day 71 in cohort 3b (200 mg)
- Minimum HBsAg reduction in all patients from cohorts 2b and 3b was 1.2 log10 (93%)
- Activity was demonstrated in all patient types (HBeAg pos/neg, NUC naïve/treated)

ARO-HBV was generally well-tolerated with generally mild and self-limiting injection site adverse events being the most common reported event in chronic HBV patients, occurring in around 10% of injections. The other most commonly reported events included symptoms consistent with upper respiratory tract infection and headache.

These results represented the first clinical data presented on ARO-HBV, which was very encouraging in our view. The data indicated that ARO-HBV is highly active in the treatment of HBV with good safety profile.

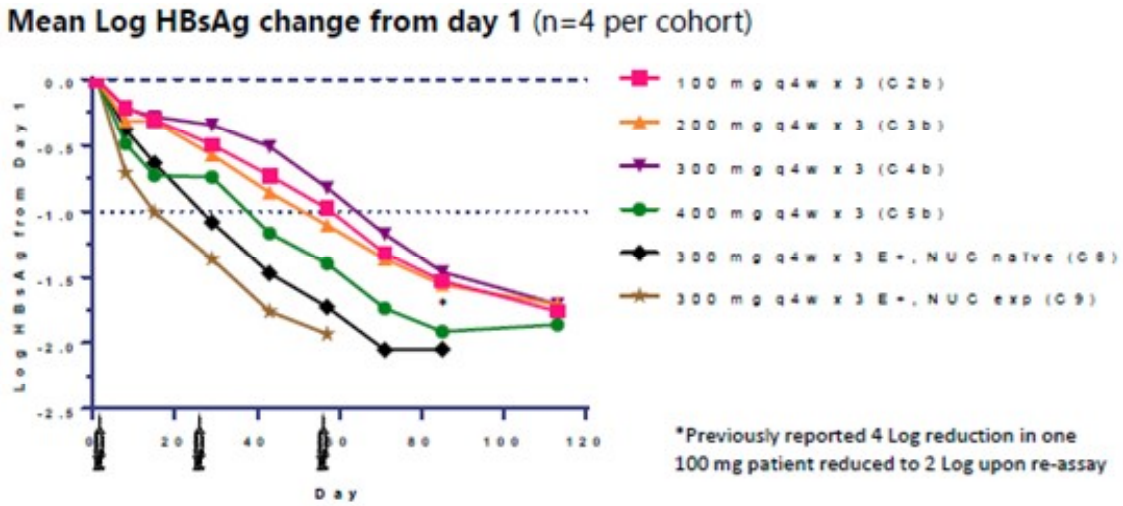
Clinical Data Presented at the AASLD in November 2018

In November 2018 preliminary data from ARWR's Phase 1/2 study of ARO-HBV for the treatment of HBV was presented as a late-breaking poster at the Liver Meeting of AASLD. This is the first data presentation of ARO-HBV since consummating the collaboration with Janssen

Following is the summary of the key clinical data presented at AASLD:

- Well-tolerated: while mild injection-site reactions were reported in ~12% of injections, ARO-HBV appears to be well-tolerated at single and multiple doses up to 400mg
- Strong HBsAg responses in both HBeAg positive and HBeAg negative patients:
  - all patients showed strong response with mean NADIR of -1.9 Log10 (-98.7%) and ranging from -1.3 (-95.0%) to -3.8 Log10 (-99.98%)
  - HBeAg-positive: Mean HBsAg NADIR in HBeAg positive (n=11) -2.1 Log10
  - HBeAg-negative: Mean HBsAg NADIR in HBeAg negative (n=13) -1.8 Log10
- Reductions similar for NUC naïve and NUC experienced patients
  - Mean HBsAg reduction on day 57 for cohort 8 (n=4) -1.7 Log10
  - Mean HBsAg reduction on day 57 for cohort 9 (n=4) -1.9 Log10
- Improved response from 1st-gen: responses observed were superior to those of the first-generation (ARC-520), which targeted only HBV transcripts
- Response silences HBV: investigators believe that the observed responses are consistent with the ability of ARO-HBV to silence HBV mRNA from cccDNA and host integrated viral DNA
- Other viral parameters showed response: including HBV DNA, HBV RNA, HBeAg and HBcrAg
- While no strong dose response…was observed between 100mg and 400mg, additional patients are enrolling to hopefully better understand possible dose response

AASLD Poster: Strong Response Observed in All Patients



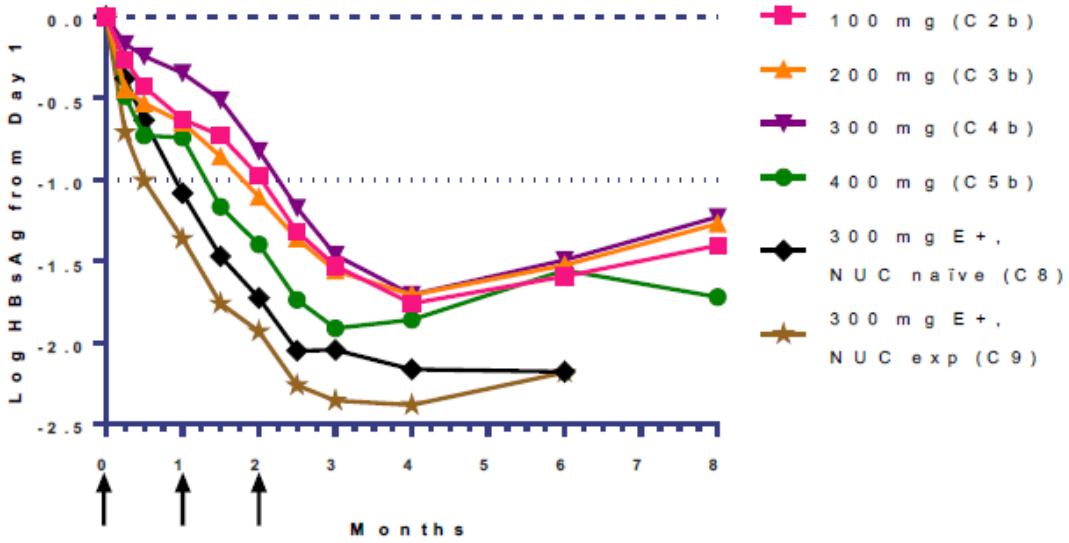
SOURCE: Gane, E. et al. ARWR. AASLD Poster Presentation. Nov 2018

40-Patients at 24+ Weeks Follow-Up Presented at EASL in April 2019

In April 2019 ARWR presented additional data from its ongoing JNJ-3989 Phase 1/2 study at EASL International Liver Congress. The data is from 40 patients through 24+ weeks follow-up. Results showed that JNJ-3989 rapidly reduced hepatitis B surface antigen (HBsAg) in patients that had 24 weeks or more HBsAg assay results. The reductions were to thresholds potentially associated with improved chance of HBsAg clearance after just three doses.

Specifically, all 40 patients achieved ≥ 1.0 log10 IU/mL HBsAg reduction, while 88% (35/40) achieved HBsAg < 100 IU/mL. In terms of safety, there were no drug-related serious adverse events reported while there were 17 mild adverse events at the injection site (such as tenderness and bruising).

Mean HbsAg reductions from baseline[3]



[3] Locarnini S. et al Short term RNA interference (RNAi) therapy in chronic hepatitis B (CHB) using JNJ-3989 brings majority of patients to HBsAg <100 IU/ml threshold. April 2019

With Janssen now onboard as a collaboration partner, there is no concern about funding the ARO-HBV development program. And, ARWR expects to recognize revenue in the amount of $198M (~$83M of which has been recognized to-date) as they complete the oversight of the Phase 1/2 study of ARO-HBV. ARWR is eligible for an additional $50M in milestones ($25M of which was earned in April 2019) related to the new triple combination cohort and initiation of the Phase 2 portion.

Update on Amgen Collaboration Programs

On August 1, 2018, Arrowhead announced that it has earned a $10 million milestone payment from Amgen following the administration of the first dose of AMG 890, formerly referred to as ARO-LPA, in a clinical study.

Amgen is evaluating **AMG 890** in a **Phase 1** clinical study designed to assess its safety in volunteers with elevated levels of lipoprotein (a) (Lp(a)). AMG 890 is an RNAi therapeutic designed to lower Lp(a) for the treatment of cardiovascular disease. Initial data from the study could be available later this year or early 2020.

In September 2016, Arrowhead announced two license and collaboration agreements with Amgen to develop and commercialize **two cardiovascular programs** based on Arrowhead's RNAi platform. These programs will utilize Arrowhead's proprietary **subcutaneous RNAi delivery technology**.

Pursuant to one agreement, Amgen receives a worldwide, exclusive license to Arrowhead's novel, RNAi **ARC-LPA program**, which is designed to reduce production of apolipoprotein A, a key component of lipoprotein(a), which has been genetically linked with increased risk of cardiovascular diseases, independent of cholesterol and LDL levels. ARC-LPA is Arrowhead's first drug candidate to use a subcutaneously administered delivery construct. Elevated lipoprotein(a), or Lp(a), is widely viewed as a key risk factor for cardiovascular diseases, including coronary artery disease, atherosclerosis, thrombosis and stroke.

Under the second agreement, Amgen receives an option to a worldwide, exclusive license for a RNAi therapy for an **undisclosed genetically validated cardiovascular target**. In both agreements, Amgen will be wholly responsible for clinical development and commercialization.

In connection with the two collaborations, Arrowhead received $35 million in upfront payments; $21.5 million in the form of an equity investment by Amgen in Arrowhead common stock (about 3 million shares); and up to $617 million in option payments, and development, regulatory and sales milestone payments. Arrowhead is further eligible to receive single digit royalties for sales of products against the undisclosed target and up to low double-digit royalties for sales of products under the ARC-LPA agreement.



Update on ARO-AAT Phase I Program for Alpha-1 Liver Disease

Background of the Phase I Study

In February 2018, Arrowhead received approval from the New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE) and from the local Ethics Committee to proceed with a first-in-human **Phase 1** study of **ARO-AAT** for the treatment of **alpha-1 antitrypsin deficiency (AATD)**. The study began **dosing** patients in March 2018.

The study, which is designated as **AROAAT1001** (NCT03362242), is a Phase I single- and multiple-ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and effect of ARO-AAT on serum alpha-1 antitrypsin levels in healthy adult volunteers. The study has two parts: double blind and unblinded.

DOUBLE BLIND PART

- 4 treatment arms
  - 35, 100, 200 and 300 mg
  - 100, 200, 300 mg receive ***3 monthly doses***
  - 4 active, 4 placebo
- Assessments of safety, tolerability, plasma levels of ARO-AAT, plasma AAT changes

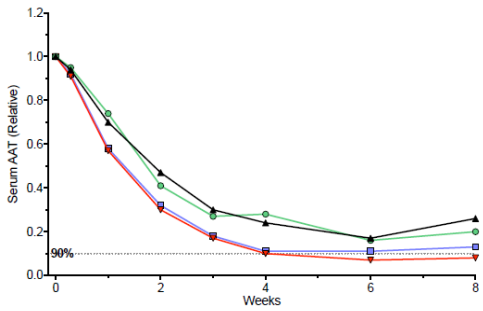
UNBLINDED PART

- No placebo
- 3 groups
  - ***Single doses*** of 100, 200 and 300 mg of ARO-AAT
  - 4 per cohort
- Assessments of safety, tolerability, depth and duration of AAT reductions after a single dose

Key Initial Clinical Data Presented at the Alpha-1 National Education Conference

In the AROAAT1001 **Phase I** clinical study, a single, open-label dose of 100 mg of ARO-AAT in four subjects achieved 93% maximum serum AAT knockdown and 87% mean maximum serum AAT knockdown. At 8 weeks post-dose, mean serum AAT knockdown remained at 83%.

Open Label AAT Plasma Data at 100 mg:
Single Dose, Healthy Volunteers



93%: Maximum Serum AAT Reduction achieved 6-weeks following a single dose
87%: Mean maximum serum AAT reduction achieved 6-weeks following a single dose

The single 100 mg dose of ARO-AAT equates to an average dose of 1.4 mg/kg (range 1.0-1.6 mg/kg) in the subjects studied, who had an average weight of 72.9 kg (range 61.8-98.9 kg).

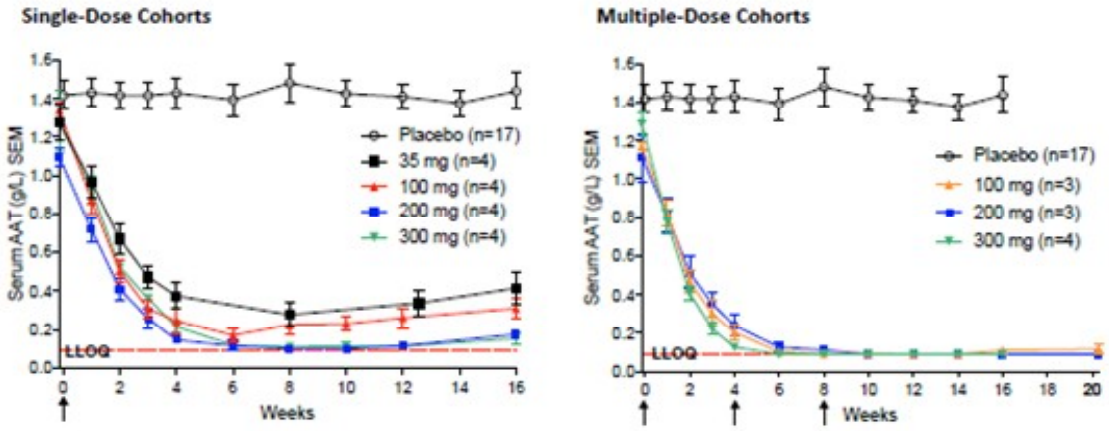
ARO-AAT appeared to be generally well-tolerated and as of the data cutoff of June 11, 2018, the following safety measures were observed in 40 subjects (24 received ARO-AAT and 16 received placebo):

- No serious or severe adverse events (AEs)
- Most AEs reported were mild (one moderate gastroenteritis)
- Two cases of injection site erythema at 100 mg after 1st dose, both were classified as mild and resolved within 48 hours
- No clinically meaningful adverse changes in BUN, creatinine, ALT, AST or total bilirubin
- No dose-related pattern of adverse laboratory changes seen

Poster Presentation at AASLD: No Serious Safety Concerns, Substantial NADIR Serum Reductions…
On Aug. 31, 2018, Arrowhead announced that it completed dosing and in November updated data from this study was the subject of a late-breaking poster presentation at AASLD (see below). Results showed that ARO-AAT was well tolerated at doses as high as 300mg administered 3x/day for 28 days and no deaths or serious adverse events were reported. Moreover, maximum serum nadir reductions were substantial even among the single-dose cohorts.

Single dose reductions were 79%, 87%, >91% and >91% at 35, 100, 200 and 300mg doses, respectively. Meanwhile, multi-dose nadir reductions were all greater than 91% with most patients below the level of quantification. Maximum serum reduction was 94% (in the 300mg multi-dose cohort). Data to-date has shown that among the 100mg cohort, a 90% reduction was sustained for at least 8 weeks (100mg cohort is the only one so far with this length of post-dosing data).

While no serious adverse events were reported, the most common (non-serious) adverse events were headache (22%) and rhinorrhea (13%), or runny nose. Given the substantial nadir reduction and duration of effect, investigators believe that quarterly or less frequent dosing may be feasible – which presumably would further benefit the safety profile.



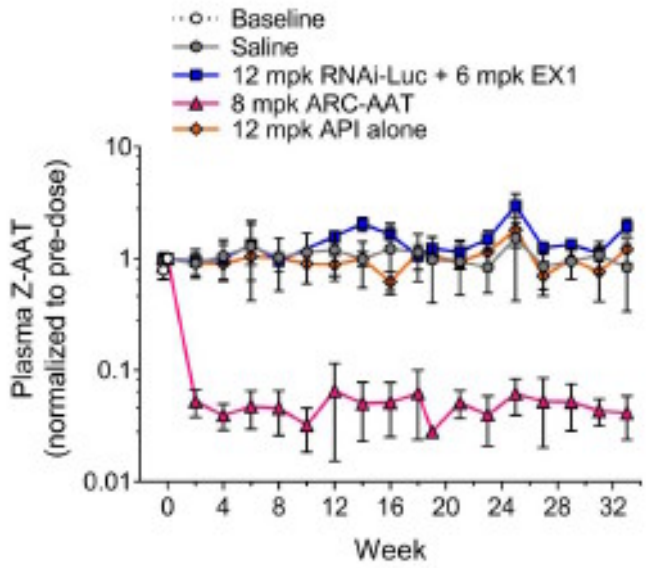
Serum AAT Relative Percentage Reduction Summary

	NADIR Single Dose				NADIR Multiple-Dose		
	35 mg N=4	100 mg N=4	200 mg N=4	300 mg N=4	100 mg N=3	200 mg N=3	300 mg N=4
Average Max	79.0	87.7	>91.5	>91.1	>92.2	>91.2	>93.0
SD	8.5	4.5	0.6	4.0	0.2	2.7	0.7
Max	91.1	93.3	>92.0	>94.9	>92.7	>93.3	>93.7
BLQ, n=	0	0	3	3	2	3	4

SOURCE: ARWR, Schwabe C. et al. AASLD Poster Presentation Nov 2018

AAT EASL Presentation
In April 2019 ARWR presented long-term preclinical data from their prior generation AAT compound at the EASL International Liver Congress. Results demonstrated that adult PiZ mice treated with ARC-AAT showed sustained RNAi reduction of the mutant Z-AAT protein. After 33 weeks of treatment with ARC-AAT, the PiZ mice showed substantial reversal of disease phenotype including deeply reduced monomeric Z-AAT protein in the liver, reduced polymeric Z-AAT in the liver, up to 98% plasma Z-ATT reduction from baseline and restoration of normal endoplasmic reticulum. While this was a prior generation, we think this lends further support for potential efficacy of AAT in the treatment of alpha-1 antitrypsin deficiency.

AAT sustained reduction of mutant Z-AAT protein[4]



ARO-AAT Phase 2/3 Trial Design
In April 2019 ARWR received IND approval to proceed with a Phase 2/3 study of ARO-AAT in alpha-1 antitrypsin deficiency. Management laid out details of the trial design on the Q2 call and noted that they believe it could potentially serve as a pivotal FDA registration study. Along with the Phase 2/3 study, called SEQUOIA, a separate open label study, called ARO-AAT 2002, will be conducted in parallel.

The purpose of ARO-AAT 2002, which ARWR anticipates commencing in Q3 of this year (i.e. slightly after SEQUOIA begins), is to essentially have insight into patient response and safety without having to unblind SEQUOIA (and therefore be susceptible to potential bias) – this, they hope, will provide them with ongoing and current data for planning purposes (it should also, we think, provide investors with potential proxy insight into safety and response of SEQUOIA).

SEQUOIA is a multiple dose, multicenter (hope to have up to 40 sites WW), placebo-controlled, adaptive Phase 2/3 study to evaluate the safety, efficacy, and tolerability of ARO-AAT administered subcutaneously to patients with alpha-1 antitrypsin deficiency. Patient, treating physician and Arrowhead will be blinded. SEQUOIA has two parts, A and B. The goal of (multi-dose) Part A is to select a single dose to be used in the two-arm, placebo controlled Part B portion. The following, taken from ARWR's Q2 2019 conference call, describes the SEQUOIA study and below that, the ARO-AAT 2002 study;

- **SEQUOIA Part A:**

[4] Reduction of hepatic Z alpha1 antitrypsin by RNA interference prevents and reverses liver disease including hepatic mitochondrial injury in the PiZ mouse model. Christine I. Wooddell at al. April 2019 EASL Poster

- The primary objective of Part A is to select a single dose level for use in Part B based on a combined evaluation of safety and pharmacodynamic dose response in each Part A cohort using change from baseline in soluble liver Z-AAT and serum AAT levels as pharmacodynamic metrics.
- Participants in Part A will require a pre-dose biopsy and those who meet the inclusion criteria will be randomized to receive ARO-AAT or placebo on days 1, 29, 113, and then every 84 days thereafter.
- There are three cohorts each using a different dose level (25mg, 100mg and 200mg). All three cohorts will be randomized in parallel.
- Once 36 subjects, 12 in each cohort have completed a Day-113 biopsy, the Part A analysis to select a single dose for Part B will occur.
- Enrollment will continue into all cohorts until the Part B dose is chosen.

- **SEQUOIA Part B:**
  - The primary objective for Part B is to evaluate efficacy as assessed by the proportion of ARO-AAT patients relative to placebo achieving a two-point improvement on a histological grading scale of alpha-1 antitrypsin deficiency associated liver disease and no worsening of liver fibrosis on end-of-study biopsy.
  - Patients enrolled during Part A will continue on study and roll over to the Part B dose level or continue to receive placebo.
  - These patients are intended to receive a minimum of six Part B doses and a minimum of nine doses overall.
  - Remaining patients needed to achieve a total enrollment of 120 will be randomized to the selected Part B dose level or placebo and will receive doses on days 1, 29 and then every three months thereafter for a total of nine doses.

- **ARO-AAT 2002 study** (conducted in parallel to SEQUOIA)
  - Open label, multi-dose, Phase 2 study to assess changes in a novel histological activity scale in response to ARO-AAT over time in patients with alpha-1 antitrypsin deficiency associated liver disease.
    - Primary objective is to evaluate effective ARO-AAT on a histologic liver disease activity scale will be assessed at 24 weeks for cohort one and week 48 for cohort two.
    - Multiple secondary 'exploratory objectives' will also be assessed.
    - Expected to include 12 subjects in two sequential cohorts
      - Cohort one consists of four patients and cohort two consists of eight patients.
        - All eligible patients will require a pre-dose biopsy completed as part of the study. Patients that had been enrolled are expected to receive a minimum of three doses of ARO-AAT in cohort one and five doses in cohort two with repeat biopsies approximately one month after the third or fifth dose, respectively.
        - Doses will be administered on days 129, 113 and approximately every 84 days thereafter. Patients who complete cohorts one or two may elect to participate in an extension cohort which would include an additional four doses, again given quarterly followed by repeat liver biopsy.

ARO-ANG3 Phase I Study

In early January 2019 Arrowhead announced commencement of dosing of the initial subjects enrolled in their Phase 1 study (ARO-ANG1001) evaluating the safety, tolerability, PK and PD effects of ARO-ANG3 in healthy individuals and those with dyslipidemia. As a reminder, ARO-ANG3 is ARWR's subcutaneously-administered RNAi-based candidate developed to target angiopoietin like protein 3 (ANGPTL3), which has shown to be involved in the regulation of lipoprotein levels, including triglycerides, LDL cholesterol, HDL and very low-density lipoprotein cholesterol.

This Phase 1 study, expected to enroll up to 70 subjects, has single and multiple dose phases. The single-dose portion will include 4 cohorts, each consisting of 10 healthy adults (6 treatment, 4 placebo), with each participant receiving a single dose (ARO-ANG3 or placebo) at 35mg, 100mg, 200mg or 300mg. The multi-dose portion encompasses up to 4 patient cohorts including those with non-alcoholic fatty liver disease (NAFLD), those on statin treatment with high LDL cholesterol and triglycerides, those with familial hypercholesterolemia, and patients with severe hypertriglyceridemia.

Preclinical (mouse and monkey models) results have been promising, showing substantial and durable reductions in serum ANGPTL3 and liver mRNA, as well as reductions in triglycerides and LDL levels. Over 90% knock down was observed in mouse models. In addition to representing a potential eventual treatment for dyslipidemia, ARO-ANG3 could have utility in certain metabolic diseases as well, including NAFLD and nonalcoholic steatohepatitis (NASH). All of these represent significantly sized markets and with unmet therapeutic needs.

Current status, as reported on the fiscal Q2 2019 earnings call in mid-May, is enrollment and dosing has completed of the SAD cohorts at 35, 100 and 200mg. Further, ARWR expects dosing of the 300mg cohort shortly. Management also noted that this study (along with the ARO-APO3 1001 study - see below) is progressing as scheduled and that they think dosing may complete for all cohorts (including multiple dose cohorts) this year. ARWR also expects to report data from this study in 2019.

ARO-APOC3 Phase I Study

On March 11, 2019 ARWR announced that they commenced dosing of their Phase 1 study of ARO-APOC3, their subcutaneously-administered RNAi-based candidate targeting apolipoprotein C-III (apoC-III) and being developed for the treatment of hypertriglyceridemia.

The study, expected to enroll up to 63 subjects, also has single and multiple dose phases and will be used to help inform subsequent development. It is expected to enroll both healthy subjects and various populations of patients with elevated triglycerides. Up to 90% knock down was observed in rodent models.

ARO-APOC 3 1001 is a Phase 1 single and multiple dose study to evaluate the safety, tolerability, PK and PD effects of ARO-APOC3 in up to 63 adult healthy volunteers with elevated triglycerides and patients with severe hypertriglyceridemia and familial chylomicronemia syndrome (FCS).

The single ascending dose portion is expected to include up to four cohorts of 10 adult healthy volunteers per cohort. SAD subject will receive a single-dose administration of either placebo or ARO-APOC3 at dose levels of 25, 50, 100, or 200 mg. The multiple-dose portion is designed to include up to three cohorts of patients with severe hypertriglyceridemia and one cohort of patients with FCS who will receive two monthly doses of ARO-APOC3.

Current status, as reported on the fiscal Q2 2019 call in mid-May, is dosing of healthy volunteers (which began in March) completed in the 25 and 50mg single dose cohorts. Following a meeting of the safety committee (and clearance to proceed), ARWR expects to begin enrollment of the 100mg single dose cohort. At that time they would also expect to begin enrollment of the first multiple dose cohort at the 50mg level. Similar to the ANG 3 1001 study, ARWR believes that they may complete dosing of all cohorts this year. They also expect to announce data from both studies this year.

Additional Pipeline Update

Arrowhead has also achieved continued progress with the company's **extra-hepatic platform** and pipeline, including:

- ARO-Lung1, Arrowhead's first candidate against an undisclosed gene target in the lung, which achieved nearly 90% target knockdown following inhaled administration in rodents
- ARO-HIF2, the Company's candidate targeting renal cell carcinoma, which achieved 85% target gene knockdown in a rodent tumor model. Arrowhead hopes to file a CTA for ARO-HIF2 this year

- ARO-ENaC, Arrowhead's candidate targeting the epithelial sodium channel (ENaC) alpha subunit for treatment of cystic fibrosis. The company hopes to file a CTA for ARO-ENaC this year

Update on ARO-HIF2 for Kidney Cancer

In September 2015, Arrowhead nominated **ARO-HIF2** as its first therapeutic candidate delivered using a new Dynamic Polyconjugate™ (DPC™) designed to target tissues outside of the liver. Arrowhead believes that ARO-HIF2, which uses RNA interference to silence transcription factor hypoxia-inducible factor 2α (HIF-2α), is a promising new candidate for the treatment of clear cell renal cell carcinoma **(ccRCC).**

ARO-HIF2 is designed to inhibit the production of HIF-2α, which has been linked to tumor progression and metastasis in ccRCC. Using ARC-HIF2 in a preclinical ccRCC tumor model, mice treated with weekly injections led to greater than 80% knockdown of HIF-2α mRNA in tumors. Furthermore, tumors from treated mice exhibited statistically significant reductions in size and weight, extensive tumor cell death, reduction in the tumor-expressed VEGF-A biomarker, and destruction of the blood vessels feeding the tumors.

The company presented positive **preclinical data** at the European Cancer Congress 2015 (ECC2015) in Vienna on September 27, 2015 in a poster titled "HIF-2α targeting with a novel RNAi delivery platform as therapy for renal cell carcinoma," (abstract #353). The company further presented positive preclinical data on ARO-HIF2 at AACR2016.

The poster presentation described data from various stages of development of ARO-HIF2, including RNAi trigger selection, HIF2-α target validation, delivery and targeting ligand validation, and multiple RCC tumor models. These data show that important advancements are being made in this program and for Arrowhead's Dynamic Polyconjugate™ (DPCTM) delivery platform generally, including the following key findings:

- Proof-of-concept ligand dependent, functional delivery was demonstrated using the DPC targeted delivery platform
- Silencing HIF2-α expression by RNA interference resulted in reduction of HIF-2α regulated genes
- In two different RCC tumor bearing mouse models, ARO-HIF2 inhibited tumor growth and promoted tumor cell death and structural degeneration

Valuation

We Remain Optimistic about the Prospect of Arrowhead

We continue to be optimistic about the prospect of Arrowhead and maintain our fair valuation of $30 per share. We believe management decision to focus on the subQ and extra-hepatic programs is prudent. The Janssen collaboration brings significant operating capital, nearly completely de-risks ARO-HBV (at least from a financial standpoint) and provides possible additional shots on goal with potential future additions to the pipeline.

Each of ARWR's pipeline candidates has been shown to be highly active against its respective target. For example, ARC-AAT achieved 90% knockdown of serum AAT, which is believed to be near full suppression of liver production of the protein, in a **Phase 1** clinical study. The AAT and HBV programs have moved along rapidly with both showing highly encouraging results to-date. Safety and tolerability appear to be acceptable while suggestive efficacy of both are, in our opinion, extremely encouraging. Phase 2 studies, if successful, could represent value inflection events.

ARO-AAT Phase 2/3 study could serve as a pivotal FDA registration study – the implications of which suggest this could represent a relatively near-term commercialization candidate. As such, we will be particularly eager to hear updates about this program, including from the ARO-AAT 2002 (parallel open label study).

ARWR's other pipeline programs, including ARO-APOC3 and ARO-ANG3, represent additional incremental - although at this stage, more option-like value, in our opinion. Further progress on the earlier-stage pipeline should provide additional insight into risk-adjustments and ultimate potential tangible commercial value of those candidates.

Our price target $30 per share values the company at about $2.8 billion in market capitalization, which we think is appropriate at this time.

PROJECTED INCOME STATEMENT

	2018 (Sept)					2019 (Sept)					2020 (Sept)
$ in millions except per share data	Q1	Q2	Q3	Q4	FYE	Q1	Q2	Q3	Q4	FYE	FYE
Revenue	$3.51	$0.65	$0.73	$11.26	$16.14	$34.66	$48.15	$60.20	$35.87	$178.88	$88.70
YOY Growth	*-19.6%*	*-92.8%*	*-92.2%*	*29.2%*	*-48.6%*	*887.5%*	*7306.0%*	*8176.3%*	*218.7%*	*1008.1%*	*155.9%*
Total Revenues	**$3.51**	**$0.65**	**$0.73**	**$11.26**	**$16.14**	**$34.66**	**$48.15**	**$60.20**	**$35.87**	**$178.88**	**$88.70**
YOY Growth	*-19.6%*	*-92.8%*	*-92.2%*	*29.2%*	*-48.6%*	*887.5%*	*7306.0%*	*8176.3%*	*218.7%*	*1008.1%*	*155.9%*
Cost of Revenue	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	**$3.5**	**$0.7**	**$0.7**	**$11.3**	**$16.1**	**$34.7**	**$48.1**	**$60.2**	**$35.9**	**$178.9**	**$88.7**
Gross Margin	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*
R&D	$12.9	$12.0	$12.1	$16.0	$53.0	$17.6	$20.8	$22.1	$24.2	$84.7	$97.4
% R&D	*368.1%*	*1846.2%*	*1657.0%*	*142.1%*	*328.1%*	*50.7%*	*43.2%*	*36.7%*	*67.5%*	*47.3%*	*109.8%*
Salary and G&A	$4.4	$3.7	$4.6	$6.4	$19.1	$6.1	$5.3	$6.2	$7.0	$24.7	$26.9
% SG&A	*125.5%*	*566.3%*	*631.6%*	*57.1%*	*118.4%*	*17.7%*	*11.1%*	*10.3%*	*19.5%*	*13.8%*	*30.3%*
Other expenses	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
% Other	*0.0%*	*0.0%*	*0.0%*	*0.1%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Operating Income	**($13.8)**	**($15.0)**	**($15.9)**	**($11.2)**	**($55.9)**	**$10.9**	**$22.0**	**$31.9**	**$4.7**	**$69.5**	**($35.6)**
Operating Margin	-	-	-	-	-	*31.6%*	*45.7%*	*53.0%*	*13.0%*	*38.9%*	*-40.1%*
Other Income (Net)	$0.6	$0.1	$0.3	$0.4	$1.5	$1.1	$1.9	$1.7	$1.5	$6.2	$3.1
Pre-Tax Income	**($13.2)**	**($14.9)**	**($15.6)**	**($10.8)**	**($54.5)**	**$12.0**	**$23.9**	**$33.6**	**$6.2**	**$75.7**	**($32.5)**
Net Taxes (benefit)	$0.0	$0.0	$0.0	$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%*	*0.0%*	*0.0%*	*0.0%*
Reported Net Income	**($13.2)**	**($14.9)**	**($15.6)**	**($10.8)**	**($54.5)**	**$12.0**	**$23.9**	**$33.6**	**$6.2**	**$75.7**	**($32.5)**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
Net Margin	-	-	-	-	-	*34.7%*	*49.6%*	*55.8%*	*17.2%*	*42.3%*	*-36.6%*
Weighted avg. Shares Out	*74.8*	*84.1*	*87.6*	*88.1*	*83.6*	*95.6*	*98.1*	*99.2*	*101.0*	*98.5*	*104.5*
Reported EPS	**($0.18)**	**($0.18)**	**($0.18)**	**($0.12)**	**($0.65)**	**$0.13**	**$0.24**	**$0.34**	**$0.06**	**$0.77**	**($0.31)**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-

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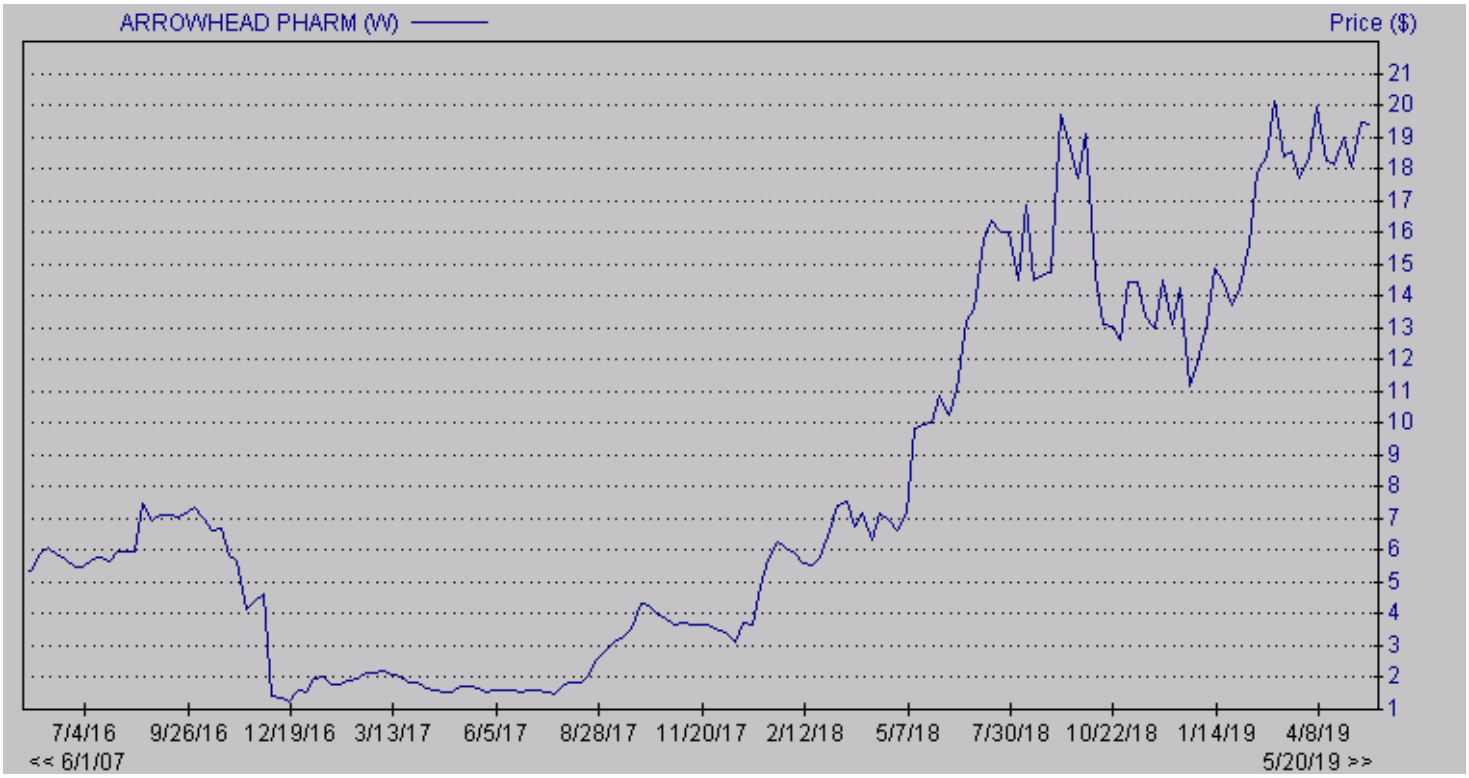

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