ARROWHEAD PHARMACEUTICALS

Fiscal 2021 Third Quarter Conference Call – Prepared Remarks

August 5, 2021

1:30 PM Pacific time

Operator

Ladies and gentlemen welcome to the Arrowhead Pharmaceuticals conference call. Throughout today's recorded presentation all participants will be in a listen-only mode. After the presentation, there will be an opportunity to ask questions. I will now hand the conference call over to Vincent Anzalone, Vice President of Investor Relations for Arrowhead. Please go-ahead Vince.

Vince Anzalone

Good afternoon everyone. Thank you for joining us today to discuss Arrowhead's results for its fiscal 2021 third quarter ended June 30, 2021.

With us today from management are president and CEO Dr. Christopher Anzalone, who will provide an overview of the quarter; Dr. Javier San Martin, our chief medical officer, who will provide an update on our pipeline; and Ken Myszkowski, our chief financial officer, who will give a review of the financials. In addition, James Hassard, our chief commercial officer, and Dr. James Hamilton, our senior vice president of Discovery & Translational Medicine, will be available during the Q&A session of today’s call.

Before we begin, I would like to remind you that comments made during today's call contain certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. All statements other than statements of historical fact, including without limitation those with respect to Arrowhead's goals, plans, and strategies are forward-looking statements. These include statements regarding our expectations around the development, safety and efficacy of our drug candidates, projected cash runway, the receipt of future milestone and licensing payments, and expected future development and commercialization activities. These statements represent management's current expectations and are subject to numerous risks and uncertainties that could cause actual results to differ materially from those expressed in any forward-looking statements. For further details concerning these risks and uncertainties, please refer to our SEC filings, including our most recent annual report on Form 10-K and subsequent quarterly reports on Form 10-Q. Arrowhead disclaims any intent and undertakes no duty to update any of the forward-looking statements discussed on today's call.

With that said, I'd like to turn the call over to Christopher Anzalone, President and CEO of the Company. Chris?

Chris Anzalone

Thanks Vince. Good afternoon everyone and thank you for joining us today.

The fiscal third quarter and the period since our last conference call has been incredibly busy for Arrowhead. We made important advances in several of our development programs. This includes discovery stage programs and early, mid,

and later stage clinical programs. It also includes programs from existing partnerships as well as a new business development transaction.

As a platform company, there are a few areas of critical importance where we focus our attention:

- First, we need to always push the boundaries of what is possible and make our TRiM™ platform better.
- Second, we need to expand the early-stage pipeline rapidly and efficiently with new clinical candidates, as this will be an important source of growth in the future.
- Third, we need to move our mid and later-stage pipeline programs through clinical studies, as it gets us closer to our goal of bringing important new medicines to patients without adequate treatment options; and,
- Lastly, we need to selectively use partnering to expand the reach and maximize the value of our TRiM™ platform, and bring in non-dilutive capital that helps to fund our internal development

I think we are doing well in all these areas. Let's take a moment to briefly review some key events in the quarter that are good examples of this.

For our discovery and early-stage clinical pipeline, we had a very productive quarter. We completed discovery and optimization work on two new pulmonary programs and nominated them both as clinical candidates. They are now in the IND-enabling stage, which includes GLP toxicology studies and manufacturing of drug product for clinical studies. We have not yet disclosed the gene and disease targets, but we will be talking more about these programs later in the year.

We also presented very promising preclinical data on ARO-DUX4, our first muscle-targeted program being developed as a treatment for patients with facioscapulohumeral muscular dystrophy, or FSHD, at the 28th Annual FSHD Society International Research Congress. The data show that the TRiM™ muscle delivery platform can achieve functional delivery to various types of skeletal muscle and achieve deep, durable, and dose-dependent knockdown of target genes. In addition, ARO-DUX4 improved multiple measures of FSHD-like muscle phenotype in relevant preclinical animal models. As DUX4 expression is recognized as the cause of muscle pathology in FSHD patients, Arrowhead believes that the selective targeting and knockdown of DUX4 using RNAi may prevent or reverse downstream myotoxicity and lead to muscle repair and improvement in muscle function in patients. There are currently no effective treatments specifically for FSHD, so patients need new therapeutic options that address the root cause of the disease.

We have been pushing aggressively toward the clinic with ARO-DUX4 as well as the two new pulmonary candidates we nominated this year. We expected to file CTAs for all three by the end of the year, but securing timely slots at CROs for IND-enabling toxicology studies has been challenging, so scheduling on the CTAs will be pushed into the first half of next year. That is unfortunate, but we have seen this become more of a bottleneck in the industry since the beginning of the pandemic.

We have continued work on a number of other early programs and I am pleased to announce a previously undisclosed target. We recently nominated ARO-C3 as a hepatocyte-directed candidate against complement C3. Overactivation of the complement cascade is thought to be causative of a number of diseases including paroxysmal nocturnal hemoglobinuria and C3 glomerulopathy, and complement

mediated injury is involved in many other conditions including IgA nephropathy as well as many other renal, vascular, hematologic and neurologic conditions. Complement C3 is a central node in all three of the complement pathways including the classical, lectin and alternative pathways of complement activation, and it has recently been shown that inhibition of C3 can be both safe and effective in the treatment of complement mediated diseases.

We have a strong track record in TRiM™-enabled hepatocyte-directed candidates, including ARO-HBV, ARO-LPA, ARO-AAT, ARO-ANG3, ARO-APOC3, and ARO-HSD. Clinical data from these programs give us confidence that positive non-clinical data from ARO-C3 may translate well in humans. We believe that an siRNA capable of substantially reducing C3 levels for three months or more could be the modality of choice for C3 inhibition, and we expect to file a CTA for ARO-C3 by the end of the year.

During the quarter we also announced positive interim data for two of our early-stage clinical programs, ARO-HIF2 and ARO-HSD.

I will start with ARO-HIF2, which is our first tumor-targeted program being developed as a potential treatment for patients with clear cell renal cell carcinoma, or ccRCC. To date, investigational ARO-HIF2 has been generally well tolerated at doses of up to 525 mg weekly. The study has now progressed to a dose of 1050 mg weekly, which is currently enrolling and dosing patients. We believe that in the first two dose cohorts ARO-HIF2 is showing clear signs of meaningful target engagement and potentially some early signs of efficacy in at least one patient. Specifically, the HIF2α protein H-score was assessed via immunohistochemistry. 9 of 17 patients had tumor samples that could be evaluated, and 7 of those 9 demonstrated reductions in HIF2α protein H-scores. These reductions ranged from

-9% to -82% with a mean reduction of -48%. In addition, one subject had a partial response with approximately 65% tumor shrinkage and 5 subjects had a best response of stable disease. We think these early results in a heavily pre-treated population are encouraging for ARO-HIF2 and our tumor-targeted platform broadly.

We also presented positive interim data for ARO-HSD, being developed as a potential treatment for patients with liver diseases, such as nonalcoholic steatohepatitis, or NASH, at the EASL International Liver Congress. ARO-HSD was well tolerated in healthy volunteers given a single dose at 25mg, 50mg, 100mg or 200 mg and in 5 patients with suspected NASH given a 100 mg dose of ARO-HSD on Days 1 and 29.

All five patients with suspected NASH showed a strong pharmacodynamic effect as measured by liver biopsy at Day 71. HSD17B13 protein was reduced by 92% and 97% in two patients, while the other three patients' Day 71 measurements were reduced to below the lower limit of quantitation. Importantly, ALT showed a mean reduction from baseline of 46%, with all patients showing reductions ranging from 26-53%. We believe that ARO-HSD is the first investigational therapeutic to demonstrate robust inhibition of hepatic HSD17B13 mRNA and protein expression. We are also highly encouraged to see ALT levels drop significantly following just two doses of ARO-HSD.

In addition to progress on our early-stage pipeline, we also achieved some important milestones for our mid- and later-stage pipeline.

I will start with our cardiometabolic programs, ARO-APOC3 being developed as potential treatment for hypertriglyceridemia and ARO-ANG3 being developed as a

potential treatment for mixed dyslipidemia. We recently started two Phase 2b studies, one for each program. We intend to initiate four or more studies across the two programs, including a Phase 3 study. Javier will give more details about the studies that have already started dosing in a few minutes but we believe the studies together will give us a robust picture on the pharmacologic activity of each medicine in various target patient populations. We are intending to identify the optimal dose and dose intervals to enable us to move confidently into multiple Phase 3 studies.

In addition to our cardiometabolic programs, we had multiple important events in the last quarter for ARO-AAT, also known as TAK-999, being co-developed with Takeda as a treatment for the rare genetic liver disease associated with alpha-1 antitrypsin deficiency.

First, we presented additional positive interim 48-week liver biopsy results at the EASL International Liver Congress. The results demonstrate that ARO-AAT treatment led to rapid improvements in multiple measures of liver health, including fibrosis, with substantial and sustained reductions in the level of mutant AAT protein. Mutant AAT protein has been identified as the cause of progressive liver disease in patients with alpha-1 antitrypsin deficiency. ARO-AAT treatment was generally well tolerated after up to 1 year of treatment. This is very important data and suggests to us that the drug is doing what it is designed to do, and that removing the mutant AAT protein can give the liver a chance to begin the healing process, even when intervening in patients with late-stage liver disease. We and our partners at Takeda were thrilled to see these results and we have received similar responses from physicians and others in the alpha-1 treating community.

We also fully enrolled the ARO-AAT Phase 2 SEQUOIA study, with the 40th patient being dosed recently. Combined with the various cohorts in the open-label 2002 study, we will have paired biopsies from approximately 50 patients receiving various dose levels and various treatment durations.

Lastly for ARO-AAT, we were granted Breakthrough Therapy designation by the U.S. FDA. ARO-AAT was also previously granted Orphan Drug designation and Fast Track designation from the FDA, and Orphan designation from the European Commission. Our goal is to expedite the development path of ARO-AAT, and each of these important designations provide potential ways to achieve that. We will work with regulatory authorities and our partners from Takeda to identify the best path to bring this important drug to patients quickly.

Now moving on to progress that we've made with partnering. As I mentioned, we believe a platform company should use partnering selectively to expand the reach and maximize the value of the platform technology, and to bring in non-dilutive capital that helps to fund internal development. This is a key component of our business strategy and an area where we've seen important recent progress.

The collaboration with Janssen, which was executed toward the end of 2018, for ARO-HBV against chronic hepatitis B infection, included an option on three additional programs. During the previous quarter, Janssen delivered written notice of its intent to exercise its option right for the first of those programs, ARO-JNJ1. This earned Arrowhead a $10 million option exercise fee and signals Janssen's intent to move forward with clinical studies.

Also, during the quarter, we announced a global collaboration and license agreement with Horizon Therapeutics for ARO-XDH, a previously undisclosed

discovery-stage candidate being developed by Arrowhead as a potential treatment for people with uncontrolled gout. Arrowhead received $40 million as an upfront payment from Horizon and is eligible to receive up to $660 million in potential development, regulatory and commercial milestones, and is further eligible to receive royalties in the low- to mid-teens range on net product sales. Horizon will receive a worldwide exclusive license to the therapeutic and will be wholly responsible for clinical development and commercialization.

This is a great example of an attractive partnering opportunity. It expanded the reach of our technology to an area that we had not intended to enter independently and brought in non-dilutive capital. It also brought in needed expertise in the gout field to help understand the disease, the clinical path, the tremendous unmet treatment need, and a dominant player in the space with an existing commercial organization. For all these reasons we thought Horizon was the ideal partner and the deal made perfect sense for both of our companies. We look forward to working closely with Horizon as we advance this potential new therapy for patients in need.

As you've heard, this was a busy quarter with lots of exciting events. However, drug development doesn't progress in a straight line and invariably there are surprises. Sometimes these surprises lead to leaps forward, such as the faster than expected liver healing in our ARO-AAT program, and sometimes these surprises can be more unwelcome. We experienced the latter in the ARO-ENaC program, our candidate being developed as a potential treatment for cystic fibrosis, last quarter.

To review, we voluntarily paused the clinical study of ARO-ENaC after receiving a preliminary update from an ongoing chronic toxicology study in rats that

contained unexpected signals of local lung inflammation. Because of this preliminary update, we instructed investigators to pause new screening, enrollment, and any further dosing of investigational ARO-ENaC pending additional data from the ongoing chronic rat toxicology study and an additional ongoing chronic primate toxicology study.

We have not seen any concerning safety or tolerability signals in people enrolled in the AROENaC1001 study. However, we place the safety of patients that participate in our clinical trials above all else, so we will continue to keep the ARO-ENaC clinical study on pause for now. We do not yet have full data back from the toxicology studies nor from additional studies that we are conducting internally, so we do not yet know the extent of the findings. We are investigating this fully and are still in the information gathering stage. We should know more in the coming weeks and months and we intend to provide an update when we are able.

With that overview, I'd now like to turn the call over to Dr. Javier San Martin. Javier?

Javier San Martin

Thank you, Chris, and good afternoon everyone.

I want to give an update on our clinical studies and provide details on the design of a couple of our newest studies.

First, I will discuss ARO-HIF2, which is designed to inhibit the production of HIF-2α to treat clear cell renal cell carcinoma or RCC. We were encouraged by the positive interim results from the first two cohorts of AROHIF21001, a Phase 1b

dose-finding clinical study in 3 cohorts with advanced clear cell RCC. We are currently enrolling cohort 3, which is designed to include up to 10 patients who will receive a weekly IV infusion of 1050 mg of ARO-HIF2. The study is designed to evaluate the safety of ARO-HIF2, to determine the recommended Phase 2 dose, and to assess pharmacokinetics and preliminary efficacy, based on RECIST, and post-dose tumoral expression of HIF2-alpha and HIF associated genes. Patients will continue to receive weekly ARO-HIF2 indefinitely until they experience disease progression, have a complete response, or they discontinue. Our intention is to share additional interim data from this study, including data from cohort 1, 2, and initial results from cohort 3 at an appropriate medical meeting in the future. We have not yet selected the intended meeting.

The next program I want to detail is ARO-HSD, our investigational candidate for the potential treatment of alcohol and nonalcohol related liver disease. We think the interim data we presented at EASL was highly encouraging, and, in fact, our presentation was highlighted in the EASL Official Scientific Press Conference on NAFLD/NASH. It was exciting to see ALT levels drop significantly following just two doses of ARO-HSD. We expected a high level of target gene knockdown, because our TRiM^{TM} system has been extraordinarily consistent across our different liver directed programs. But the improvement in ALT at this early timepoint was a very welcome surprise.

These data and the strong genetic evidence of HSD17B13 as a potential therapeutic target provide us with increased confidence as we design further clinical studies for ARO-HSD. We are thinking about innovative designs that seek to answer key questions about the medicine, the disease, the mechanism of HSD17B13 inhibition, and what early signs of improvement may look like. We are approaching this in a similar way to how we approached ARO-AAT. In the meantime, we are still

conducting the Phase 1/2 in patients with NASH or suspected NASH, and we are happy to report that the study is fully enrolled.

As Chris mentioned, we started dosing in two Phase 2b studies of our cardiometabolic candidates, ARO-APOC3 and ARO-ANG3 during the last quarter. I will give a brief description of these study designs, so you all can think through potential timing. We intend to initiate additional studies shortly and we will provide details on the design of the additional studies when they start.

For ARO-APOC3, we initiated AROAPOC3-2001, a double-blind, placebo-controlled Phase 2b study to evaluate the efficacy and safety of ARO-APOC3 in adults with severe hypertriglyceridemia, or SHTG. Three dose levels of ARO-APOC3 (10 mg, 25 mg, and 50 mg) will be evaluated against placebo in participants who have mean fasting triglycerides of greater than or equal to 500 mg/dL at screening. A total of approximately 300 participants will be enrolled in the study. All dose cohorts will enroll in parallel with 100 participants per dose cohort randomly assigned in a 3:1 ratio to receive ARO-APOC3 or placebo. Each participant will receive subcutaneous injections on day 1 and week 12. The duration of the study is approximately 54 weeks from screening to the week 48 end-of-study examination. The primary objective of the study is to evaluate the safety and efficacy of ARO-APOC3 in adults with SHTG and to select a dosing regimen for later stage clinical studies in this patient population.

For ARO-ANG3, we initiated AROANG3-2001, a double-blind, placebo-controlled Phase 2b study to evaluate the efficacy and safety of investigational ARO-ANG3 in adults with mixed dyslipidemia. Three dose levels of ARO-ANG3 (50 mg, 100 mg, and 200 mg) will be evaluated against placebo in participants with mixed dyslipidemia who had the following at screening:

1. LDL-cholesterol greater than or equal to 70 mg/dL or non-HDL-cholesterol greater than or equal to 100 mg/dL; and,
2. Mean fasting triglycerides between 150 and 500 mg/dL

A total of approximately 180 participants will be enrolled in the study. All dose cohorts will enroll in parallel with 60 participants per cohort randomly assigned in a 3:1 ratio to receive a subcutaneous injection of ARO-ANG3 or placebo on day 1 and week 12. The duration of the study is approximately 42 weeks from screening to the week 36 end-of-study examination. After completing the week 36 visit, participants will be eligible to continue in an open-label extension study. The primary objective of the AROANG3-2001 study is to evaluate the safety and efficacy of ARO-ANG3 in adults with mixed dyslipidemia and select a dosing regimen for later stage clinical studies in this patient population.

I will now turn the call over to Ken Myszkowski, Arrowhead's Chief Financial Officer. Ken?

Ken Myszkowski

Thank you, Javier, and good afternoon everyone.

As we reported today, our net loss for the quarter ended June 30, 2021 was $29.9 million or $0.29 per share based on 104.1 million fully-diluted weighted average shares outstanding. This compares with net loss of $13.6 million, or $0.13 per share based on 101.8 million fully-diluted weighted average shares outstanding, for the quarter ended June 30, 2020.

Revenue for the quarter ended June 30, 2021 was $45.9 million, compared to $27.4 million for the quarter ended June 30, 2020. Revenue in the current period primarily relates to the recognition of a portion of the $300 million upfront payment received under our collaboration agreement with Takeda, as well as a $10 million option exercise payment received from Janssen for the ARO-JNJ1 program in May 2021. Revenue for the Takeda agreement will be recognized as we continue to work toward completing our performance obligations of managing clinical trials in process and certain manufacturing related services. The remaining $230 million of revenue associated with the Takeda collaboration is anticipated to be recognized over approximately 2 years. Any additional milestones achieved with our collaboration partners would be additive to this projection. Revenue in the prior period primarily related to the recognition of a portion of the milestones received from our license and collaboration agreements with Janssen. Our performance and revenue recognition under the Janssen agreement for HBV is substantially complete.

Total operating expenses for the quarter ended June 30, 2021 were $77.8 million, compared to $43.3 million for the quarter ended June 30, 2020. This increase is primarily due to increased candidate specific and discovery R&D costs as the Company's pipeline of clinical candidates has both increased and advanced.

Net cash used by operating activities during the quarter ended June 30, 2021 was $29.6 million, compared with net cash used by operating activities of $33.4 million during the quarter ended June 30, 2020. The key driver of this change was the $10 million option exercise payment received from Janssen for the ARO-JNJ1 program in May 2021. Excluding any potential milestones from our collaboration partners, we estimate our cash burn run rate to be $50 to $60 million per quarter.

Turning to our balance sheet, our cash and investments totaled $644.7 million at June 30, 2021, compared to $453.0 million at September 30, 2020. The increase in our cash and investments was primarily due to the upfront payment received from Takeda, offset by cash used for operating activities. In July, we also collected the $40 million upfront payment due under our recent collaboration with Horizon.

Our common shares outstanding at June 30, 2021, were 104.2 million.

With that brief overview, I will now turn the call back to Chris.

Chris Anzalone

Thanks Ken.

As I mentioned, we think we're making strong progress across the spectrum of activities required to be a successful platform company. We are innovating on the platform and pushing the bounds of what our TRiM™ technology can do. We are rapidly and efficiently feeding the early-stage pipeline with new candidates that may be engines of growth for Arrowhead in the future. We are moving our mid- and later-stage clinical programs progressively closer to our goal of bringing important new medicines to the patients who need them. And, lastly, we are selectively and responsibly using partnering and business development when it makes sense to do so.

This last quarter saw important and tangible progress in all these areas.

Thanks again for joining us today. I would now like to open the call to your questions. Operator?

Operator