ARROWHEAD PHARMACEUTICALS

Fiscal 2023 First Quarter Conference Call – Prepared Remarks

February 6, 2023

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 and thank you for joining us today to discuss Arrowhead's results for its fiscal 2023 first quarter ended December 31, 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 Chief 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 chief commercial officer, and Patrick O'Brien, our chief operating officer and general counsel, will 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.

Arrowhead currently occupies a unique position within the biopharma world. I believe that RNAi as a modality, and our proprietary TRiM™ platform in particular, are considered increasingly validated. RNAi is a potentially powerful way to treat many disease states, it appears to largely work as intended across numerous clinical studies, has the potential to be highly specific, and has been generally well tolerated. Overlay on top of this a scarcity premium. There is a clear scarcity of companies capable of developing RNAi therapeutics well and extreme scarcity of those capable of bringing RNAi outside the liver. These factors combine to position Arrowhead to create substantial value for our

shareholders and the patients who rely on us for life-altering new medicines. I think this also frames how we should view Arrowhead currently, the progress we will discuss today, and what these mean for the future. The two primary components to this sort of analysis are: the ways in which we are expanding our technological reach; and the ways in which we are leveraging our more proven technology.

Let's begin with how we are expanding our reach. As you know, our pulmonary franchise is currently comprised of three clinical candidates, ARO-RAGE, ARO-MUC5AC, and ARO-MMP7. With our announcement last week that the ARO-MMP7 P1/2 study initiated, we are now treating subjects in all three programs. We remain on track to begin early data disclosures for ARO-RAGE and ARO-MUC5AC in the second quarter. This is an important milestone for us. We view the lungs as a target-rich environment and don't see 2 or 3 drugs coming out of that franchise, but rather potentially 8 or 9. As with hepatocytes, once we have clinical validation that we are able to address a cell type and reduce expression of a target gene in a well-tolerated fashion, we believe the franchise will be substantially de-risked. At that point, we have an expectation of success for future programs in terms of our ability to safely silence a target gene. As such, clinical proof of concept in the first 1 or 2 programs within a cell type has the potential to unlock substantial value. We believe we will be there for our pulmonary franchise next quarter, and given what we learned with ARO-ENAC and our non-clinical data using ARO-RAGE, ARO-MUC5AC, and ARO-MMP7 across several animal models, we are optimistic that we will see clinically relevant gene knockdown in a well-tolerated fashion.

We have not spoken about our muscle-targeting franchise for some time, and I am pleased to announce that we intend move ARO-DUX4, our candidate designed to

treat Fascioscapulohumoral Muscular Dystrophy, or FSHD, into clinical studies next quarter. This is another example of our drive to apply RNAi to unmet medical needs, wherever they are. We have completed a large number of non-clinical studies including acute and chronic GLP toxicity studies, and we look forward to bringing this potentially important medicine to the patients who need it.

Another important milestone relating to technology expansion that we expect next quarter is disclosure of the next cell type we will be targeting and a presentation of our supporting non-clinical data. This and our work in the pulmonary and skeletal muscle spaces represent substantial growth opportunities for the company and would bring RNAi closer to reaching its full promise as a revolutionary therapeutic modality with the potential to address many new diseases. These programs are early, but they are the next great leaps forward for Arrowhead. The second calendar quarter of 2023 is, indeed, a busy time for demonstrating Arrowhead innovation.

Let us now turn to our liver programs. We have demonstrated across multiple candidates in many clinical studies and in thousands of patients that our liver directed candidates appear to achieve high levels of target engagement and have encouraging safety and tolerability profiles. As such, we are focused on executing on our current liver programs and aggressively expanding our pipeline where we can.

Last month we announced topline results from the Phase 2 SEQUOIA clinical study of fazirsiran for the treatment of liver disease associated with alpha-1 antitrypsin deficiency. The active treatment arm had results that were highly consistent with the AROAAT-2002 open-label study, which we previously published in The New England Journal of Medicine. Fazirsiran appears to be active

against its target, with all treated patients achieving a high level of reduction of the mutant Z-AAT protein which is known to be the root cause of AATD liver disease. This reduction over 12 months led to promising downstream changes in markers of liver disease, including reductions in inflammation and 50% of patients experienced a regression in fibrosis.

These encouraging results are exactly what we had hoped for. The only data point that was a bit difficult to interpret, was in the placebo arm. There, 3 of the 8 patients with paired biopsies showed an improvement in fibrosis. We know that scoring fibrosis is a notoriously noisy measure and a way to smooth out such data is to ensure a large enough sample size. Unfortunately with just 8 patients, a single patient in either direction can lead to confusing percentages. We believe that is what happened here. Fortunately, we can look to previous studies for guidance on what fibrosis should look like in untreated patients. For instance, a previous natural history study that followed over 50 AATD patients showed about 15% had an improvement in fibrosis. We believe that the 50% of patients who showed improvement in fibrosis on fazirsiran is a reliable measure because: (a) the treatment groups had a larger sample size than placebo; and (b) the improvement in fibrosis was part of a larger data set that make sense together. Patients on fazirsiran had dramatic reductions in AAT monomer and globules, and they demonstrated decreased inflammation. The patients in the placebo arm showed none of those features.

Takeda is now initiating a Phase 3 study that will enroll up to 160 patients, which is designed to be sufficiently large to smooth that variability to approximately the levels expected based on natural history. Arrowhead is eligible to receive a milestone payment from Takeda when the Phase 3 study starts.

During the previous quarter, two of our other partnered programs generated milestone payments as they advanced into the next stage of development. Horizon Therapeutics enrolled the first subject in a Phase 1 study of HZN-457, formerly called ARO-XDH, for the treatment of gout earning Arrowhead a $15 million milestone payment.

In addition, we earned a $25 million milestone payment from Amgen after the first subject was enrolled in Amgen's Phase 3 trial of olpasiran for the treatment of cardiovascular disease. We believe in that program and in the potential of olpasiran to help patients with risk of cardiovascular disease associated with elevated levels of Lp(a). However, with the recent presentation and publication of positive Phase 2 data we determined that the timing was right to monetize our royalty stream associated with potential future olpasiran sales. To that end, in exchange for rights to the olpasiran royalties, Royalty Pharma paid us $250 million in cash upfront, and up to $160 million in additional payments contingent on the achievement of certain clinical, regulatory, and sales milestones. In addition, we retained rights to $400 million in development, regulatory, and sales milestone payments potentially due from Amgen from the 2016 license agreement, including the $25 million milestone payment I just mentioned.

During the quarter, promising new clinical data across three late-breaking presentations were presented at the American Heart Association meeting on three investigational candidates for cardiometabolic diseases, ARO-APOC3, ARO-ANG3, and olpasiran. The totality of these data demonstrates the significant progress achieved in RNAi drug development and they specifically suggest a potential future treatment paradigm where RNAi may be prominently leveraged in preventive cardiology. As I mentioned, a P3 study has already been initiated with olpasiran. ARO-APOC3 is also being investigated in a P3 study against FCS, and

we expect that 48-week study to be fully enrolled next quarter. We also expect end of P2 meetings this year to speak with regulators about P3 studies using ARO-APOC3 in sHTG patients as well as broad mixed dyslipidemia populations. My expectation is that we will launch those P3 studies at the end of the year. Similarly, I expect that we will move ARO-ANG3 into P3 studies in familial hypercholesterolemia patients this year. I also expect several data presentations from 4 P2 studies with these candidates throughout the year.

Finally, we continue to make progress in our P1/2 study of ARO-C3, our candidate designed to treat several complement-mediated diseases. I expect to release initial data next quarter. Janssen has also made progress with its P1 study of JNJ-0795, our partnered candidate against NASH, and we expect a data disclosure that includes liver fat reduction this quarter. Turning to JNJ-3989, we have seen the media reports about Janssen deprioritizing HBV broadly, and that is consistent with our understanding. We have not received a termination letter for our license agreement and it is our understanding that some legacy HBV studies are continuing but we do not know where JNJ-3989 will ultimately end up. We will assess our options and rights when Janssen decides the path forward for the program.

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 describe the fazirsiran SEQUOIA data that we presented last month and then give an update on where we are with mid and late-stage studies of our cardiometabolic candidates.

As Chris mentioned earlier, the SEQUOIA data from the treatment arms were very encouraging and consistent with the prior data generated from the 2002 open-label study. This is what we and our partners at Takeda wanted to see.
Patients receiving 25, 100, or 200 mg of fazirsiran who had baseline fibrosis demonstrated a dose dependent mean reduction in serum Z-AAT concentration at week 48 of 74%, 89%, and 94%, respectively. All three doses led to a dramatic reduction in total liver Z-AAT with a median reduction of 94% at the postbaseline liver biopsy visit. In addition, PAS-D globule burden, a histological measure of Z-AAT accumulation, had a mean reduction of 68%. Improvement in portal inflammation was observed in 42% of patients while only 7% showed worsening. Lastly, 50% of patients achieved an improvement in fibrosis of at least one point by METAVIR stage.

In contrast, by week 48 patients receiving placebo who had baseline fibrosis saw no meaningful changes from baseline in serum Z-AAT, had a 26% increase in liver Z-AAT, and had no meaningful change in PAS-D globule burden. No placebo patients experienced an improvement in portal inflammation while 44% experienced worsening. 3 of the 8 placebo patients experienced an improvement in fibrosis at the postbaseline liver biopsy visit. This finding highlights the known variability on histologic fibrosis assessment. With a larger sample size, like in the planned Phase 3 study, the rate of improvement in patients receiving placebo may more closely approximate results from natural history studies of untreated patients with AATD.

Fazirsiran has been well tolerated with treatment emergent adverse events reported to date generally well balanced between fazirsiran and placebo groups. There were no treatment-emergent adverse events leading to drug discontinuation, dose interruptions, or premature study withdrawals in any study group. Compared with placebo, no dose-dependent or clinically meaningful changes were observed in pulmonary function tests over 1 year with fazirsiran.

These are all encouraging signs for the program and for patients. We know this is a progressive disease of the liver caused by one thing: the accumulation of the mutant Z-AAT protein, which cannot efficiently get out of the liver. The data suggest that fazirsiran can reduce the production of new Z-AAT and then the liver starts the process of breaking down and clearing the accumulated Z-AAT in the liver, reducing inflammation, and ultimately regressing fibrosis. This is essentially the cascade of progressive liver disease in reverse. We believe that this reversal can only start with the removal of the insult to the liver, which is the accumulation of the mutant Z-AAT protein. These data represent hope for physicians and their patients with this disease who have no approved treatment options.

We also announced that Takeda is initiating a randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of fazirsiran in patients with F2 to F4 fibrosis. Approximately 160 patients will be randomized 1:1 to receive fazirsiran or placebo. The primary endpoint of this study is a decrease from baseline of at least 1 stage of histologic fibrosis METAVIR staging in the centrally read liver biopsy done at Week 106 in patients with METAVIR stage F2 and F3 fibrosis.

I also want to give a brief update on where we are with our cardiometabolic candidates, ARO-APOC3 and ARO-ANG3.

ARO-APOC3 is our investigational RNAi therapeutic targeting apolipoprotein C-III, or APOC3, being developed as a treatment for patients with mixed dyslipidemia, severe hypertriglyceridemia, and familial chylomicronemia syndrome. APOC3 is a key regulator of lipid and lipoprotein metabolism that inhibits lipoprotein lipase and mediates hepatic uptake of remnant particles in an LPL-independent pathway. In clinical studies, ARO-APOC3 improved multiple lipid parameters and may provide clinical benefit in a broad population with dyslipidemias. For ARO-APOC3 we have the following ongoing studies:

- The SHASTA-2 Phase 2 study in patients with severe hypertriglyceridemia
- The MUIR Phase 2 study in patients with mixed dyslipidemia
- And the PALISADE Phase 3 study in patients with familial chylomicronemia syndrome

SHASTA-2 and MUIR are on schedule for data readouts later this year. These studies will inform the development path, regulatory interactions, and Phase 3 study design. PALISADE continues to enroll patients efficiently and we believe we will achieve full enrollment in the second quarter of 2023. It is a year long study, so this would allow study completion in Q2 2024.

ARO-ANG3 is our investigational RNAi therapeutic designed to silence the hepatic expression of angiopoietin-like protein 3, or ANGPTL3, being developed as a treatment for homozygous familial hypercholesterolemia, or HoFH, and heterozygous familial hypercholesterolemia, or HeFH. ANGPTL3 is a key regulator of lipid and lipoprotein metabolism that inhibits Lipoprotein Lipase and Endothelial Lipase. ARO-ANG3 has a unique mechanism of action to address

hypercholesterolemia distinct from other LDL-C-lowering therapies. For ARO-ANG3 we have the following ongoing studies:

- The ARCHES-2 Phase 2 study in patients with mixed dyslipidemia
- And the GATEWAY Phase 2 study in patients with homozygous familial hypercholesterolemia

All patients in ARCHES-2 have completed treatment and we should have data processed and analyzed in the middle of the year. GATEWAY is fully enrolled and we should have initial data around the middle of the year as well. We intend to interact with regulators about our plans for Phase 3 studies this year.

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

James Hamilton

Thank you, Javier.

We announced last week the initiation of a Phase 1/2 study of ARO-MMP7, so I want to talk about that first.

ARO-MMP7 is designed to the reduce expression of matrix metalloproteinase 7, or MMP7, as a potential treatment for idiopathic pulmonary fibrosis, or IPF. MMP7 is thought to play multiple roles in IPF pathogenesis, including promoting inflammation and aberrant epithelial repair and fibrosis. Significant unmet medical need exists for patients with IPF, who experience progressive decline of lung function despite current therapies.

AROMMP7-1001 is a Phase 1/2a single ascending dose and multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ARO-MMP7 in up to 56 healthy volunteers and in up to 21 patients with IPF.

Now, moving on to our two other pulmonary programs, ARO-MUC5AC and ARO-RAGE, our investigational RNAi therapeutics designed to reduce production of mucin 5AC, or MUC5AC, and the receptor for advanced glycation end products, or RAGE, respectively, as potential treatments for various muco-obstructive and inflammatory pulmonary diseases.

As Chris mentioned, we are on schedule to have initial data from the healthy volunteer portion of the Phase 1/2 studies in the first half of this year. The healthy volunteer portion of these studies has two parts: a single ascending dose part and a multiple ascending dose part. The studies are designed to assess safety and tolerability, pharmacokinetics, and pharmacodynamics. We will be assessing pharmacodynamics by measuring available biomarkers in bronchoalveolar lavage fluid, induced sputum, and for RAGE we are also measuring serum sRAGE protein.

The second portion of the studies is in patients with moderate to severe asthma. We recently initiated enrollment in asthma patient cohorts in both the ARO-MUC5AC and ARO-RAGE studies. Initial data should be available around the end of the year.

Finally, moving on to ARO-C3, which is our investigational hepatocyte targeted RNAi therapeutic targeting hepatic C3 expression as a potential treatment for

complement mediated hematologic and renal diseases. We remain on track to report data from Part 1 of the study in healthy volunteers in the first half of this year. Based on an analysis of data from all healthy volunteer single and multiple escalation dose cohorts, we anticipate selecting doses for the Part 2, open label patient cohorts this month, and we are on track to open patient cohorts enrollment in the first half of this 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 quarter ended December 31, 2022 was $41.3 million or $0.39 per share based on 106.0 million fully-diluted weighted average shares outstanding. This compares with net loss of $62.9 million or $0.60 per share based on 104.5 million fully-diluted weighted average shares outstanding, for the quarter ended December 31, 2021.

Revenue for the quarter ended December 31, 2022 was $62.5 million, compared to $27.4 million for the quarter ended December 31, 2021. Revenue in the current period primarily relates to our collaboration agreements with Amgen, Horizon and Takeda.

Revenue is 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 $107 million of revenue to be

recognized associated with the Takeda collaboration which we anticipate will be recognized over the next one to two years. Additionally, Horizon enrolled the first subject in a Phase 1 trial of HZN-457, formerly known as ARO-XDH, which triggered a $15.0 million milestone payment to us, and Amgen enrolled the first subject in its Phase 3 registrational trial of Olpasiran, which triggered a $25.0 million milestone payment to us. Both milestone payments were received in the second quarter of fiscal 2023. Revenue in the prior period primarily related to the recognition of a portion of the payments received from our license and collaboration agreements with Takeda and Horizon.

Total operating expenses for the quarter ended December 31, 2022 were $104.7 million, compared to $90.8 million for the quarter ended December 31, 2021. The key driver of this change was increased candidate costs and salaries as the Company's pipeline of clinical candidates has both increased and advanced into later stages of development.

Net cash used by operating activities during the quarter ended December 31, 2022 was $75.5 million, compared with $61.3 million for the quarter ended December 31, 2022. The increase in cash used by operating activities is driven primarily by higher research and development expenses. We expect our operating cash burn to be $70 to $90 million per quarter in fiscal 2023 and capital expenditures up to $200 million as we approach completion on our footprint expansion projects, including GMP manufacturing.

Turning to our balance sheet, our cash and investments totaled $617.6 million at December 31, 2022, compared to $482.3 million at September 30, 2022. The increase in our cash and investments was primarily related to the $250.0 million

payment from Royalty Pharma, offset by our operating cash burn along with continuing capital projects.

Our common shares outstanding at December 31, 2022, were 106.1 million.

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

Chris Anzalone

Thanks Ken.

We are making good progress on our 20 in ’25 initiative where we expect to have 20 individual drug candidates in clinical trials or at market in the year 2025. We currently have 12 drug candidates in clinical studies, 6 of which are wholly-owned and 6 are partnered. I expect that 12 to become 15 or 16 by the end of this year. I mentioned ARO-DUX4 moving into the clinic next quarter and I expect 2 or 3 additional new candidates this year, and we have never talked about any of them publicly. Having such a large clinical pipeline provides us with a broad base from which to build value and spread risk, and it also gives us consistent opportunities to share data and progress.

In the near term, we think these opportunities will include the following:

- P1 NASH data from JnJ-0795 this quarter
- Fazirsiran SEQUOIA full 12-month biopsy data in the second quarter
- Initiation of ARO-HSD P2b in Q1 or Q2
- Early ARO-RAGE P1/2 data in the second quarter

- Early ARO-MUC5AC P1/2 data in the second quarter
- Early ARO-C3 P1/2 data in the second quarter
- Initiation of the ARO-DUX4 P1/2 study in the second quarter
- Disclosure of our next cell type and supporting data in the second quarter
- ARO-APOC3 data throughout the year
- ARO-ANG3 data throughout the year
- Initiation of 2-3 new P1 studies toward the end of the year
- Initiation of a JnJ-0795 P2 in Q3 or Q4
- Early ARO-MMP7 data in Q4
- Initiation of ARO-ANG3 P3 studies in Q4
- Initiation of additional ARO-APOC3 P3 studies in Q4

As you can see, we expect a busy 2023. Thank you for joining us today and I would now like to open the call to your questions. Operator?

Operator