ARROWHEAD PHARMACEUTICALS

Fiscal 2022 Third Quarter Conference Call – Prepared Remarks

August 4, 2022

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 2022 third quarter ended June 30, 2022.

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 mid and later stage clinical pipeline; Dr. James Hamilton, our senior vice president of Discovery & Translational Medicine, who will provide an update on our earlier stage programs; and Ken Myszkowski, our chief financial officer, who will give a review of the financials. In addition, Tracie Oliver, our newly appointed chief commercial officer, and Patrick O'Brien, who was recently promoted to chief operating officer and general counsel, will both be available during the Q&A portion of the 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 are forward-looking statements 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 our quarterly reports on Form 10-Q.

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.

Before I cover key events and progress during the previous quarter, I want to talk about some recent management additions that make us a stronger company today and, importantly, as we grow into a vertically integrated, commercial stage pharmaceutical company.

We are currently conducting one phase 3 study for a wholly-owned drug candidate and I expect us to begin one or two additional phase 3 studies next year. As such, there are important strategic decisions we need to begin considering that will effect how we ultimately commercialize these drug candidates. We are thrilled to

welcome Tracie Oliver as Chief Commercial officer to start to build out our commercial infrastructure and, more immediately, contribute to the planning of our late-stage programs to ensure that our future commercial requirements are harmonized with clinical datasets and ultimate drug labels.

Tracie has over 30 years of global experience in the biopharmaceutical industry leading both R&D and commercial organizations. Prior to joining Arrowhead, she had her own consulting practice focused on providing guidance to small, emerging commercial stage biotech companies on the proper strategy, timelines, methods, and ultimately the buildout of new commercial organizations. Those skills and experience are critical to Arrowhead as we look to take the next steps in our growth as a company.

Prior to her consulting business, Tracie was with Shire Pharmaceuticals through the acquisition of Baxalta and was Global Head of New Product Planning and Device Strategy. Prior to that she held several commercial roles at Baxter and Baxalta including establishing a new oncology franchise and leading the North America Immunology Business Unit and Autoimmune Franchise. Tracie began her career in the biopharmaceutical industry with Johnson & Johnson and served as head of Ortho Biotech Nephrology Business Unit in Canada, Ortho McNeil Neurologics, and McNeil Pediatrics in the USA.

As we continue with this type of growth in personnel and departments, we need to be more deliberate in our drive to continue operational excellence. There can be a tendency toward an inverse relationship between the size of an organization and its ability to operate efficiently, creatively, and rapidly. It is important to us that we maintain our operational excellence as we grow, and Patrick O'Brien, our General

Counsel, will now also take on the role of Chief Operating Officer to help ensure this.

I will now move on to review some of our recent progress. We view setbacks as a normal part of innovation and if we can learn something from them, they may serve as an investment in the future. The recent progress we've made in our pulmonary platform is a good example of this, and a powerful illustration of how fast Arrowhead can move.

As you know, our first candidate in the clinic using the pulmonary targeted TRiM™ platform was ARO-ENaC for the treatment of cystic fibrosis. Last year, we decided to pause enrollment in the ARO-ENaC first-in-human clinical study as we further investigated some findings from a nonclinical toxicology study that suggested some local lung inflammation after chronic treatment at certain high doses. Many open questions remained.

James will speak to what we learned in more detail later in the call, but after extensive investigation, consultation with internal and external toxicology experts, and additional studies it appears that findings were consistent with what is called lung macrophage overload. Essentially, the volume of material, not necessarily the specific drug or target, was swamping the lungs' clearance mechanisms and causing an inflammatory response. So, the clear way to move forward is to understand the amount of material that triggers this phenomenon and develop more potent, longer acting candidates to stay below the assumed cumulative dose threshold.

I believe we have done that for our next generation candidates, ARO-RAGE and ARO-MUC5AC, resulting in three important improvements:

- First, we think we can now achieve better knockdown with less exposure.
- Second, we think we can give a single dose as opposed to our previous need to dose on three consecutive days.
- And third, we believe we can now stretch the dose interval substantially. For example, ARO-ENaC was going to be dosed three times every two or three weeks, and ARO-RAGE has duration that potentially lasts multiple months after a single dose.

Each of these improvements are important on their own but taken together we believe they dramatically change the profile of our next generation pulmonary candidates.

So, where are we now? The work and lessons that went into this happened over an extended period, culminating this last quarter in two important events. We held a pulmonary R&D day to go over our findings and present nonclinical data for our next generation candidates ARO-RAGE, ARO-MUC5AC, and then shortly after, we began dosing patients in two clinical studies. As I said, I think this is a great example of what Arrowhead is capable of. We went from pausing enrollment of the ARO-ENaC clinical program to initiating clinical studies and dosing human subjects with next generation candidates that potentially have dramatically improved profiles in about 12 months.

There was an enormous amount of work, thought, creativity, technology, and innovation that enabled this result. The pulmonary TRiM™ platform is an important expansion of our technology that we expect will help a large number of patients and create a substantial amount of value, but it is just one example of how we are growing our platform. We expect many more going forward.

Another set of key accomplishments during the quarter relate to execution on our later stage programs for our cardiometabolic candidates, ARO-APOC3 and ARO-ANG3. Between the two candidates, we have five active clinical studies that range from ultra-rare disease populations to high prevalence diseases. The design and execution of clinical studies for diseases on opposite ends of the size spectrum typically have different tactics and require specialized expertise. I'm happy to report that our clinical development and clinical operations teams have been successfully running all these studies.

On the rare disease side, the Phase 3 PALISADE study of ARO-APOC3 in patients with FCS is efficiently enrolling patients and we have worked hard during the quarter to identify and open new countries and sites that should contribute to rapid enrollment of the study. In addition, during the quarter we initiated the Phase 2 GATEWAY study of ARO-ANG3 in patients with HoFH. This study is also enrolling patients efficiently and we look forward to seeing data in the future.

On the high prevalence disease side, we have three ongoing studies. For ARO-APOC3 we are running the SHASTA-2 Phase 2 study in patients with severe hypertriglyceridemia and the MUIR Phase 2 study in patients with mixed dyslipidemia. We have executed well on both studies, and we believe we are on schedule for readouts both studies in 2023. In fact, we recently reached total planned enrollment for MUIR. For ARO-ANG3, there is one high prevalence disease study, the Phase 2 ARCHES-2 study in patients with mixed dyslipidemia. This study was fully enrolled earlier in the year and should be complete at the end of the year and enable a readout in the first half of next year.

The other two accomplishments from the recent quarter that I want to highlight are related to corporate goals that aim to maximize the value of our technology over the long term.

First, we announced that we broke ground on the construction of a new commercial scale manufacturing facility and received awards of up to $18.5 million in incentives to invest in the local region and create new jobs. This is an important investment in Arrowhead's future as a vertically integrated commercial stage pharmaceutical company. It helps us control the manufacturing process both operationally and strategically for our wholly-owned programs and potentially for our partnered programs in the future. It potentially reduces the cost of our clinical and commercial drug supply and, importantly, helps eliminate any future bottlenecks related to drug manufacturing.

Lastly, related to corporate goals, during the last quarter we also announced that Arrowhead formed Visirna Therapeutics, a joint venture with Vivo Capital in which Arrowhead is a majority shareholder, to expand the reach of innovative medicines in Greater China. Arrowhead licensed four investigational RNAi therapeutics to Visirna for cardiometabolic diseases in mainland China, Hong Kong, Macau, and Taiwan. Vivo Capital provided $60 million in initial funding to Visirna. This transaction potentially allows us to expand our reach into geographies that are beyond our core focus while retaining a substantial economic interest.

So in summary, Arrowhead had a productive quarter where we saw progress in our pipeline of industry leading RNAi therapeutics, our wide reaching and expanding TRiM technology platform, and our corporate goals.

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.

First, I want to highlight data on the Phase 2 '2002 study of fazirsiran, formerly called ARO-AAT and TAK-999, presented in July at the EASL International Liver Congress and published simultaneously in the New England Journal of Medicine.

The presentation generated significant enthusiasm within the audience, welcoming positive data to address a liver disease with no approved therapy and the validation of a New England publication.

Fazirsiran is a potential first-in-class investigational RNAi therapy designed to reduce production of a mutant form of the alpha-1 antitrypsin protein, called Z-AAT, as a potential treatment for the rare genetic liver disease associated with alpha-1 antitrypsin deficiency. Z-AAT accumulation is believed to be the cause of progressive liver disease in patients with AAT deficiency. Reducing production of the pro-inflammatory Z-AAT protein has the potential to halt the progression of liver disease and potentially allow the liver to regenerate and repair.

The data from this program are exciting and encouraging. The open label AROAAT-2002 Phase 2 study in 16 patients with AATD liver disease suggest a strong effect and the potential to improve multiple downstream markers of liver health.

Decrease in fibrosis severity of at least 1 stage occurred in 7 of 12 patients, or 58%, receiving the 200-mg dose, including 2 patients with cirrhosis. All patients had reductions in accumulated total mutant Z-AAT in the liver with a median reduction at week 24 or 48 of 83%. Reductions in liver Z-AAT concentrations were also associated with histologic improvements in inflammation. After treatment, all patients had a decreased histologic globule burden, with the mean score decreasing by 69% at week 24 or 48.

Biomarkers of liver injury were also reduced. At baseline, mean ALT concentrations were above the upper limit of the normal range in all cohorts. After treatment, ALT concentrations decreased in all cohorts from week 16 through week 52. All 12 patients with ALT concentrations above the upper limit of the normal range at baseline had reductions to normal levels at week 52.

In addition to activity and efficacy measures, safety and tolerability measures continue to be encouraging. Fazirsiran was generally well tolerated in the 2002 study. Over a period of 1.5 years, there were no deaths, discontinuations of treatment with fazirsiran, or dose interruptions. The most common adverse events that emerged or worsened after the first administration of fazirsiran were arthralgia and transient increased concentrations of blood creatinine kinase. There were no apparent dose dependent increases in the frequency or severity of adverse events.

So far, there have been no major pulmonary adverse events resulting in drug or trial discontinuations. Four of the six patients who entered the trial while receiving AAT augmentation therapy had a history of emphysema, and none reported exacerbations.

The fazirsiran Phase 2 placebo-controlled SEQUOIA study has also reached the end of the treatment period. We collected the final 12-month biopsy from the final patient recently, and will now be processing samples and analyzing data over the coming months. The deadline is in September to submit a late-breaker to present at the AASLD Liver Meeting in November. The timing will be tight to have enough data to justify a late-breaker, so it is a low probability that we will be presenting data at that congress. We should, however, have a rather complete data-set on SEQUOIA in the fourth quarter of this year, so we and our partners at Takeda will together determine the best way to communicate those results publicly.

Regarding status of a Phase 3 study, we and Takeda are in the process of having discussions with regulators on the development path. We do not want to comment specifically on those discussions as they are ongoing.
Moving on to our cardiometabolic candidates, I will provide the status of the VISTA studies of ARO-ANG3 and the SUMMIT studies of ARO-APOC3.

The VISTA program of ARO-ANG3, our investigational medicine designed to reduce production of angiopoietin-like protein 3 as a potential treatment for patients with dyslipidemia, has two ongoing studies. The first, ARCHES-2 in 204 patients with mixed dyslipidemia, is fully enrolled. We anticipate that ARCHES-2 will be complete around the end of 2022 and topline data will be available to share in the first half of 2023. In addition to the planned study period, patients will be eligible to continue in an open-label extension period after completing the week 36 visit.

The second active study of ARO-ANG3 is GATEWAY in up to 16 subjects with homozygous familial hypercholesterolemia, or HoFH. We anticipate that this study

will be fully enrolled by the end of the year, and we intend to share data in 2023 when possible.

Moving on to ARO-APOC3. The SUMMIT program of ARO-APOC3, our investigational medicine targeting apolipoprotein C-III being studied in patients with various lipid disorders, has three ongoing studies: two Phase 2 studies; SHASTA-2 in patients with severe hypertriglyceridemia, or sHTG; and MUIR in patients with mixed dyslipidemia; and the Phase 3 PALISADE study in patients with familial chylomicronemia syndrome, or FCS.

MUIR has now reached the total planned enrollment of 320 patients. We have a number of patients still in screening, so we will allow some additional patients to join the study but are not screening any new patients. SHASTA-2 has enrolled over 80% of the planned number of patients and we anticipate full enrollment this year. This would allow for both studies to be completed in 2023.

PALISADE is planned to enroll approximately 72 patients with FCS. We continue to open new clinical sites around the world and enroll new patients into the study. We are still on schedule and anticipate that PALISADE will reach full enrollment in the middle of 2023 which would allow for study completion in 2024.

I will now turn the call over to Dr. James Hamilton. James?

James Hamilton

Thank you, Javier.

I want to give updates on some of our earlier stage development programs. Let's start with the pulmonary platform.

As Chris mentioned, we hosted an R&D day on our emerging pipeline of pulmonary targeted RNAi therapeutics and the technology platform that these candidates are built upon. We have learned a great deal about the platform with details provided in the archived pulmonary R&D Day web cast available on our website.

In summary, we believe that we now have improved siRNA triggers with longer pharmacodynamic duration allowing less frequent dose administration, which are less likely to overload lung clearance mechanisms and/or are less likely to induce pulmonary inflammation. This gives us increased confidence in the platform as we move forward with current and planned future clinical studies and additional toxicology studies.

We also presented preclinical data on the development of our next generation pulmonary candidates, ARO-MUC5AC and ARO-RAGE, which have recently begun dosing in clinical studies, and on ARO-MMP7, which will be approaching clinical studies later this year.

ARO-MUC5AC is the first investigational medicine to directly silence expression of pathologic MUC5AC, a mucin protein with upregulated expression in the asthmatic airway, and potentially address muco-obstructive disease, characterized by mucus hypersecretion, in a fundamentally different way than current therapies. Preclinical results have shown deep silencing of up to 70-90% of induced MUC5AC expression in mice and primates. In a sheep model of allergic asthma, ARO-MUC5AC effectively preserved airway function.

ARO-RAGE is an investigational medicine designed to reduce expression of the receptor for advanced glycation end products that aims to achieve broader anti-inflammatory effects compared to current biologics and with a more convenient inhaled mode of administration. Preclinical studies have shown that single inhaled doses of ARO-RAGE in rats and primates led to reductions of greater than 90% in lung RAGE mRNA and in serum sRAGE protein, a circulating biomarker for RAGE target engagement in the lung. Pharmacodynamic response appears to be highly durable enabling bimonthly or quarterly dosing.

Earlier this month we announced that we had dosed the first subjects in Phase 1/2a clinical trials of both ARO-MUC5AC and ARO-RAGE. We have since completed dosing the first cohort of healthy volunteers in both studies. Both studies have three parts consisting of single ascending and multiple ascending doses in normal healthy volunteers, and multiple dose cohorts in asthma patients with dose levels selected for patient cohorts based on data from normal healthy volunteers.

The third pulmonary program we discussed at the R&D day is ARO-MMP7, our newest and previously undisclosed candidate designed to the reduce expression of matrix metalloproteinase 7, or MMP7, as a potential treatment for idiopathic pulmonary fibrosis, or IPF. MMP7 plays multiple roles in IPF pathogenesis, including promoting inflammation and aberrant epithelial repair and fibrosis. Silencing MMP7 expression in a rat IPF model reduced inflammatory cell infiltration, limited lung fibrosis, and preserved pulmonary function. We are conducting CTA-enabling work and preparation now, and we are on track to file this year to initiate first-in-human clinical studies.

Our last early-stage clinical program is ARO-C3, our investigational RNAi therapeutic designed to reduce production of complement component 3, or C3, as a potential therapy for various complement mediated diseases. We are approaching the final healthy volunteer cohort in Part 1 of a Phase 1/2 study. Data from Part 1 will inform dose selection for Part 2, which will include eligible subjects with paroxysmal nocturnal hemoglobinuria, or PNH, and complement-mediated renal diseases, including IgA nephropathy and C3 glomerulopathy. We anticipate that Part 2 of the study will start before the end of the year.

I will now turn the call over to Ken Myszkowski. Ken?

Ken Myszkowski

Thank you, James, and good afternoon everyone.

As we reported today, our net loss for the three months ended June 30, 2022 was $72.0 million or $0.68 per share based on 105.8 million fully-diluted weighted average shares outstanding. This compares with net loss of $29.9 million, or $0.29 per share based on 104.1 million fully-diluted weighted average shares outstanding, for the three months ended June 30, 2021.

Revenue for the quarter ended June 30, 2022 was $32.4 million, compared to $45.9 million for the quarter ended June 30, 2021. Revenue in the current period primarily relates to our collaboration agreements with Takeda and Horizon. Revenue will be recognized as we complete our performance obligations, which include managing the ongoing AAT phase 2 clinical trials for Takeda, and delivering a phase 1 ready candidate to Horizon. There remains $142.1 million of revenue to be recognized associated with the Takeda collaboration which we

anticipate will be recognized over approximately 2 years, and there remains $13 million of revenue to be recognized for Horizon, which we anticipate will be recognized by the end of calendar 2022. 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 and Takeda.

Total operating expenses for the quarter ended June 30, 2022 were $105.3 million, compared to $77.8 million for the quarter ended June 30, 2021. This increase is driven by higher employee compensation expense including stock compensation expense, as well as higher R&D discovery expense.

Net cash used by operating activities during the quarter ended June 30, 2022 was $68.9 million, compared with net cash used by operating activities of $29.6 million during the quarter ended June 30, 2021. The increase in cash used by operating activities is driven by higher expenses research and development expenses. We expect our operating cash burn to be $70 to $80 million next quarter and I will provide additional guidance during our year end conference call.

Turning to our balance sheet, our cash and investments totaled $582.4 million at June 30, 2022, compared to $613.4 million at September 30, 2021. The decrease in our cash and investments was primarily due to cash used for operating activities, mostly offset cash inflows from Horizon, GSK and by the cash investment in our Joint Venture, Viserna. Our common shares outstanding at June 30, 2022, were 105.8 million.

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

Chris Anzalone

Thanks Ken.

We have a large and growing pipeline of clinical drug candidates, providing us the opportunity to help millions of patients and create a substantial amount of value. It also affords us the opportunity to regularly report clinical data so stakeholders can follow our progress. However, with the development of next generation pulmonary candidates and timing of other studies, we have been in a bit of a data desert over the last several quarters. We are now emerging from that desert. Between now and the end of next year, I expect at least 12 clinical readouts between our wholly-owned and partnered programs. They include the following:

1. Biopsy data from the Sequoia study in AAT with fazirsiran
2. P1/2 data from ARO-C3 in healthy volunteers and different patient populations
3. P1/2 data from ARO-RAGE in healthy volunteers and patients
4. P1/2 data from ARO-MUC5AC in healthy volunteers and patients
5. P2 data from olpasiran in Amgen's LP(a) study
6. P2 data from the ARO-ANG3 Arches-2 study in mixed dyslipidemia
7. P2 data from the ARO-ANG3 Gateway study in HoFH
8. P2 data from the ARO-APOC3 Muir study in mixed dyslipidemia
9. P2 data from the ARO-APOC3 Shasta-2 study in severe hypertriglyceridemia
10. P1 data from ARO-MMP7 in healthy volunteers and possibly IPF patients
11. P2 data from various Janssen studies of JnJ-3989 in HBV patients, and
12. P1 data from Janssen's NASH study with JnJ-0795

We are excited about these and other programs and look forward to updating you on our progress.

Thank you for joining us today and I would now like to open the call to your questions. Operator?

Operator