# Arrowhead Pharmaceuticals Presents Phase 3 SHASTA-3 and SHASTA-4 Data Demonstrating Plozasiran Reduced Acute Pancreatitis Events in Patients with Severe Hypertriglyceridemia

August 30, 2026

- Plozasiran reduced triglycerides (TG) by 79% and 81% versus placebo in SHASTA-3 and SHASTA-4 across the broad sHTG population -

- More than 90% of plozasiran-treated patients achieved triglycerides below thresholds for AP risk, 500 mg/dL at Month 12, and more than half achieved triglycerides below 150 mg/dL -

- Plozasiran reduced cumulative acute pancreatitis (AP) events by 78% versus placebo in patients with TG above 500 mg/dL, with or without a prior history of AP -

- Greater absolute benefit of AP risk reduction was observed in patients at higher risk -

- In the highest-risk subgroup, patients with TG above 880 mg/dL and a prior history of AP, there was a 100% reduction in events versus placebo -

- Plozasiran demonstrated a favorable safety and tolerability profile, with overall treatment-emergent adverse events similar between plozasiran and placebo groups -

- Arrowhead plans to file a supplemental New Drug Application with the U.S. FDA by year-end 2026 and utilize a Priority Review Voucher -

- Detailed results presented at the European Society of Cardiology (ESC) Congress 2026 in Munich as a Hot Line Late-Breaking Science session -

PASADENA, Calif.--(BUSINESS WIRE)--Aug. 30, 2026-- Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR) today presented results from the pivotal Phase 3 SHASTA-3 and SHASTA-4 studies of plozasiran in adults with severe hypertriglyceridemia (sHTG) during a Hot Line Late-Breaking Science session at the European Society of Cardiology (ESC) Congress 2026 in Munich, Germany.

SHASTA-3 and SHASTA-4 met their primary and all prespecified secondary endpoints and demonstrated deep and durable reductions in triglycerides (TG), with median reductions from baseline of 79% and 81%, respectively at Month 12 ($p<0.0001$ in both studies). In a prespecified pooled analysis, plozasiran also significantly reduced acute pancreatitis (AP) events across the broad sHTG study population, with greater absolute benefit observed among patients at higher risk of AP. More than 90% of plozasiran-treated patients in both studies achieved TG levels below 500 mg/dL (<5.65 mmol/L) at Month 12, and more than half achieved TG levels below 150 mg/dL (<1.69 mmol/L).

“These SHASTA-3 and -4 results build on the compelling topline data we reported in July and further strengthen our view that plozasiran has the potential to fundamentally change how severe hypertriglyceridemia is treated,” said Christopher Anzalone, Ph.D., President and Chief Executive Officer at Arrowhead. “The depth and consistency of triglyceride lowering across two large pivotal studies are impressive, but what may be most important for patients and physicians is the significant reduction in acute pancreatitis. The benefit was particularly pronounced among patients with a prior history of pancreatitis, a population with substantial ongoing risk. Combined with quarterly dosing and a favorable safety and tolerability profile, we believe these data demonstrate a highly differentiated profile for plozasiran and unequivocally support our plans to seek regulatory approval for the broader sHTG population. Our purchase of a U.S. FDA Priority Review Voucher, announced earlier this month, will potentially accelerate our goal of getting this important new medicine to patients.”

James Hamilton, M.D., MBA, Chief Medical Officer and Head of R&D at Arrowhead, added, “SHASTA-3 and SHASTA-4 enrolled a broad population that reflects the heterogeneity and substantial disease burden seen in patients with severe hypertriglyceridemia. Plozasiran produced deep and durable reductions in triglycerides and other atherogenic lipoproteins, and more than 90% of treated patients achieved triglyceride levels below the severe hypertriglyceridemia threshold at Month 12. Importantly, the reduction in acute pancreatitis events was observed across the pooled population and became increasingly more meaningful in patients at higher risk. We believe the totality of these data provides strong evidence supporting APOC3 reduction in the liver with plozasiran as a potentially important treatment approach for patients with sHTG.”

Arrowhead intends to leverage data from the Phase 3 SHASTA-3, SHASTA-4 and MUIR-3 studies to seek marketing authorization for plozasiran in the broader sHTG population in multiple global geographies, beginning with a planned supplemental New Drug Application (sNDA) with the U.S. Food and Drug Administration (FDA) before the end of 2026. On August 4, 2026, the company announced it had purchased an FDA Priority Review Voucher, which it intends to utilize for this application.

**SHASTA-3 and SHASTA-4 Phase 3 Results**

SHASTA-3 and SHASTA-4 were global, randomized, double-blind, placebo-controlled Phase 3 studies evaluating plozasiran 25 mg administered subcutaneously once every three months in adults with sHTG. Across the two studies, 757 patients were randomized to receive plozasiran or placebo.

**Triglyceride and Lipoprotein Effects**

- At Month 12, median TG levels were reduced from baseline by 79% in SHASTA-3 and 81% in SHASTA-4 in patients receiving plozasiran 25 mg ($p<0.0001$ in each study).
- Among patients with baseline TG ≥880 mg/dL (≥9.94 mmol/L), median TG reductions at Month 12 were 85% in both SHASTA-3 and SHASTA-4.
- At Month 12, 91% and 93% of plozasiran-treated patients in SHASTA-3 and SHASTA-4, respectively, achieved TG levels <500 mg/dL (<5.65 mmol/L), compared with 51% and 50% of placebo-treated patients ($p<0.0001$ for each comparison).
- 52% and 55% of plozasiran-treated patients in SHASTA-3 and SHASTA-4, respectively, achieved TG levels <150 mg/dL (<1.69 mmol/L), compared with 7.9% and 2.0% of placebo-treated patients ($p<0.0001$ for each comparison).
- Plozasiran also produced significant reductions in APOC3, remnant cholesterol (VLDL-C) and non-HDL cholesterol.

**Acute Pancreatitis**

In a prespecified pooled analysis of AP events from SHASTA-3 and SHASTA-4:

- Plozasiran reduced the rate of all AP events by 78% versus placebo (RR 0.22; 95% CI: 0.07, 0.67; p=0.008), corresponding to a 4.1% absolute risk reduction and a number needed to treat to prevent one AP event over one year (NNT), of 24.
- Plozasiran significantly reduced the risk of a first AP event (HR 0.26; 95% CI: 0.09, 0.78; p=0.016).
- Among patients with TG ≥ 500 mg/dl (5.65 mmol/L) any prior history of AP, plozasiran reduced the AP event rate by 91% versus placebo (RR 0.09; 95% CI: 0.02, 0.41; p=0.002), corresponding to a 34% absolute risk reduction and NNT over one year, of 3.

**Safety and Tolerability**

Plozasiran demonstrated a favorable safety and tolerability profile in SHASTA-3 and SHASTA-4. Overall treatment-emergent adverse events (TEAEs) were reported in 73% of patients in both the pooled plozasiran and placebo groups. Serious TEAEs occurred in 8.3% of patients receiving plozasiran and 10% receiving placebo. TEAEs leading to study drug discontinuation were uncommon, occurring in 1.4% of plozasiran-treated patients and 0.8% of placebo-treated patients.

The most common TEAEs occurring in at least 5% of plozasiran-treated patients included worsening glycemic control (14.3%) and diarrhea (5.6%), compared with 8.7% and 3.2%, respectively, in placebo-treated patients. Despite the imbalance in reported glycemic control-related TEAEs, mean HbA1c showed minimal to modest absolute change from baseline with no worsening of mean HbA1c over time.

Injection-site reactions occurred in 3.2% of plozasiran-treated patients and 2.0% of placebo-treated patients. There were no cases of anaphylaxis or systemic hypersensitivity. No clinically meaningful changes in platelet counts or meaningful elevations in ALT or AST relative to placebo were observed, and no cases met Hy's law criteria. In a prespecified MRI-PDFF sub study, there was no statistically significant treatment-emergent increase in hepatic fat fraction (p=0.70).

Three fatal events occurred in plozasiran-treated patients, consisting of two cardiovascular deaths and one death due to chronic myelomonocytic leukemia. All three were attributed to pre-existing cardiovascular or hematologic disease and assessed as unrelated to study treatment**.**

**Conference Call and Webcast**

Arrowhead will host a conference call and webcast on August 31, 2026 (14:00 CEST/ 8:00 am EDT/ 5:00 am PDT) to discuss the detailed SHASTA-3 and SHASTA-4 results presented at ESC Congress 2026. For more information and to register for the webcast, visit Events & Presentations on www.arrowheadpharma.com.

**About Severe Hypertriglyceridemia**

Severe hypertriglyceridemia (sHTG) is characterized by triglyceride (TG) levels greater than 500 mg/dL (5.65 mmol/L), with the most severe form being familial chylomicronemia syndrome (FCS) where TGs typically exceed 880 mg/dL (9.94 mmol/L). SHTG significantly increases the risk of acute pancreatitis (AP), which can often include recurrent attacks requiring repeat hospital admissions and worsening outcomes. AP risk is proportional to the number, characteristics, and concentration of triglyceride rich lipoproteins (TRLs), particularly chylomicrons, and increases as TGs rise. Elevated TGs can also increase the risk of atherosclerotic cardiovascular disease (ASCVD). Limited treatment options exist to sustainably reduce TGs below guideline directed risk thresholds.

**About SHASTA-3 and SHASTA-4 Phase 3 Studies**

SHASTA-3 (NCT06347003) and SHASTA-4 (NCT06347016) are global double-blind, placebo-controlled, Phase 3 studies to evaluate the efficacy and safety of plozasiran in adults with severe hypertriglyceridemia. Between the two studies, approximately 750 participants were randomized to receive 4 doses (once every 3 months) of 25 mg plozasiran or placebo. The primary endpoint is percent change in fasting serum triglyceride levels from baseline to month 12 compared to placebo. After Month 12, eligible participants are offered an opportunity to continue in an optional open-label extension.

**About REDEMPLO® (plozasiran)**

REDEMPLO (plozasiran) is currently approved by the U.S. Food and Drug Administration, Health Canada, China's National Medical Products Administration, the Australian Therapeutic Goods Administration, and by the European Commission as an adjunct to diet to reduce triglycerides for adults with FCS. REDEMPLO is the first and only siRNA treatment approved in these countries to be studied in both clinically diagnosed and genetically confirmed patients living with FCS.

REDEMPLO is designed to suppress the production of apolipoprotein C-III (APOC3), a protein produced in the liver that raises triglyceride levels by slowing their breakdown and clearance. By targeting APOC3 with sustained silencing, REDEMPLO delivers significant reductions in triglyceride levels. REDEMPLO is self-administered via subcutaneous injection once every three months.

REDEMPLO has been granted Orphan Medicinal Product Designation by the EMA for the treatment of patients with FCS, and Breakthrough Therapy Designation, Fast Track Designation, and Orphan Drug Designation by the U.S. FDA for the treatment of patients with FCS and was also granted Breakthrough Therapy designation by the U.S. FDA in severe hypertriglyceridemia.

Sanofi acquired the rights to develop and commercialize REDEMPLO in Greater China, with Arrowhead retaining rights to REDEMPLO in all geographies, outside of Greater China.

For more information about REDEMPLO, visit Our Medicines.

**About Arrowhead Pharmaceuticals**

Arrowhead Pharmaceuticals (NASDAQ: ARWR) is a commercial-stage pharmaceutical company developing medicines that treat intractable diseases by silencing the genes that cause them, harnessing the natural RNA interference (RNAi) mechanism. The company has built a broad portfolio of clinical and commercial RNAi therapeutics through its industry-leading targeted RNAi molecule (TRiM™) platform, which can precisely silence genes in a wide range of cell types, including liver, lung, muscle, adipose, and central nervous system tissue. At Arrowhead, we rapidly advance potential best- and first-in-class RNAi treatments for diseases with significant unmet medical need, because every day matters to the patients we serve.

For more information, please visit www.arrowheadpharma.com, or follow us on X (formerly Twitter) at @ArrowheadPharma, LinkedIn, Facebook, and Instagram. To be added to the Company's email list and receive news directly, please visit http://ir.arrowheadpharma.com/email-alerts.

**Safe Harbor Statement under the Private Securities Litigation Reform Act:**

*This news release contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. Any statements contained in this release except for historical information may be deemed to be forward-looking statements. Without limiting the generality of the foregoing, words such as "may," "will," "expect," "believe," "anticipate," "hope," "intend," "plan," "project," "could," "estimate," "continue," "target," "forecast" or "continue" or the negative of these words or other variations thereof or comparable terminology are intended to identify such forward-looking statements. In addition, any statements that refer to projections of our future financial performance, trends in our business, expectations for our product pipeline, products or product candidate or other characterizations of future events or circumstances are forward-looking statements. These forward-looking statements include, but are not limited to, statements about our beliefs and expectations regarding the long-term impacts of REDEMPLO® (plozasiran) on patient health and the health care system; our beliefs and expectations regarding the pricing, value, or expected timing for availability of our drugs and drug candidates; and our believes and expectations around the potential uses and value of the TRiM™ platform. These statements are based upon our current expectations and speak only as of the date hereof. Actual results or outcomes may differ materially and adversely from those expressed in any forward-looking statements as a result of numerous factors and uncertainties the safety and efficacy of our products and product candidates, pricing and reimbursement decisions related to our products, demand for our products, decisions of regulatory authorities and the timing thereof, the duration and impact of regulatory delays in our clinical programs, our ability to finance our operations, the likelihood and timing of the receipt of future milestone and licensing fees, the future success of our scientific studies, the timing for starting and completing clinical trials, rapid technological change in our markets, the enforcement of our intellectual property rights, and the other risks and uncertainties described in our most recent Annual Report on Form 10-K, subsequent Quarterly Reports on Form 10-Q and other documents filed with the Securities and Exchange Commission from time to time. We assume no obligation to update or revise forward-looking statements to reflect new events or circumstances.*

**Source:** Arrowhead Pharmaceuticals, Inc.

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Source: Arrowhead Pharmaceuticals, Inc.