**ARROWHEAD PHARMACEUTICALS**

**Fiscal 2024 Third Quarter Conference Call – Prepared Remarks**

**August 8, 2024**

**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 Vince 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 2024 third quarter ended June 30, 2024.

With us today from management are president and CEO Dr. Chris Anzalone, who will provide an overview of the quarter; Dr. Bruce Given, interim chief medical scientist, who will provide an update on our cardiometabolic pipeline; Andy Davis, Senior Vice President and Head of Global Cardiometabolic Franchise, who will provide an update on commercial activities, and Ken Myszkowski, chief financial officer, will give a review of the financials. Dr. James Hamilton, Chief of Discovery & Translational Medicine and Patrick O'Brien, COO and General Counsel, will also 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.

I'd now 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 has spent a substantial amount of time building a scalable platform on which a large number of diverse and innovative new medicines have been and will continue to be built. This is the basis of our "20 in '25" initiative, where we expect to grow our pipeline to at least 20 clinical-stage or marketed products by next year. Think about what that means for any company, much less one our size. This initiative represents our commitment to reduce the overall risk profile of the company while expanding our upside potential, and this is important for our long-term value creation. In the short-term, however, we need to balance our platform development work with intense focus on bringing our first wholly-owned drug candidate to market as quickly and efficiently as possible. We expect that

candidate will be plozasiran and we expect the initial launch to be next year, if approved for use in familial chylomicronemia syndrome, or FCS.

We're working hard to ensure that plozasiran moves rapidly through regulatory NDA and MA filing for FCS, while executing Phase 3 clinical studies for SHTG, the second potential indication, and a cardiovascular outcomes trial or CVOT study for mixed hyperlipidemia, the third potential indication. We believe that plozasiran represents a pipeline within a single drug, given the multiple patient populations we can address with it. Bruce will talk about the progress in this program in a moment.

We are currently building out our commercial infrastructure to enable an initial launch in 2025 and then scale to support progressively larger patient populations over the coming years. Andy will talk about where we are now with this process in a moment.

On September 1st, 1987, the first statin was approved by the FDA. This event changed the world because it ushered in an era during which physicians would appreciate the risks associated with high LDL-cholesterol and, importantly, would have the tools to lower it. It feels to us like we are at a similar point with triglycerides, with a few notable differences. First, we have the luxury of being able to grow our way into a large market: we expect to begin commercializing plozasiran in the small FCS market, then grow into the large SHTG market around 2027, and ultimately serve the very large mixed hyperlipidemia market after a CVOT is complete. Second, we feel like we are virtually alone in our ability to drastically lower triglycerides and, therefore, serve these markets appropriately. While there have been 8 FDA-approved statins to compete to lower LDL, our data suggest to us that there is simply no other near-term therapy that can match

plozasiran's activity. If triglycerides are bad actors, wouldn't patients and physicians want to lower them as much as possible? We believe they will. This is a big commercial opportunity and we believe Arrowhead has the most promising medicine that is poised to make a big impact over the coming years.

Before discussing other progress we've made recently, I want to talk about the announcement we made this afternoon. I think it's clear that we have dramatic upside opportunities in plozasiran in the near-term and in multiple other programs over the medium and long-term. What was less clear to investors, was how we would finance these development programs until we get to a point where commercial revenue becomes a significant source of capital and ultimately brings us to a cash flow positive position.

To that end, today we announced a transaction with Sixth Street that provides an immediate and meaningful strengthening of our balance sheet with long-term, low-cost, non-dilutive capital to fund innovation and growth opportunities across Arrowhead's pipeline. The $500 million senior secured credit facility includes $400 million funded at close with an additional $100 million available at Arrowhead's option, subject to mutual agreement between Sixth Street and Arrowhead, during the seven-year term of the agreement.

This is debt, but the risk-sharing structure is very attractive to us. There are no scheduled amortization payments during the term and no scheduled cash pay coupon interest payments. In addition, it has an attractive 7-year term during which we hope to be building our commercial revenue substantially. It has other risk-sharing characteristics, where payments are to be made to partially repay loans under the credit facility with a portion of the proceeds from certain transactions, such as future inflows from partnerships and collaborations, and commercial

revenue. So, we don't really have cash outflow obligations unless we have cash inflows from other sources. This deal makes a lot of sense for us and the great team at Sixth Street has been creative in building a custom structured product that is appropriate for Arrowhead. This growth capital comes at a perfect time.

During the quarter we also announced a $50 million milestone payment that we received from Royalty Pharma following the completion of enrollment of the Phase 3 OCEAN(a) - Outcomes Trial of olpasiran, being conducted by Amgen.

These are important steps to build our balance sheet, but not the last. We view our capital needs through the lens of plozasiran development and see the potential for significant revenues coming out of the SHTG market. As such, we want to ensure that we have a financial bridge to that market, which we believe we could launch into in 2027. We have many tools to fund operations over those 3 years, including: potential milestone payments from our existing 4 partnerships; new partnerships and license agreements; possible financing in return for capped royalties on plozasiran sales; and revenue from commercializing into the FCS market, which we expect to begin next year.

Before turning the call to Bruce to discuss the plozasiran clinical programs and data, I want to review a few other key accomplishments from the recent period.

First, we announced topline results from the pivotal Phase 3 PALISADE study of plozasiran in patients with FCS. The study met its primary endpoint and all key secondary endpoints.

We see these data as best in class. This is Arrowhead's first therapy to show clinical efficacy in a Phase 3 study, which represents validation of all the hard

work from so many talented Arrowhead employees, our collaborators, and the FCS community over the years.

Also during the quarter we presented new interim clinical data on ARO-RAGE, our investigational RNAi-based medicine for the treatment of inflammatory lung diseases, such as asthma, at the American Thoracic Society 2024 International Conference.

These were important data as they represent not only translation of preclinical data to clinical data in normal healthy volunteers, but also to an asthma patient population. We are currently working on the design of a Phase 2 study of ARO-RAGE.

Turning to the earlier side of our pipeline, we presented preclinical data on ARO-INHBE at the American Diabetes Association, or ADA, 84th Scientific Sessions. INHBE is an investigational RNAi-based medicine that we are studying for the treatment of obesity and metabolic diseases. In pharmacological studies in obese and diabetic mouse models, INHBE siRNA administration resulted in multiple promising findings, including the following:

- 95% reduction in INHBE mRNA expression
- 19% suppression of body weight compared to saline controls
- 26% loss of fat mass;
- And, importantly, preservation of lean mass

Our preclinical data presented at ADA suggest that INHBE reduction with siRNA is a promising new approach to address obesity and metabolic diseases and we think support advancing ARO-INHBE into clinical trials. We will be discussing

these data and also announcing a new program that directly targets adipose tissue next week at our R&D webinar on obesity and metabolic diseases. These are exciting additions to our cardiometabolic franchise.

Please note the new date of this event is August 14. It was originally planned for August 15, but the date was changed to accommodate the schedule of an external speaker who will be joining us. Be sure to listen in as these early-stage programs in our cardiometabolic pipeline are particularly interesting and fit well with our growing development and commercial presence in the space.

Lastly, since we have so much going on in our broad pipeline, during the quarter we launched the 2024 Summer Series of R&D webinars to highlight some of our work. Each month, starting in May and ending in September, we highlight different therapeutic areas and programs in our pipeline.

We have now completed webinars on our muscle programs, our late-stage cardiometabolic programs, and our pulmonary programs. As I mentioned, next week on August 14 we will cover our obesity and metabolic programs and in September we will cover our CNS programs, including updates on the delivery platforms and on undisclosed candidates planned to enter clinical development this year.

Clearly, there is a lot going on and a lot to be excited about at Arrowhead.

With that overview, I'd now like to turn the call over to Bruce.

**Bruce Given**

Thank you, Chris, and Good Afternoon everyone.

We have been very impressed with the clinical data generated with plozasiran in each patient population we've studied, and we believe it to be best-in-class across the board. Starting in healthy volunteers, and moving to patients with mixed hyperlipidemia, severe hypertriglyceridemia, or SHTG, and on to patients with genetic or clinically-diagnosed FCS, we have seen very consistent and high levels of target engagement and downstream changes to lipids and lipoproteins.

This makes sense and was our expectation, but it is still gratifying to see data meet or exceed expectations. To review apolipoprotein C-III, or APOC3, is the gene target for plozasiran. It is a component of triglyceride rich lipoproteins, or TRLs, and a known regulator of triglyceride metabolism. APOC3 inhibits the breakdown of TRLs by lipoprotein lipase and inhibits uptake of remnant cholesterols in the liver. The goal of treatment with plozasiran is to reduce the level of APOC3, thereby reducing triglycerides and restoring lipids to more normal levels.

Over the last few months, we have presented and published Phase 2 data on plozasiran in patients with mixed hyperlipidemia in the MUIR study and in patients with SHTG in the SHASTA-2 study. We have also reported topline results from the PALISADE Phase 3 study in patients with FCS.

I want to spend a moment going over some highlights from those studies.

Starting with mixed hyperlipidemia in the MUIR study. Treatment with plozasiran in the MUIR study achieved reductions in triglyceride rich lipoproteins, a genetically validated target associated with increased risk of atherosclerotic cardiovascular disease. These data were presented in an oral presentation at the

European Atherosclerosis Society, or EAS, 92nd Congress and simultaneously published in the New England Journal of Medicine.

At week 24, representing trough effect after 2 quarterly doses, plozasiran treatment was associated with placebo adjusted reductions in triglycerides of up to -62%. Fasting triglyceride levels were normalized, which means patients achieved levels below 150 mg/dL, in 79-92% of patients randomized to a treatment arm. Commensurate reductions in APOC3 of up to 79%, with strong positive correlations with changes in triglyceride levels were observed.

There were other important changes in other atherogenic lipoprotein parameters including non-HDL-C, apolipoprotein B and remnant cholesterol with strong correlations with the reductions in triglyceride levels.

Plozasiran demonstrated a favorable safety profile in the MUIR study. The overall rates of occurrence of treatment-emergent adverse events and discontinuations were similar for plozasiran and placebo throughout the 48 weeks of observation.

Mixed hyperlipidemia, also called mixed dyslipidemia, is a highly prevalent disorder characterized by elevated LDL-Cholesterol and triglyceride levels. Despite the efficacy of LDL lowering therapies in reducing atherosclerotic cardiovascular disease in mixed hyperlipidemia, there remains substantial residual risk attributed to elevated non-HDL cholesterol driven by remnant cholesterol in triglyceride-rich lipoproteins. Genome-wide association and Mendelian randomization studies also support a causal role for triglyceride rich lipoproteins in ASCVD.

Based on the promising results from the MUIR study, we are now gearing up to initiate the Phase 3 CAPITAN cardiovascular outcomes trial, designed to enroll patients with mixed hyperlipidemia, who have had or are at high risk for, a cardiovascular event.

Moving on to the SHTG population, these are patients with much higher triglyceride levels than generally seen in the mixed hyperlipidemia population. For SHTG we presented data from the SHASTA-2 study at ACC and simultaneously published the results in the journal JAMA Cardiology. In SHASTA-2, treatment with plozasiran led to dose-dependent placebo-adjusted reductions at week 24 in triglycerides of up to -57% driven by reductions in APOC3 of up -77%. Mean maximum, non-placebo adjusted reductions from baseline in triglycerides and APOC3 were up to 86% and 90%, respectively, and typically occurred around week 16 or week 20.

Among subjects treated with plozasiran, at the week 24 trough timepoint, greater than 90% receiving the 25 or 50 mg doses achieved triglycerides less than 500 mg/dL, a threshold level associated with increased risk of acute pancreatitis. In addition, around half of the subjects at these doses achieved normal triglyceride levels of less than 150 mg/dL at week 24, which is surprising given the high mean starting levels of almost 900 mg/dL.

In addition to reductions in triglycerides, subjects treated with plozasiran also showed improvements in multiple atherogenic lipid and lipoprotein levels, including remnant cholesterol, HDL-cholesterol, and non-HDL cholesterol.

Plozasiran demonstrated a favorable safety profile in SHASTA-2. Observed adverse events generally reflected the comorbidities and underlying conditions of the study population.

SHTG is characterized by triglyceride levels greater than 500 mg/dL and is known to significantly increase the risk of ASCVD and acute pancreatitis, which can occur with recurrent attacks requiring repeat hospital admissions and worsening outcomes. Pancreatitis risk increases as triglycerides levels increase. Currently available drug therapies generally don't sustainably reduce TGs below the pancreatitis risk threshold in this patient population.

Based on the promising SHASTA-2 data, we have initiated and started dosing in both the SHASTA-3 and SHASTA-4 Phase 3 studies in patients with SHTG. We are also working towards initiating SHASTA-5, a Phase 3 study in patients with SHTG that are at high risk of acute pancreatitis. SHASTA-5 will have a primary endpoint of incidence of new episodes of pancreatitis compared with placebo. We do not see this study as necessary for regulatory approval in SHTG, but we do see it as an important study to potentially show the value of treatment with plozasiran in reducing the risk of acute pancreatitis. If positive, these results should be helpful for all stakeholders, including patients, health care providers, and payors.

Lastly, during the quarter we gave a topline report on the Phase 3 PALISADE study in patients with genetically confirmed or clinically diagnosed FCS. The strong results from PALISADE, significantly build upon the promising results from the Phase 2 SHASTA-2 and MUIR studies.

The primary endpoint for the PALISADE study was placebo adjusted median change in triglycerides at Month 10. At that timepoint, patients treated with

quarterly doses of 25 and 50 mg plozasiran achieved median triglyceride reductions of -80% and -78%, respectively. At month 12, patients treated with 25 and 50 mg plozasiran achieved median triglyceride reductions of -78% and -73%, respectively. These compared with the median triglyceride reductions in placebo-treated patients of -17% at month 10, with a p value of less than 0.001, and -7% at month 12. Mean reductions in APOC3 at month 10 were -88% and -94% at 25 and 50 mg plozasiran, respectively.

PALISADE successfully met the primary endpoint and all key secondary endpoints, including reducing the incidence of acute pancreatitis compared to placebo.

There were 4 multiplicity-controlled key secondary endpoints:

1) Percent change from baseline at Months 10 and 12 averaged in fasting triglycerides.
2) Percent change from baseline at Month 10 in fasting APOC3.
3) Percent change from baseline at Month 12 in fasting APOC3; and,
4) Incidence of positively adjudicated events of acute pancreatitis during the randomized period.

Plozasiran demonstrated a favorable safety profile in the PALISADE study. The number of subjects reporting treatment emergent adverse event were similar in plozasiran and placebo groups. Severe and serious AEs were less common with plozasiran than with placebo. The most common AEs reported were abdominal pain, COVID-19, nasopharyngitis, headache and nausea.

This study was accepted as a Late-breaker oral presentation at the European Society of Cardiology Congress 2024 on September 2, 2024, in London. Since that is Labor Day in the US, we also plan to have an investor call the following day on

September 3, 2024. Dr. Gerald Watts, a principal investigator for PALISADE and presenter of the data at ESC, will join the investor call to present the data and discuss the exciting results.

I will now turn the call over to Andy to give a few remarks on where we are with commercial planning and readiness.

**Andy Davis**

Thank you, Bruce.

We are on track with our launch preparations for plozasiran in familial chylomicronemia syndrome, or FCS.

Let me begin by talking a little bit about our Expanded Access Program, or EAP. We initiated the EAP to ensure patients who roll off our PALISADE trial maintain access to plozasiran and to make investigational plozasiran available outside of a clinical trial for other patients with FCS who meet certain program eligibility criteria if requested by their treating physician.

We've fielded requests for additional information about the EAP from physician societies and treating physician who may have appropriate FCS patients, and our Medical Affairs Team is already out in the field engaging with these folks to help them understand the program.

As you know, this is Arrowhead's first commercial product, so we are building a best-in-class organization that will support the patients who we hope will benefit from plozasiran. This is obviously a big task, but we are up for the challenge. The

build-out of our medical affairs and commercial infrastructure is right where it needs to be at this time in commercialization. Our entire Medical Affairs and Commercial Leadership team is solidly in place and the team we've assembled has deep experience in the cardiometabolic and lipid therapeutic areas.

We have already done extensive mapping of the health care professionals, or HCPs, most likely to treat FCS patients and prescribe plozasiran, if approved. Our market research leads us to believe these HCPs have been impressed with the top-line results from our PALISADE trial, with particular note of the (1) unprecedented triglyceride lowering and (2) statistically significant reduction of acute pancreatitis risk. As Bruce mentioned, plozasiran achieved deep and durable reductions in triglycerides of approximately -80% from baseline, demonstrating for the first time the real possibility for FCS patients to lower their triglycerides below important guideline-directed thresholds of acute pancreatitis risk.

Finally, our best-in-class patient and caregiver support program is taking shape. We have selected an exclusive specialty pharmacy and patient hub with expert support for patients with rare conditions and we are presently crafting the finer details of our patient and caregiver support ecosystem to ensure patients can easily start and stay on therapy.

I look forward to talking more with you in the future about how we see the commercial market opportunity and how we intend to bring plozasiran to the many patients who may benefit from this new therapy.

I will now turn the call over to Ken.

**Ken Myszkowski**

Thank you, Andy, and good afternoon everyone.

As we reported today, our net loss for the quarter ended June 30, 2024 was $170.8 million or $1.38 per share based on 124.2 million fully-diluted weighted average shares outstanding. This compares with net loss of $102.9 million or $0.96 per share based on 107.0 million fully-diluted weighted average shares outstanding for the quarter ended June 30, 2023.

No revenue was recorded in the quarter ended June 30, 2024. Revenue of $15.8 million was recorded in the quarter ended June 30, 2023.

Revenue is recognized as we complete our performance obligations or key developmental milestones are reached. Revenue in the prior period primarily related to the recognition of payments received from our license and collaboration agreement with Takeda.

Total operating expenses for the quarter ended June 30, 2024 were $176.1 million, compared to $118.5 million for the quarter ended June 30, 2023. The key drivers of this change were increased research and development costs, primarily discovery and candidate costs as the Company's pipeline of discovery candidates has advanced into novel therapeutic areas and tissue types and clinical candidates has increased and progressed into later stages of development.

Net cash used in operating activities during the quarter ending June 30, 2024 was $115.4 million, compared with $21.4 million during the quarter ending June 30, 2023. The increase in cash used in operating activities is driven primarily by higher

research and development expenses, as well as lower cash revenue versus the prior year.

Our footprint expansion is mostly complete with final payments to be made over the next several months totaling about $30 million, after which we expect capital expenditures to be nominal.

Turning to our balance sheet, our cash and investments totaled $436.7 million at June 30, 2024, compared to $403.6 million at September 30, 2023. The increase in our cash and investments was primarily related to the $450 million equity issuance, partially offset by our ongoing cash burn.

Today we announced a financing agreement with Sixth Street for significant, long-term, non-dilutive capital. The $500 million senior secured credit facility includes $400 million funded at close and an additional $100 million available at Arrowhead's option, subject to mutual agreement between Sixth Street and Arrowhead.

Inclusive of the upfront cash from Sixth Street, before deducting fees, our proforma cash balance is approximately $840 million and significantly enhances our liquidity towards our global commercial launch of plozasiran while also supporting advancement of our late stage clinical trials, and other discovery efforts.

Our common shares outstanding at June 30, 2024, were 124.2 million.

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

**Chris Anzalone**

Thanks Ken.

We had a highly productive quarter and feel all the pieces are now in place to begin the transition into a commercial stage company.

We have a completed Phase 3 study in PALISADE that we intend to use to file for regulatory approval to launch plozasiran in patients with FCS.

The SUMMIT suite of clinical studies, including PALISADE and the SHASTA, MUIR, and CAPITAN studies are all underway or at advanced stages and are designed to show the value of plozasiran in multiple patient populations. As I mentioned, we view plozasiran as a pipeline within a single drug, and these studies have the potential of enabling that.

Our commercial organization is taking shape, and we have a thoughtful strategy to grow in support of plozasiran as the clinical studies and ultimately the product label grows into progressively larger patient populations.

And lastly, we have taken the next steps to execute on our long-term financing strategy and now have a stronger balance sheet enabling us to better fund innovation and growth opportunities across Arrowhead's robust and diverse pipeline of RNAi therapeutics.

We have focused most of this call on plozasiran, but of course we have a large stable of value drivers under it that continue to move forward. Our pulmonary franchise, with 3 current clinical candidates, our muscle franchise with 2 current clinical candidates, and our complement franchise with 2 current clinical

candidates all continued to progress over the quarter. By the end of the year, we expect to file CTAs in support of 2 obesity candidates and 2 CNS candidates, and you will hear more about those programs at our webinars on August 14 and September 25th, respectively.

Our partnered programs also made progress, as the olpasiran P3 against LP(a) is fully enrolled and the fazirsiran P3 against AAT continues to enroll patients. Our HBV and HSD programs with GSK are both in P2 studies, and we continue to weigh our options with the PNPLA3 program that we started with JnJ and we now wholly own.

We think these potential value drivers will play an important role in the future of Arrowhead, either as marketed products themselves our part of the steps that we use to bridge plozasiran to commercialization.

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

**Operator**