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Arrowhead Pharm (ARWR-NASDAQ)

ARWR: Pivotal Studies in View, TRiM Pipeline Progress Continues

Relative valuation metrics indicates fair value of $58/share.

Current Price (02/25/20)	$34.94
Valuation	**$58.00**

OUTLOOK

The story remains almost entirely intact at Arrowhead as broad-based progress continues across their vast (and growing) pipeline. That swift progress has meant, among other positive implications, that the initiation of one or more (potentially, several) FDA pivotal studies is something that is more likely than not to happen, in our opinion, within the next 12 to 18 months.

In addition to continued clinical stage progression of existing programs and platforms, Arrowhead has also been successful in deepening (as well as broadening) the pipeline bench. With new TRiM programs either recently added or potentially on-deck and taking a more targeted direction to areas outside of the liver, management clearly understands that long-term shareholder value is built not by resting on laurels but through uncovering and exploiting growth opportunities. The recent significant equity value creation is a direct result of their pipeline successes and deepening R&D bench.

SUMMARY DATA

52-Week High	**$73.72**
52-Week Low	**$17.27**
One-Year Return (%)	**90.32**
Beta	**1.95**
Average Daily Volume (sh)	**2,375,949**
Shares Outstanding (mil)	**102**
Market Capitalization ($mil)	**$3,543**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**63**
Insider Ownership (%)	**4**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**389.8**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**68.7**
P/E using 2020 Estimate	**N/A**
P/E using 2021 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)
2018	3.50 A	0.65 A	0.73 A	11.26 A	16.14 A
2019	34.66 A	48.15 A	42.70 A	43.29 A	168.8 A
2020	29.45 A	18.00 E	18.52 E	26.62 E	86.59 E
2021					73.22 E

Price/Sales Ratio (Industry = 2.5x)

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2018	-$0.18 A	-$0.18 A	-$0.18 A	-$0.12 A	-$0.65 A
2019	$0.13 A	$0.24 A	$0.21 A	$0.11 A	$0.69 A
2020	-$0.03 A	-$0.13 E	-$0.16 E	-$0.15 E	-$0.47 E
2021					-$0.77 E

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

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WHAT'S NEW

Pipeline 'Wins' Continue with Broad-Based Progress: Pivotal Studies In-View...

The story remains almost entirely intact at Arrowhead as broad-based progress continues across their vast (and growing) pipeline. That swift progress has meant, among other positive implications, that the initiation of one or more (potentially, several) FDA pivotal studies is something that is more likely than not to happen, in our opinion, within the next 12 to 18 months.

In addition to continued clinical stage progression of existing programs and platforms, Arrowhead has also been successful in deepening (as well as broadening) the pipeline bench. With new TRiM programs either recently added or potentially on-deck and taking a more targeted direction to areas outside of the liver, management clearly understands that long-term shareholder value is built not by resting on laurels but through uncovering and exploiting growth opportunities. The recent significant equity value creation is a direct result of their pipeline successes and deepening R&D bench.

ARWR's near-term goals include having 10 TRiM clinical programs ongoing, including eight wholly-owned, by current year-end. As many as three pivotal studies could be on the short-term horizon. And with more and more evidence supporting the therapeutic value of their RNAi technology in non-liver conditions (i.e. oncological), the depth of the potential pipeline and related growth opportunity could be nearly limitless.

Cash balance was recently further fortified which should provide more than enough fuel to fund the current slate of programs for some time. It likely also affords some flexibility in further expanding their development bench or, potentially, for other opportunistic or strategic growth initiatives. Cash and liquid investments as of fiscal Q1 quarter-end (Dec 31, 2019) stood at nearly $530M.

For some cash-burn context, in fiscal 2019 (ending Oct 31, 2019) we estimate ARWR's cash-related opex was just under $100M and another ~$12M cash used for PP&E-related capex (i.e. ~$110M used for ops and capex in 2019). Through fiscal Q1 2020 those same cash-use metrics were ~$34M and $4M, respectively (i.e. ~$38M of cash used in ops and capex).

Pipeline Highlights:

ARO-APOC3 / ARO-ANG3 Orphan Designation, Positive Ph1 SAD, MAD Data: Pivotal Studies in 2020?
Arrowhead received orphan drug designation for ARO-APOC3 for the treatment of familial chylomicronemia syndrome (FCS) and for ARO-ANG3 for the treatment of homozygous familial hypercholesterolemia (HoFH) in June and July of 2019, respectively. FCS and HoFH are both rare metabolic disorders with high unmet needs and are associated with impaired quality of life and certain potentially serious health complications that, if left untreated, can result in death.

FCS is a genetic disorder characterized by inability to properly break down fats (as a result of dysfunctional lipoprotein lipase), which can result in severe hypertriglyceridemia (dangerously high levels of triglycerides), pancreatitis and even death. Worldwide prevalence of FCS is estimated at between 1 in 1M and 1 in 2M people.

HoFH is an inherited disorder which impairs the body's ability to remove low-density lipoprotein. This can lead to severely elevated LDL, early and rapid narrowing / blockage of the arteries and eventually, death. It is estimated that HoFH affects between 1 in 160k to 1 in 1 million people around the world.

Orphan status, combined with the recently announced positive topline Ph1 data, sets the stage for what could be further acceleration of these programs through mid/late-stage development. In fact, additional clinical data, announced in early February 2020, provides further support of the potential effectiveness and safety and should bolster the eventuality of beginning pivotal U.S. studies for both candidates.

In September 2019 ARWR announced positive topline data from Phase I studies of ARO-APOC3 and ARO-ANG3. Presented at The Global Summit on Cardiology and Heart Diseases in Dubai, the data provided the first substantive look at safety and target activity in the clinical setting and results appear to have been exactly what had been hoped for – more specifically, that each candidate effectively reduced their respective targets and triglyceride levels and did so without any serious side effects. Perhaps just as encouraging, this initial topline data – which is from just a single dose (in healthy volunteers) - also suggested long duration of activity.

AROAPOC31001 is a Ph1 (n= ~80) single and multiple dose-escalating study evaluating the safety, tolerability, pharmacokinetics and pharmacodynamic effects of ARO-APOC3 in adult healthy volunteers, patients with hypertriglyceridemia and patients with FCS. AROANG1001 is a Ph1 (n= ~94) single and multiple dose study evaluating the safety, tolerability, pharmacokinetics and pharmacodynamic effects of ARO-ANG3 in adult healthy volunteers and patients with dyslipidemia.

Then, earlier this month additional data was announced - this time from the multiple dose portions. Encouragingly, the interim data of multi-dose cohorts of both APOC3 and ANG3 again showed substantive reductions of triglycerides and other lipid parameters and, also similar to the single-dose data, long duration of activity. As it relates to safety, ARWR noted that APOC3 and ANG3 both continue to look like their other TRiM candidates (i.e. implying no significant concerns) with no drug-related dropouts. Durability of effect, coupled with satisfactory safety and tolerability, provides potential for less burdensome dosing regimen as compared to other therapies – a benefit which can significantly improve dosing compliance and, by extension, clinical outcomes. As such and assuming data continues to confirm these results, this has the potential to provide even greater substantive value-added differentiation against competing therapeutics and represent a meaningful demand driver for both APOC3 and ANG3.

As a reminder of the background of these programs and hypothesis behind their respective targets - large genetic studies discovered that certain rare mutations that disrupt the functioning of apolipoprotein C3 (i.e. APOC3) and angiopoietin-like 3 gene (i.e. ANGPTL3) are associated with lower levels of plasma triglycerides and, in the case of ANGPTL3, also decreased plasma levels of low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. As these lipid fractions have been shown to be predictors of cardiovascular disease (CVD), targeted therapeutic antagonism of APOC3 and ANGPTL3 is hypothesized to reduce risk of CVD. This theory, already supported by laboratory and rodent models, has become much more compelling given the recent single and (even more recent) multiple-dose clinical trial data.

While we will wait for results of the larger data set to offer a more determined opinion, **we would characterize the data- to-date (single and interim multi-dose)** – clean safety and signs of durability of effect - **as about the best as could have been expected.** Management anticipates additional data from both studies to be presented at industry and scientific conferences through the remainder of 2020. This will likely include the complete treatment course of the single ascending dose portions and additional data from the multiple ascending dose cohorts (in various patient populations). And, as we also anticipate additional activity specific to each candidates' respective orphan drug indications, there could be a regular amount of clinical news flow for APOC3 and ANG3 over the coming quarters - which **we think further benefits the likelihood of potential value-inflection announcements.**

The topline Ph1 data announced in September 2019 week related to the SAD portion which, for both studies (i.e. AROAPOC3001 and AROANG1001), included 4 cohorts of 10 adult healthy volunteers with (6 active / 4 placebo). AROAPOC3001 participants received a single dose of either placebo or ARO-APOC3 at dose levels of 10, 25, 50, or 100mg while AROANG1001 participants received a single dose of either placebo or ARO-ANG3 at dose levels of 35, 100, 200, or 300mg.

Of note, **AROAPOC3001 was recently amended**, eliminating what had originally included a 200mg as the highest dose. The amendment, which management stressed was based "solely on positive

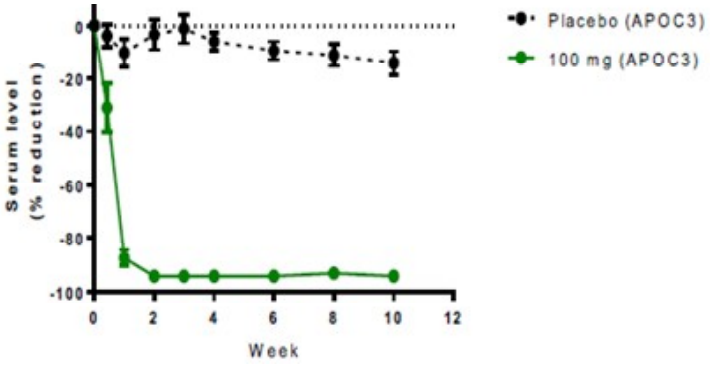
pharmacodynamic activity and not due to any concern or finding with respect to safety or tolerability", also added a 10mg dose (25mg had initially been the lowest dose). Including this lower dose, management noted, should provide additional insight into dose response of APOC3.

Ph1 Topline Results showed:

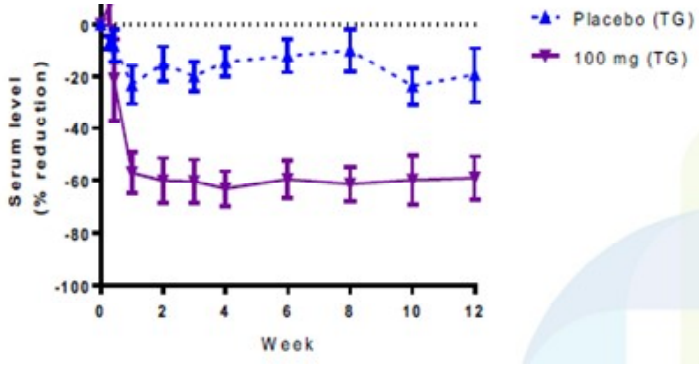
- 100mg of ARO-APOC3 was associated with 63% reduction in plasma triglycerides and 94% reduction in APOC3. Particularly noteworthy is the durability of this robust effect, which appears (see graphs below) to have remained at or near trough level through week 12.

  These results also compare favorably to those of studies of other (non-ARWR associated) clinical stage apolipoprotein C-III-targeting candidates including AKCEA-APOCIII-L_{Rx} (Akcea Ther / Ionis Pharma), in Ph2 testing for the treatment of serious cardiometabolic diseases caused by lipid disorders (see table, below, from ARWR's Ph1 topline results presentation)

APOC3



Triglycerides

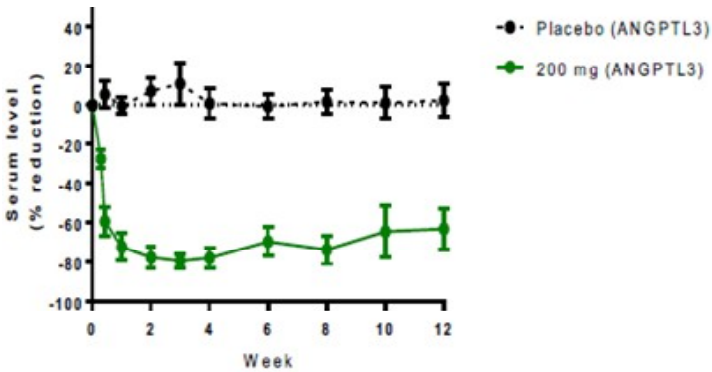


Source: ARWR GSCHD Presentation Sept 2019

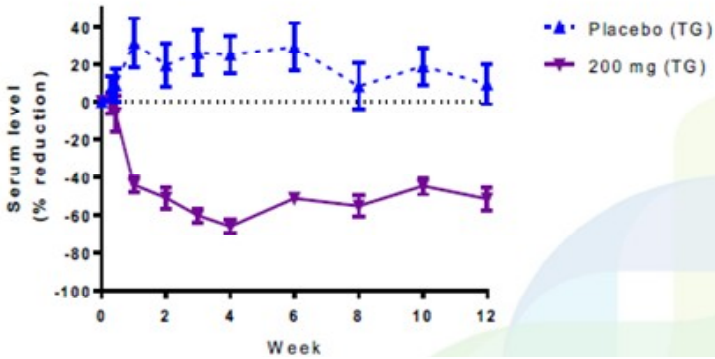
- 200mg of ARO-ANG3 was associated with 66% reduction in plasma triglycerides and 79% reduction in ANGPTL3. Similar to the APOC3 data, ANG3 showed potent durability of effect with maximum reduction largely maintained through 12 weeks.

  These results also compare favorably to those of studies of other (non-ARWR associated) clinical stage angiopoietin like protein 3-targeting candidates including AKCEA-ANGPTL3-L_{Rx} (Akcea Ther / Ionis Pharma) and Evinacumab (Regeneron) - see table, below. AKCEA-ANGPTL3-L_{Rx} is in Ph2 testing for patients with hypertriglyceridemia, type 2 diabetes and nonalcoholic fatty liver disease. Evinacumab is a monoclonal antibody in separate Ph2 trials for patients with severe hypertriglyceridemia as well as those with refractory hypercholesterolemia (also in Ph3 for patients with homozygous familial hypercholesterolemia).

ANGPTL3



Triglycerides



Source: ARWR GSCHD Presentation Sept 2019

- Clean safety profile: In both studies no drug-related serious or severe adverse events were observed

APOC3 Topline Ph1 Data Stacks Up Favorably to Other Clinical Candidates

Mean Maximal % reduction from baseline (SD)	Serum ApoC3	Triglycerides
ARO-APOC3 (100 mg)	94.2% (1.3)	63.2% (16.9)
AKCEA-APOCIII-L_{Rx} (60 mg)*[1]	64.7% (21.7)	43% (19.7)
AKCEA-APOCIII-L_{Rx} (120 mg)**[1]	91.2% (2.5)	79.6% (3.7)

ARO-APOC3 inclusion criteria of TG > 80 mg/dL
*60 mg dose was the highest dose given to subjects with fasting TG ≥ 90 mg/dL
** 120 mg dose was the highest dose given to subjects with inclusion criteria of TG >200 mg/dL
[1]Alexander et al, Eur Heart J, 2019 40:2785-2796.

Source: ARWR GSCHD Presentation Sept 2019

ARO-ANG3 Topline Ph1 Data Stacks Up Favorably to Other Clinical Candidates

Mean Maximal % reduction from baseline (SD) [unless noted]	Serum ANGPTL3	Triglycerides
ARO-ANG3 (200 mg)	79.4% (8.4)	66.2% (7.6)
AKCEA-ANGPTL3-L_{Rx} (80 mg)*[1]	61.7% (1.1)	56.1% (1.1)
Evinacumab (250 mg, SC)[2]	NR**	51.1%[&]
Evinacumab (250 mg, SC)[3]	NR**	55.5%[&]

* Inclusion criteria of TG = 90-150 mg/dL
** Dose-depended increases in ANGPTL3 indicating target binding of evinacumab were observed
[&] Median % change
[1] Graham et al, NEJM 2017 377:222-232
[2] Dewey et al, NEJM 2017 377:211-221
[3] Ahmad et al, Circulation 2019 140: 470-486

Source: ARWR GSCHD Presentation Sept 2019

ANG3, APOC3 Initial Multi-Dose Data (Feb 2020) Also Supports Durability of Effect, Safety…

Initial interim results of Phase 1/2a AROANG1001 (ANG3 multi-dose portion) and AROAPOC31001 (APOC3 multi-dose portion), announced in early February, helped to confirm the durability of effect and clean safety/tolerability of both candidates as evidenced in the respective single-dose portions. The

interim data of multi-dose cohorts of both APOC3 and ANG3 again showed substantive reductions of triglycerides and other lipid parameters and, also similar to the single-dose data, long duration of activity. As it relates to safety, ARWR noted that APOC3 and ANG3 both continue to look like their other TRiM candidates (i.e. implying no significant concerns) with no drug-related dropouts.

Interim initial multi-dose results included (per ARWR's Feb 5, 2020 PR):

- AROANG1001
    - Hypercholesterolemia patients on a stable LDL-C lowering treatment regimen including statins, with or without ezetimibe, and some receiving PCSK9 inhibitors, with at least 29 days of data after receiving the first dose (100-300 mg dose, n=22)
        - Mean maximum reductions in ANGPTL3 of 79-88%
        - Mean maximum reductions in LDL-C of 39-42%

    - Hypertriglyceridemia patients with at least 29 days of data after receiving the first dose (200 mg dose, n=5)
        - Mean maximum reductions in ANGPTL3 of 83%
        - Mean maximum reductions in TG of 79%

- APOC31001
    - Severe hypertriglyceridemia patients with at least 29 days of data after receiving the first dose (50 mg dose, n=3)
        - Mean maximum reductions in APOC3 of 97%
        - Mean maximum reductions in triglycerides (TG) of 95%
        - Mean maximum absolute reduction in TG of -3183 mg/dL

Durability of effect, coupled with satisfactory safety and tolerability, provides potential for less burdensome dosing regimen as compared to other therapies – a benefit which can significantly improve dosing compliance and, by extension, clinical outcomes. As such and assuming data continues to confirm these results, this has the potential to provide even greater substantive value-added differentiation against competing therapeutics and represent a meaningful demand driver for both APOC3 and ANG3.

Assuming no adverse surprises related to the remainder of results of these Ph1/2a studies, ARWR believes that pivotal trials for both APOC3 and ANG3 could commence by current year-end. Anticipated regular data releases over the coming quarters related to APOC3 and ANG3, in addition to optionality related to development specific to orphan indications, bolsters the potential that these two candidates have value-inflection opportunity over the very near-term. We note that APOC3 and ANG3 do not represent nearly the potential aggregate upside value as ARWR's other therapeutic candidates, their wholly-owned status and relative (assumed) inexpensive development pathway means that they are, in our opinion, one of the most attractive from an optionality standpoint.

APOC3 / ANG3 Pivotal Studies, (a preview)…

While too early to stake the ground with what pivotal studies may look like, ARWR has laid out initial thoughts (expectations?). While these could change based on additional data and following discussions with regulators (FDA, EMA), tentative plans include…

APOC3 (tentative pivotal study thinking):

- Single pivotal study (N = 50 - 60) in FCS w/ 24-week duration
    - Endpoint: reduction in plasma triglycerides
- Safety: support safety profile with polygenic patient study w/ severely elevated triglycerides and history of pancreatitis (discuss potential patient-specific labeling w/ FDA)
- Supplemental indications: may explore additional indications such as FPL, secondary prevention

ANG3 (tentative pivotal study thinking):

- Single pivotal study (N = 50 - 60) in HoFH w/ 24-week duration
    - Endpoint: reduction in LDL-C
- Safety: support safety profile with HeFH patient study failing to meet goals w/ max statin ± PCSK9-inhibitors (patient-specific labeling discussion w/ FDA)
- Supplemental indications: may explore additional indications such secondary prevention, NASH

ARO-AAT: Fast Track Status Speeds Timeline of Ph2/3 SEQUOIA, Open Label On-Deck

Development of ARO-AAT, the company's second generation subcutaneously administered RNAi therapeutic being developed as a treatment for a rare genetic liver disease associated with alpha-1 antitrypsin deficiency, also continues to rapidly progress. And with Fast Track status granted by FDA in mid-June 2019 (complementing Orphan Drug designation in the U.S. and E.U. which was granted in early 2018), we could see the development timeline further accelerate.

Encouragingly, **SEQUOIA**, a Ph2/3 trial which was announced in 2019 and could serve as a pivotal U.S. registrational study (which would make it the first U.S. pivotal study of ARWR's TRiM platform), appears to be moving quickly. IDE approval came in April 2019, multiple sites continue to enroll and are dosing patients and new sites are expected to come online. ARWR appears intent on leveraging the Fast Track status, noting that they have sped up clinical site activity including getting additional locations operational and enrolling. U.S. sites were the first to be operational and ARWR has since opened additional sites in both North America and Europe.

Meanwhile, the timeline for **ARO-AAT 2002**, the parallel open label study, appears to largely continue tracking prior expectations. The European study began dosing in early 2020 with the initial cohort fully enrolled. Biopsies will take place at 6 months, 12 months, 18 months and 24 months of treatment. Initial (i.e. 6-month) biopsies are anticipated sometime in calendar Q3'20.

JNJ-3989 (fka ARO-HBV): Ph1/2 Cohort 12 Completes Enrollment, New Ph2 Janssen Study

JNJ-3989 (targeting chronic HBV and the initial program under the Janssen collaboration) not only continues to progress through an ongoing Ph1/2 clinical study – which includes completion of enrollment of the (recently added) triple combination cohort ('cohort 12', 12 patients with chronic HBV over 12 weeks) – but is also now being used in REEF-1, Janssen's Ph2b triple combination study (with targeted enrollment of 450) evaluating different combination drug regimens in the treatment of chronic HBV for up to 48 weeks.

Compelling Ph2 data, in two separate posters, was presented at The Liver Meeting 2019 in November…

JNJ-3989 combined with nucleos(t)ide analogue treatment in chronic HBV patients showed impressive reduction in hepatitis surface antigen (HBsAg), HBV DNA and HBV RNA. Meanwhile, hepatitis B e antigen (HBeAg) and hepatitis B core-related antigen (HBcrAg) reductions were less meaningful. Specifically (per ARWR 11/8/19);

- HBsAg reductions were similar in HBeAg positive and HBeAg negative patients
- Expanded cohorts with 100–400 mg JNJ-3989 confirmed previous findings that HBsAg declines were similar with these doses; 97% (31/32) of these patients achieved a ≥1.0 log10 (90%) reduction in HBsAg
- The 25 mg and 50 mg JNJ-3989 doses were active in reducing HBsAg, and appeared less effective than higher doses

    - HBsAg responses with JNJ-3989 are consistent with its ability to silence HBV RNA from cccDNA and host-integrated viral DNA (which is a major source of HBsAg in certain CHB populations)
    - JNJ-3989 was well tolerated at doses up to 400 mg Q4w for three doses
- Investigators concluded that JNJ-3989 demonstrated anti-HBV characteristics desirable for an effective RNAi therapy

JNJ-3989 used in triple-combo therapy in Chronic Hepatitis B (CHB): JNJ-73763989 (JNJ-3989), JNJ-56136379 (JNJ-6379) And a Nucleos(T)ide Analogue (NA). This is the initial tolerability and efficacy data using this combo therapy against CHB. Results showed:

- Therapy was well tolerated
- All patients achieved robust reductions in HBsAg, HBV DNA, and HBV RNA. Reductions in HBeAg and HBcrAg were generally less pronounced during the dosing period
- All patients (n=12) achieved a ≥1.0 log10 IU/mL (90%) reduction (nadir ranged from –1.01 to –2.26 log10 IU/mL) in HBsAg
- HBsAg reductions were similar in HBeAg positive and HBeAg negative patients
- Studies of longer duration with this triple combination are underway aimed at assessing functional cure rates in patients with CHB

The positive clinical data to-date coupled with the fact that this was the first glimpse of JNJ-3989 as a triple combo therapy for chronic HBV (which has a great unmet need for finite curative therapies) means that AROHBV1001 cohort 12 data, while not designed to necessarily tell us anything definitive, was, we think, highly informative and value-additive.

Meanwhile, REEF-1, which will treat for up to 48 weeks, could inform on the curative potential of JNJ-3989 as part of a triple combination therapy. REEF-1 (NCT03982186) is a Phase 2b, multicenter, double-blind, active-controlled, randomized study to investigate the efficacy and safety of different combination regimens for the treatment of chronic hepatitis B virus infection. Regimens include JNJ-3989, and/or JNJ-6379, and a nucleos(t)ide analog (NA). REEF-1 is planned to include up to 450 patients who will be randomized to receive up to 48 weeks of treatment. (JNJ-6379 is Janssen's investigational orally administered capsid assembly modulator of the class that forms normal capsid structures).

ARWR received $25M (in August) from Janssen, tied to their collaboration agreement, upon dosing of the fifth patient in REEF-1. This is the second (of two) development-related payments from Janssen (the first of which, also $25M, was received in April 2019 and associated with initiation of dosing of Ph1 cohort 12).

And, beyond the milestone payments (which, along with ~$250M upfront, including $175M in cash, have provided ARWR with a rich source of non-dilutive funding since the deal was penned in October 2018), we think inclusion of JNJ-3989 in REEF-1 represents a win in and of itself for ARWR given the potentiality implications (in regards to safety and utility in chronic HBV treatment) as well as it representing another shot on goal towards possible eventual commercialization of the compound (ARWR is eligible for royalties on any eventual sales of JNJ-3989).

In addition, any and all development successes of JNJ-3989 presumably bodes well for ARWR's working relationship with Janssen and furthers the likelihood that they collaborate on additional TRIM-based RNAi targets (and, potentially, expanding their relationship outside of their current agreement). Their October 2018 agreement provides Janssen with the option to collaborate with ARWR on up to three additional RNAi therapeutics (for new targets to be selected by Janssen) – the first of which, 'JNJ1', was just recently announced. JNJ1, per ARWR, is being developed against an undisclosed liver-expressed target. As a reminder, ARWR is responsible for preclinical development (fully funded by Janssen) up to filing of an IND, at which point Jansen has the option to take an exclusivity license and continue development. Additional success of JNJ-3989 and initial progress with JNJ1 (which management

indicated has moved swiftly) should further bolster the chances of a long-lasting relationship between ARWR and Janssen in our opinion.

ARO-HSD: latest pipeline addition, CTA filing anticipated this year…
ARO-HSD, targeting HSD17B13 for potential indications in alcohol and non-alcohol related liver diseases, is the most recent addition to ARWR's pipeline. A CTA filing for ARO-HSD was made in December and ARWR subsequently received regulatory and IRB approvals to commence the study. This study is expected to begin dosing any day now. ARO-HSD will represent ARWR's sixth clinical TRiM program.

17β-Hydroxysteroid dehydrogenase type 13 (17β-HSD type 13), an enzyme encoded by the HSD17B13 gene, is involved in lipid metabolism in the liver. Genetic studies have shown that loss-of-function mutations to HSD17B13 are associated with decreased risk of development of alcohol and non-alcohol related liver diseases. Specifically, a study conducted by Regeneron and published in March 2018 in the NEJM found that individuals with two copies of this loss-of-function variant of HSD17B13 had a 53% and 30% lower risk of alcoholic liver disease and nonalcoholic liver disease, respectively, as compared to individuals with two functioning copies of the gene. Non-functioning carriers were also found to have a 73% lower risk of alcoholic cirrhosis and 49% lower risk of nonalcoholic cirrhosis as compared to those with two working copies of the gene.[1]

TriM Programs Continue to Grow…
ARWR recently filed for IND approval to begin Ph1 testing of ARO-HIF2 for the treatment of clear cell renal cell carcinoma. This, in addition to ARO-HSD, will further expand ARWR's TriM program portfolio. As a reminder ARO-HIF2 achieved 85% target gene knockdown in a rodent tumor model. ARO-HIF2 would represent their seventh TRiM program.

Meanwhile IND-enabling studies of ARO-ENaC, Arrowhead's candidate targeting the epithelial sodium channel (ENaC) alpha subunit for treatment of cystic fibrosis, had been delayed which pushed back the IND/CTA filing timeline. Now underway, ARWR hopes to have initial human studies started by mid-2020 (calendar).

- Pulmonary epithelial TRiM™-enabled delivery platform increased potency of RNAi trigger-mediated silencing of αENaC mRNA, and durably reduced whole lung gene expression in rodents
- In normal sheep, inhaled ARO-ENaC produced dose-dependent acceleration of mucociliary clearance, which is a lung physiology endpoint linked to pulmonary function in patients with CF
- Inhaled ARO-ENaC preserves lung clearance in a sheep disease model of mucostasis
- ARO-ENaC may offer a new renal-sparing, genotype-agnostic therapy for all patients with CF, and exhibiting the potential for an extended duration of action that should minimize treatment burden
- ARWR is also expanding its pulmonary delivery platform to address additional lung disease targets, particularly those that are inaccessible to traditional small molecule or antibody approaches

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Valuation

ARWR continues to make rapid, nearly error- and delay-free, progression of their pipeline and has done so without significant dilution to shareholders. Recently secured orphan designations and positive (safety and activity, including duration) initial human trial data of APOC3 and ANG3 sets the stage for a potentially accelerated and an unambiguous regulatory pathway for both candidates. Orphan status, combined with the recently announced positive topline Ph1 data, sets the stage for what could be further acceleration of these programs through mid/late-stage development. In fact, additional clinical data, announced in early February 2020, provides further support of the potential effectiveness and safety and should bolster the eventuality of beginning pivotal U.S. studies for both candidates.

[1] Noura S. Abul-Husn, M.D., Ph.D, et al. A Protein-Truncating HSD17B13 Variant and Protection from Chronic Liver Disease. N Engl J Med 2018; 378:1096-1106

The Janssen/J&J collaboration has already shown to be a 'win' for the company (and shareholders), providing over $200M of dilutive-free funds in less than 12 months and facilitating the speedy development pace of ARO-HBV (JNJ-3989). We think it is reasonable to assume that the clean safety (to-date) profile and JNJ-3989 having already moved into a large, potentially curatively-powered Ph2b (triple combo) study, is bolstering Janssen's confidence in both the potential of the therapy (and, perhaps, the TRiM platform as a whole) and their working relationship with ARWR. Having now pulled the trigger on the first option to collaborate with ARWR on (up to three) additional RNAi therapeutics is, we think, another indication of the potential upside that Janssen sees in ARWR's technology and capabilities.

ARO-AAT also continues to make rapid development progress and Fast Track status, granted in June 2019, could help accelerate that pace. Encouragingly, SEQUOIA, a Ph2/3 trial which was just announced earlier this year and could serve as a pivotal U.S. registrational study (which would make it the first U.S. pivotal study of ARWR's TRiM platform), appears to be moving quickly. IDE approval came in April 2019, multiple sites continue to enroll and are dosing patients and new sites are expected to come online. ARWR appears intent on leveraging the Fast Track status, noting that they have sped up clinical site activity including getting additional locations operational and enrolling. U.S. sites were the first to be operational and ARWR has since opened additional sites in both North America and Europe.

With APOC3, ANG3 and AAT all possibly entering pivotal studies in the near-term and JNJ-3989 now in what could prove to be a curative study (for HBV, which could draw massive appeal), we could soon have a lot more information to gauge the potential commercializability (and value) of Arrowhead's development portfolio. This, by extension, also bolsters the potential likelihood of significant value-inflection events/announcements (over the same timeframes).

We also remain highly encouraged by ARWR's seeming determination to continue to deepen their development pipeline. With another three CTA filings anticipated, the company could soon have eight TRiM clinical programs ongoing. ARO-HSD, targeting HSD17B13 for potential indications in alcohol and non-alcohol related liver diseases, is the most recent addition and which ARWR hopes to have in clinical studies next year.

The rapid and largely error and delay-free progress of the existing clinical pipeline, coupled with the company continuing to deliver on its guidance related to increasing the number of high-potential TRiM candidates under development, has moved our targeted market capitalization to $5.9B, or ~$58/share.

PROJECTED INCOME STATEMENT

	2019 (Sept)					2020 (Sept)					2021 (Sept)
$ in millions except per share data	Q1	Q2	Q3	Q4	FYE	Q1	Q2	Q3	Q4	FYE	FYE
Revenue	$34.66	$48.15	$42.70	$43.29	$168.80	$29.45	$18.00	$18.52	$20.62	$86.59	$73.22
YOY Growth	*887.5%*	*7306.0%*	*5770.0%*	*284.7%*	*945.7%*	*-38.8%*	*-57.8%*	*-57.2%*	*-87.8%*	*149.8%*	*52.1%*
Total Revenues	**$34.66**	**$48.15**	**$42.70**	**$43.29**	**$168.80**	**$29.45**	**$18.00**	**$18.52**	**$20.62**	**$86.59**	**$73.22**
YOY Growth	*887.5%*	*7306.0%*	*5770.0%*	*284.7%*	*945.7%*	*-38.8%*	*-57.8%*	*-57.2%*	*-87.8%*	*149.8%*	*52.1%*
Cost of Revenue	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$20.0	$0.0	$20.0	$0.0
Gross Income	**$34.7**	**$48.1**	**$42.7**	**$43.3**	**$168.8**	**$29.5**	**$18.0**	**$1.5**	**$20.6**	**$66.6**	**$73.2**
Gross Margin	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*-8.0%*	*100.0%*	*76.9%*	*100.0%*
R&D	$17.6	$20.8	$19.3	$23.4	$81.0	$23.4	$23.1	$24.7	$25.3	$96.5	$101.6
% R&D	*50.7%*	*43.2%*	*45.2%*	*54.0%*	*48.0%*	*79.4%*	*128.5%*	*133.2%*	*122.8%*	*111.4%*	*138.7%*
Salary and G&A	$6.1	$5.3	$4.8	$10.3	$26.6	$10.9	$11.2	$11.7	$12.2	$46.1	$52.2
% SG&A	*17.7%*	*11.1%*	*11.3%*	*23.7%*	*15.7%*	*37.1%*	*62.3%*	*63.4%*	*59.3%*	*53.3%*	*71.3%*
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%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Operating Income	**$10.9**	**$22.0**	**$18.6**	**$9.6**	**$61.2**	**($4.9)**	**($16.3)**	**($37.9)**	**($16.9)**	**($76.0)**	**($80.6)**
Operating Margin	*31.6%*	*45.7%*	*43.6%*	-	*36.3%*	-	-	-	-	*-87.8%*	*-110.1%*
Other Income (Net)	$1.1	$1.9	$1.7	$2.2	$7.0	$2.2	$2.7	$2.0	$1.7	$8.7	
Pre-Tax Income	**$12.0**	**$23.9**	**$20.3**	**$11.9**	**$68.1**	**($2.7)**	**($13.6)**	**($35.9)**	**($15.2)**	**($67.3)**	**($80.6)**
Net Taxes (benefit)	$0.0	$0.0	$0.0	$0.2	$0.2	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*1.5%*	*0.3%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Reported Net Income	**$12.0**	**$23.9**	**$20.3**	**$11.7**	**$68.0**	**($2.7)**	**($13.6)**	**($35.9)**	**($15.2)**	**($67.3)**	**($80.6)**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
Net Margin	*34.7%*	*49.6%*	*47.6%*	-	*40.3%*	-	-	-	-	*-77.8%*	*-110.1%*
Weighted avg. Shares Out	*95.6*	*98.1*	*98.9*	*101.8*	*98.6*	*97.1*	*101.7*	*101.9*	*102.0*	*100.7*	*104.5*
Reported EPS	**$0.13**	**$0.24**	**$0.21**	**$0.11**	**$0.69**	**($0.03)**	**($0.13)**	**($0.35)**	**($0.15)**	**($0.67)**	**($0.77)**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-

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