ARROWHEAD PHARMACEUTICALS

Fiscal 2025 Third Quarter Conference Call – Prepared Remarks

August 7, 2025

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 2025 third quarter ended June 30, 2025.

With us today from management are president and CEO Dr. Chris Anzalone, who will provide an overview; Dr. Bruce Given, interim chief medical scientist, who will provide an update on late-clinical and regulatory; Andy Davis, senior vice president and head of the global cardiometabolic franchise, who will provide an update on commercialization activities; Dr. James Hamilton, chief medical officer and head of R&D, who will discuss our earlier stage development programs; and Dan Apel, chief financial officer, who will give a review of the financials.

Following management’s prepared remarks, we will open the call to questions.

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.

Before discussing the progress we've made over the past quarter, I'd like to address questions surrounding our partnership with Sarepta Therapeutics. Sarepta has recently experienced high-profile setbacks in products and programs that are unrelated to those licensed from Arrowhead. Nevertheless, this situation has negatively affected our stock price, so I'd like to talk about what we think is important from an Arrowhead shareholder perspective.

Sarepta recently announced a strategic restructuring plan that includes cost cutting measures and a pipeline review that prioritizes funding, development, and

commercialization of the programs the company in-licensed from Arrowhead. Sarepta management has clearly stated that it believes this represents the future of the company, and this gives us confidence that Sarepta will continue to meet its financial, development, and commercial obligations under the agreement.

The collaboration is continuing to operate as expected which is, of course, a good thing for Arrowhead. It represents a source of capital to fund internal programs, platforms, and commercial build-out while ensuring that assets licensed to Sarepta are developed and commercialized. Should Sarepta fail to meet its obligations, the agreement has clear termination provisions that in our view would cause potentially valuable assets and associated intellectual property to be returned to Arrowhead without Arrowhead having to repay any of the capital we have received from Sarepta. That would also be an acceptable outcome.

Let's now move on to our progress in the recent period. The biotech market has been challenging over the past several years, but we have no control over the broader sentiments. What we can control is our drive to serve patients and create shareholder value. We view these broadly as 3 interrelated mandates:

- Create novel medicines capable of real impacts on human health;
- Generate the capital to fund development of them; and
- Build an engine to drive the growth of both.

We made important progress in all these areas during the recent period. Let's begin with development. This is clearly led by Plozasiran. We continued to have productive interactions with regulators in the US and Europe about our market authorization applications for the treatment of FCS and we look forward to our November 18 U.S. PDUFA date. We are also on track with commercial buildout

and our complete team is nearly assembled to support an FCS launch. Further, we achieved full enrollment in SHASTA-3, SHASTA-4, and MUIR-3, Arrowhead's Phase 3 studies designed to support regulatory submissions for plozasiran in the treatment of severe hypertriglyceridemia, or sHTG. These studies enrolled approximately 2200 patients in 24 countries in a very short period of time. The primary endpoint is focused on triglyceride reduction at 12 months, so with full enrollment reached in June 2025, we are on track for study completion by mid-2026.

Zodasiran, Arrowhead's candidate designed to reduce expression of ANGPTL3, is being developed as a potential treatment for homozygous familial hypercholesterolemia, or HoFH, a rare genetic condition that leads to severely elevated LDL-cholesterol and early onset cardiovascular disease. We initiated the YOSEMITE Phase 3 study and enrolled the first patient in July. Approximately 60 subjects over the age of 12 will be randomized to receive 4 quarterly doses of 200 mg zodasiran or placebo. The primary endpoint of YOSEMITE is the percent change in fasting LDL-cholesterol from baseline to month 12. We think that given our P2 data, this feels like a relatively low risk P3, potentially enabling a commercial opportunity that overlays well with the team we are building for plozasiran. Therefore, with a relatively small investment in a 1 year 60-subject Phase 3 study, we see an opportunity to extract more value from the commercial infrastructure we are already building.

Beyond plozasiran and zodasiran, there are 2 additional investigational RNAi-based candidates developed by Arrowhead that are currently in late-stage pivotal studies. Fazirsiran, being developed for alpha-1 antitrypsin liver disease, is partnered with Takeda. Arrowhead retains 50-50 profit share in the U.S., 20-25% royalties outside the U.S., and up to $527.5 of remaining regulatory and

commercial milestones. Takeda has guided that it's Phase 3 study could be fully enrolled this year, and the study has a primary endpoint at 2 years. Olpasiran, being developed for ASCVD, is licensed to Amgen, which announced that its Phase 3 cardiovascular outcomes trial was fully enrolled in the first half of 2024. We are eligible for up to $485 million of remaining milestones related to this program.

I highlight these 4 late-stage drug candidates because we expect them to be substantial value drivers in the near- to mid-term. They also set up the possibility of multiple launches between November 2025 and the end of 2028.

As we've discussed in the past, plozasiran and our other late-stage drug candidates together form the basis of our near-term value proposition. But these are enhanced by several programs underneath them, all of which made good progress in the recent period.

Broadening out the cardiometabolic franchise are our first 2 obesity candidates: ARO-INHBE and ARO-ALK7. ARO-INHBE began a P1/2 study early in the year, and we recently announced that we dosed the first subjects in a Phase 1/2 clinical trial of ARO-ALK7, which we believe is the first investigational RNAi therapeutic to enter clinical studies targeting adipose tissue. We expect to have initial, early datasets for both candidates at the end of the year.

Expanding the cardiometabolic franchise, we expect to reach the clinic this year for what we believe will be the first RNAi dimer in clinical studies. It is designed to reduce expression of both PCSK9 and APOC3, and could be a powerful agent in the treatment of ASCVD in patients with mixed hyperlipidemia. There is substantial unmet medical need in this large patient population and we should have

a good idea how well this drug candidate lowers LDL-c and triglycerides in 2026. We continue to make good progress in manufacturing, toxicology studies, and clinical trial planning, and we are on track to file a CTA in the coming months.

Our burgeoning, systemically-delivered, CNS franchise is also a potential near- to mid-term value driver. Should this platform translate from primates to humans, we think it would represent a transformational leap forward in CNS therapies. Importantly, later this year we expect to file a CTA for ARO-MAPT, our wholly-owned candidate against Alzheimer's disease and various Tauopathies. We are hopeful that we can achieve initial proof of concept with this platform and candidate as early as late 2026.

Beyond these, we have a wealth of other clinical-stage programs to drive longer-term value and serve as sources of capital through business development. In fact, we are on track to meet our 20 in '25 initiative whereby we would have 20 individual drug candidates in clinical studies or at market by the end of 2025. Nine of these are partnered. The 11 wholly-owned clinical candidates serve as potential partnering targets and provide value redundancy for our other programs, and we expect several data readouts through the end of the year. Together, these give us a tremendous amount of ammunition to create value.

This brings us to the second important component of building durable value: an adequate source of financing independent on the capital markets. We currently have a strong balance sheet relative to our needs over the next few years. In addition, we have made important progress sourcing new capital in the recent period.

We announced that our Visirna Therapeutics majority-owned subsidiary signed an asset purchase agreement whereby Sanofi will acquire rights to develop and commercialize plozasiran as a potential treatment for FCS and sHTG in Greater China.

Visirna will receive an upfront payment of $130 million and be eligible to receive milestone payments of up to $265 million upon approval of plozasiran in FCS and SHTG in mainland China. Arrowhead is further eligible to receive royalties on net commercial product sales in Greater China as part of the Arrowhead-Visirna license which was assigned in part to Sanofi.

When we co-founded Visirna in 2022, we saw greater China as an important, but undervalued, potential future market for multiple programs in Arrowhead's pipeline. We licensed Chinese rights for plozasiran, zodasiran, and ARO-HSD to Visirna, which received outside funding to support development. Sanofi has a strong presence in China and is well positioned to assume commercialization of plozasiran, should it be approved by Chinese regulatory authorities.

We did not use any Arrowhead funds to advance China specific development or regulatory activities, and upon closing we will own approximately 56% of Visirna. There are tax considerations and other costs, but we ultimately expect to realize a sizable amount from this deal. We hope that over time we may monetize Chinese rights to zodasiran and ARO-HSD in a similar fashion.

The next key capital-building event I want to mention is reaching the first of two prespecified enrollment targets in a Phase 1/2 clinical study of ARO-DM1 for the treatment of type 1 myotonic dystrophy, which is partnered with Sarepta. Reaching this milestone triggered a $100 million payment, which is due from Sarepta within

60 days of when it was earned. We believe we are on track to meet the second enrollment target at the end of the year, which would trigger an additional $200m payment.

Our large pipeline and expectation that we have cash into fiscal 2028 suggest that we have the first 2 categories of value creation under control. This leads us to the third priority: creating an engine to drive the growth of both. I think it is rather clear that we have built this as well. We are now able to address gene targets in 5 different areas: hepatocytes, pulmonary, adipose, skeletal muscle, and CNS. We also believe we are capable of silencing 2 genes with a single molecular entity using our dimer technology. This gives us broad reach to go where disease is, and, coupled with our expectation of introducing 3-4 new drug candidates into clinical studies *every* year, we expect to continue to grow our ability to impact human health very rapidly. This also reads on our ability to continue to access significant capital through business development before and after achieving substantial product revenue.

Ultimately, we are doing all of this to bring important medicines to the patients who need them, and this does not happen without careful preparation. We are building a right-sized commercial organization staffed with what we think are the top people in the field with extensive experience in cardiometabolic and rare disease. We've made strong progress in market access, analytics, operations, marketing, and building a commercial sales team. U.S. launch preparations are now if full swing for plozasiran in FCS and we intend to be launch ready even before our PDUFA date on November 18th.

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

Bruce Given

Thanks Chris and Good Afternoon everyone.

Since we last spoke, we've continued the forward momentum in our development of plozasiran to treat FCS and severe hypertriglyceridemia. Our US NDA to support FCS treatment was submitted last year and our PDUFA date is November 18, 2025. Filings in Europe, Australia, and Canada are all progressing, as well. We are reassured that the cadence of our interactions with US and global regulators has not changed, nor have our expectations of adhering to established timelines.

Two months ago, we completed enrollment in our SHASTA severe hypertriglyceridemia development program well ahead of expectations. The SHASTA program is comprised of SHASTA-3 and SHASTA-4, two adequate and well-controlled trials designed to meet the statutory requirement of substantial evidence requirement for effectiveness, along with the supportive MUIR-3 trial in mixed hyperlipidemia, which provides additional safety data in a relevant patient population to satisfy regulatory requirements for a complete file.

The sizing of the Phase 3 SHASTA-3 and 4 studies was informed by the needs of regulatory authorities to demonstrate safety, while confirming the efficacy suggested by the Phase 2 SHASTA-2 trial where the primary endpoint of difference in triglycerides at week 24 compared to baseline at the 25 mg dose was -53 % with a p value of <0.0001 which was accompanied by a numerical decrease in adjudicated events of acute pancreatitis. The 2 SHASTA phase 3 trials are similarly designed, totaling around 700 patients, and are very highly powered to demonstrate statistically significant improvement in triglycerides with 25 mg plozasiran compared with placebo over 12 months of treatment. After accounting

for randomization allocation in the SHASTA studies, the placebo controlled double blind MUIR-3 study was designed to demonstrate statistically significant improvement in triglycerides with 25 mg plozasiran compared with placebo over 12 months of treatment and is also expected to achieve a high level of significance while primarily serving to enhance the safety database for the sHTG filing. Assuming positive data, these three separate Phase 3 studies should support our planned sNDA filing for sHTG in the fourth quarter of 2026. Although SHASTA-3 and 4 were not prospectively designed to be outcomes studies, given the sizing of the combined studies and observed event rates in the SHASTA-2 study, we hope to observe at least a favorable trend in plozasiran's impact on documented acute pancreatitis within the studies.

However, the SHTG program also features a unique outcomes study named SHASTA-5 designed to directly assess the ability of plozasiran to reduce the time to first event of positively adjudicated acute pancreatitis in high risk SHTG patients. While it is possible that this trial will be submitted to regulatory agencies for possible inclusion in labeling, the primary audience and impetus for this study is actually national health technology assessment organizations. On the basis of observational data demonstrating the causal link between elevated triglycerides and risk of pancreatitis and observed effects of plozasiran in sHTG patients, it is expected that less than 150 patients will be recruited to accrue sufficient events in this outcomes study. We look forward to presenting more details on design and rationale of this study at an upcoming major medical meeting.

The broader cross-functional cardiometabolic clinical team has been present at key medical congresses this past quarter, including ENDO, National Lipid Association (NLA) and the American Society of Preventive Cardiology (ASPC). We continue

to share new data to demonstrate the value of plozasiran and the reception from the scientific and clinical communities has been engaged and enthusiastic.

Turning our attention to Zodasiran, another genetically validated RNAi drug candidate designed to reduce expression of Angiopoietin protein like 3 or AngPTL3 is now in development for the treatment of homozygous familial hypercholesterolemia (HoFH), a rare genetic disorder characterized by exceptionally high LDL cholesterol levels due to very low or absent LDL receptor function. The results of GATEWAY, our open-label phase 2 study in this population, were presented this year at European Atherosclerosis Society, and showed robust and durable reductions in LDL-C and other atherogenic lipoproteins. The efficacy results were similar to those of evinacumab, a monoclonal antibody against ANGPTL3 requiring monthly infusions, but with convenient quarterly, subcutaneous dosing. We are pleased to report that YOSEMITE, the Phase 3 study of zodasiran in HoFH, began earlier this year and the first patient was randomized last month. Assuming successful demonstration of safety and efficacy, data from YOSEMITE could support regulatory filings for zodasiran as early as 2028 or 2029.

I will now turn the call over to Andy Davis.

Andy Davis

Thank you, Bruce.

The FDA PDUFA date for Plozasiran, set for November 18, is now less than four months away, and I'm pleased to report that our commercialization preparations are fully on track.

When I last updated you in May, we were in the midst of building out our commercial sales organization. I'm proud to share that as of this month, our National Sales Leader, full team of Regional Sales Leaders, and fit-for-purpose field force of Rare Disease Specialists are now onboard and undergoing training. By the end of this month, this team will begin engaging with key healthcare professionals, advancing FCS disease education in preparation for launch.

Our Market Access team continues to execute exceptionally well against our Pre-Approval Information Exchange strategy. To date, we've connected with payers representing over 85% of U.S. covered lives, delivering compelling data on the clinical value and anticipated profile of Plozasiran. We remain highly encouraged by payer interest, particularly in Plozasiran's potential to:

- Deeply lower triglycerides,
- Support achievement of guideline-directed goals, and
- Significantly reduce the risk of acute pancreatitis.

We're also seeing positive developments in the FCS landscape, which reinforce our confidence heading into launch. The significant unmet need in the FCS community is clear and acknowledged by both payers and providers.

On the payer front, dynamics appear to be favorable, with access being granted to both genetically confirmed patients and those patients satisfying the diagnostic scoring tools designed to discriminate patients with SHTG from those whose signs, symptoms, and medical history mimic genetic FCS. This is especially motivating given that Plozasiran is currently the only APOC3 inhibitor to demonstrate clinical results in both genetic and clinical FCS in a Phase 3 registrational study.

From a provider perspective, the specialty mix we're observing — preventative cardiologists, endocrinologists, and lipidologists — is exactly what we anticipated and aligns well with our launch targeting strategy.

In summary, we remain on schedule and energized by the opportunity to bring investigational Plozasiran to individuals living with FCS and their families. We are excited for what Plozasiran, a potential first-in-class siRNA therapy, could mean to those suffering from this difficult disease.

I will now turn the call over to James Hamilton.

James Hamilton

Thank you, Andy.

I'd like to provide an overview and updates on several of our earlier stage clinical and translational development programs. In obesity, our ARO-INHBE and ARO-ALK7 programs, both targeting the Activin pathway are currently being investigated as treatments for obesity in Phase 1 studies. The INHBE study is currently enrolling multi-dose cohorts using ARO-INHBE in combination with tirzepatide. The ARO-ALK7 study is in the single dose escalation phase, with multi-dose and combination cohorts opening soon. We anticipate sharing data from both the ALK7 and INHBE studies at the end of the year.

Regarding our muscle clinical programs partnered with Sarepta, the ARO-DM1 Phase 1/2a study has completed the single dose cohorts and is now enrolling multi-dose cohorts of patients with myotonic dystrophy. Similarly, the ARO-DUX4

Phase 1/2a study has nearly completed enrollment of single dose cohorts and the first year long multi-dose cohort is open for enrollment. Consistent with previous guidance, we are on track for data availability by year end. However, final timing on data release is determined by Sarepta.

Our wholly owned ARO-MAPT program is on track for submission of a CTA by year end. As a reminder, ARO-MAPT uses subcutaneous administration of a novel siRNA delivery platform designed to deliver a siRNA targeting CNS Tau protein expression across the blood brain barrier. Tau aggregated into neurofibrillary tangles is believed to be one of the causative factors of Alzheimer's disease and is also causative of various other Tauopathies. Non-clinical evaluations in monkeys with subcutaneous administration of ARO-MAPT using clinically translatable doses have shown better than 75% knockdown of tissue level MAPT mRNA in the CNS. Importantly, monkey tissue level knockdown has translated into CSF tau protein reductions of better than 75%, with duration of effect supportive of either monthly or potentially quarterly subcutaneous dose regimens. The monkey CSF Tau protein knockdown data is an important translational step as we move this program towards the clinic. Full pre-clinical data will be presented at an upcoming scientific conference.

I will now turn the call over to Dan Apel.

Dan Apel

Thank you, James, and good afternoon everyone.

As we reported today, our net loss for the quarter ended June 30, 2025 was 175.2 million dollars, or 1.26 dollars per share, based on 139 million fully diluted weighted

average shares outstanding. This compares with a net loss of $170.8 million or $1.38 per share for the quarter ended June 30, 2024 based on 124.2 million fully-diluted weighted average shares outstanding in that prior year quarter.

Revenue for the quarter ended June 30, 2025 was $27.8 million driven almost entirely by the recognition of revenue related to our license and collaboration agreement with Sarepta. Of the 27.8 million, roughly 20 million related to the on-going recognition of initial Sarepta consideration… and seven million related to reimbursement of collaboration related costs.

After the end of our third fiscal quarter, we announced two important events… each of which will have a positive impact on our financial position.

Firstly, there is the 100 million dollar DM1 milestone payment from Sarepta which Chris mentioned earlier on the call. As this event occurred after June 30th, revenue associated with this milestone will be recognized in our fiscal fourth quarter financial results. We anticipate achieving the second DM1 development milestone—valued at $200 million—by the end of the calendar year.

Secondly, on August 1st, we announced that Sanofi signed an agreement to acquire exclusive rights to develop and commercialize investigational plozasiran in Greater China from Visirna Therapeutics, Arrowhead's majority-owned subsidiary. Visirna will receive 130 million dollars upfront upon closing. Additionally, Visirna will receive up to 265 million dollars in potential future regulatory milestone payments, and potential royalties associated with sales of Plozasiran in greater China. We expect to record revenue of 130 million dollars in the fourth quarter associated with the upfront payment only.

Turning to expenses, total operating expenses for the quarter ended June 30, 2025 were $193.3 million, compared to $176.1 million in the prior year quarter, an increase of $17.2 million. The year-over-year increase was driven by, amongst other things, roughly 10 million of higher R&D costs primarily as a result of our phase 3 registrational trials for Plozasiran in sHTG, as well as higher costs related to active candidates in the preclinical stage. It's worth bearing in mind that, year to date, approximately 70% of our clinical trial spend can be attributed to the phase 3 registrational trials for Plozasiran in sHTG. As Bruce mentioned, these studies are now fully enrolled and we expect data to read out next year.

Additionally, as planned, our SG&A costs have increased by $7 million year-over-year, driven primarily by our preparations for commercialization in advance of the FDA's upcoming PDUFA action date later this year… on November 18th.

Turning to cash, net cash used in operating activities during the quarter ended June 30, 2025 was $154.7 million, compared with net cash used in operating activities of $115.4 millionin the prior year quarter. The increase in cash used in operating activities is driven by several factors including the aforementioned higher operating expenses… and timing of clinical trial payments.

Turning to the balance sheet, our cash and investments totaled $900.4 million as of June 30, 2025.

Our common shares outstanding as of the end of the quarter were 138.1 million.

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

Chris Anzalone

Thanks Dan.

Arrowhead continues to achieve strong execution in discovery, clinical, regulatory, and business development. Our pipeline has become increasingly mature, with four Arrowhead discovered candidates currently in pivotal Phase 3 studies. In addition, our commercial buildout is designed to make us launch ready very quickly, should plozasiran receive regulatory approval on the November 18, 2025, PDUFA date. And, lastly, we have a strong balance sheet that we think gives us the financial resources to continue to move multiple innovative new medicines through the clinical and regulatory process and ultimately get them to the patients who need them.

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

Operator