Arrowhead Pharmaceuticals Presents Plozasiran Data Highlighting Sustained Triglyceride Reductions and Reduced Acute Pancreatitis Rates

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ARO-DIMER-PA Data Demonstrating Simultaneous Reductions in LDL Cholesterol and Triglycerides at American Heart Association Scientific Sessions 2026

- Pooled SHASTA-3 and SHASTA-4 analysis showed plozasiran reduced acute pancreatitis event rates by 78% overall and 91% in sHTG patients with a recent history of acute pancreatitis versus placebo
- PALISADE open-label extension showed sustained reductions in triglycerides and APOC3 with plozasiran through up to 36 months of treatment in patients with FCS
- Single doses of investigational dual-functional ARO-DIMER-PA produced mean LDL-C reductions of up to 65% and median triglyceride reductions of up to 78% from baseline

PASADENA, Calif.--(BUSINESS WIRE)--Nov. 7, 2026-- Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR) today presented results on two of the RNA interference (RNAi) based therapies in its cardiometabolic pipeline at the American Heart Association (AHA) Scientific Sessions 2026 in Chicago. The presentations included multiple studies of plozasiran in patients with familial chylomicronemia syndrome (FCS) and severe hypertriglyceridemia (sHTG), and interim results from a Phase 1/2a study of investigational ARO-DIMER-PA in patients with mixed hyperlipidemia.

Christie Ballantyne, M.D., Chief of Cardiology and Cardiovascular Research, Baylor College of Medicine, and Director, Center for Cardiometabolic Disease Prevention at the Houston Methodist DeBakey Heart and Vascular Center, Houston, TX, presented results from the pooled analysis of SHASTA-3 and SHASTA-4 evaluating acute pancreatitis risk and the effects of plozasiran in patients with severe hypertriglyceridemia (sHTG) at a late-breaking oral session.

Luke Laffin, M.D., Co-Director, Center for Blood Pressure Disorders, and Medical Director of Cardiac Rehabilitation at the Cleveland Clinic, Cleveland, OH, presented the ARO-DIMER-PA interim results across single-dose cohorts, including LDL-C and TG reductions, effects on ApoB and remnant cholesterol, and a fuller characterization of safety and tolerability at the same late-breaking oral session.

“Together, these data demonstrate the breadth of our cardiometabolic portfolio and our progress toward addressing serious consequences of lipid disorders,” said Chris Anzalone, Ph.D., President and Chief Executive Officer at Arrowhead. “Plozasiran’s reduction in acute pancreatitis event rates in SHASTA-3 and SHASTA-4, alongside sustained triglyceride lowering through up to three years of treatment in PALISADE, reinforces its potential to make a meaningful difference for patients. With ARO-DIMER-PA, we are extending the capabilities of our TRiM™ (Targeted RNAi Molecule) platform by targeting two genes with a single RNAi molecule, with the goal of addressing both LDL cholesterol and triglyceride-rich lipoproteins in people with mixed hyperlipidemia.”

“These findings highlight the importance of looking beyond triglyceride levels alone to understand a patient’s risk of acute pancreatitis,” said James Hamilton, M.D., MBA, Chief Medical Officer and Head of R&D at Arrowhead. “In the SHASTA-3 and SHASTA-4 pooled analysis, plozasiran reduced acute pancreatitis event rates by 78% overall versus placebo and by 91% among patients who had experienced pancreatitis within five years before screening. The PALISADE long-term extension found sustained triglyceride and APOC3 reductions through up to three years of treatment in patients with FCS. Meanwhile, the early ARO-DIMER-PA results show the potential to address multiple lipid abnormalities with a single molecule, supporting further evaluation of this approach for patients with mixed hyperlipidemia.”

Plozasiran Data at AHA Scientific Sessions 2026

Select SHASTA-3/4 Pooled Analysis

Results from the pooled analysis of SHASTA-3 and SHASTA-4 evaluating acute pancreatitis risk and the effects of plozasiran in patients with severe hypertriglyceridemia (sHTG) were presented. The analysis examined the individual and combined associations of baseline TG level and a history of acute pancreatitis (AP) within the previous five years with subsequent AP events over 12 months and evaluated the effects of plozasiran across these risk strata.

The studies randomized 757 adults with severe hypertriglyceridemia to plozasiran 25 mg or placebo administered every three months. The pooled analysis identified recent AP history as an important marker of subsequent AP risk across the severe hypertriglyceridemia spectrum, including among patients with baseline TG levels from 500 to 880 mg/dL.

Across the pooled population, plozasiran reduced the rate of all adjudicated AP events by 78% versus placebo. Among patients with a history of prior AP within the previous five years, the AP event rate was reduced by 91%. Among patients with prior AP and baseline TG levels from 500 to 880 mg/dL, the event rate was reduced by 82%. No AP events occurred among 35 plozasiran-treated patients with both prior AP and TG levels ≥880 mg/dL, compared with five events among 17 placebo-treated patients. These findings highlight the importance of considering both TG level and recent AP history when assessing AP risk in patients with sHTG.

In the pooled safety population, TEAEs occurred in 73% of patients in both groups, and serious TEAEs occurred in 8.3% of plozasiran-treated patients and 10% of placebo-treated patients. Worsening glycemic control was reported in 14% and 8.7%, respectively. Three deaths in the plozasiran group were attributed to pre-existing cardiovascular or hematologic disease and assessed as unrelated to study treatment.

PALISADE Open-Label Extension

The PALISADE open-label extension evaluated longer-term plozasiran treatment in patients with clinically diagnosed or genetically confirmed familial chylomicronemia syndrome (FCS). Through 24 months of the extension, representing up to 36 months of total treatment, median reductions from baseline were 76% for TGs and 89% for APOC3. At Month 24 of the extension, 57% of patients achieved TG levels < 880 mg/dL and 48% achieved levels < 500 mg/dL. AP events remained infrequent during longer-term follow-up. The results were presented by Robert Rosenson, M.D., Dr. Rony

Shimony Distinguished Professor of Cardiovascular Medicine at the Icahn School of Medicine at Mount Sinai and System Director of Metabolism and Lipids for the Mount Sinai Health System, New York, NY.

During the extension, three adjudicated AP events were reported: one mild incident event in a patient who continued plozasiran and two recurrent events in a patient who switched from placebo to plozasiran. The extension had no concurrent placebo control, and its findings are descriptive.

Among 63 patients in the extension safety analysis, TEAEs occurred in 49 (78%), serious TEAEs in seven (11%), and TEAEs leading to study drug discontinuation in three (5%). Increased HbA1c was reported in five patients (8%), with elevated HbA1c associated with two discontinuations. One death due to cardiac arrhythmia was assessed by the investigator and sponsor as unrelated to plozasiran. The study reported no clinically meaningful hematologic, hepatic, or renal laboratory findings considered related to plozasiran and no cases met Hy's law criteria.

Select ARO-DIMER-PA Single-Ascending Dose Phase 1/2a Interim Results

Today's presentation included single ascending dose data across doses of 25 mg, 50 mg, 100 mg, 200 mg, and 400 mg. The baseline and safety tables report 21 ARO-DIMER-PA-treated participants and 10 placebo-treated participants. The primary endpoint evaluates safety and tolerability, and secondary efficacy endpoints include changes from baseline in PCSK9, APOC3, LDL-C, and TGs.

ARO-DIMER-PA Data at AHA Scientific Sessions 2026

A single dose of ARO-DIMER-PA produced simultaneous suppression of PCSK9 and APOC3, accompanied by reductions in low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs). The study team reported mean LDL-C reductions from baseline ranging from 26% to 65% and median TG reductions ranging from 56% to 78%, together with reductions in apolipoprotein B (ApoB) and remnant cholesterol. These findings provide clinical proof of concept for simultaneously targeting two complementary lipid pathways with a single RNAi therapeutic.

Across the reported dose cohorts and available follow-up, the presentation summarized the following reductions from baseline:

- PCSK9: mean reductions of 50% to 89%.
- APOC3: mean reductions of 43% to 95%.
- LDL-C: mean reductions of 26% to 65%.
- Triglycerides: median reductions of 56% to 78%.
- ApoB: mean reductions of 32% to 66%.
- Remnant cholesterol: mean reductions of 52% to 73%.

These interim results reflect different dose cohorts and available assessment times, with participant numbers varying by endpoint and visit. The reported lipid changes represent changes from baseline and are not placebo-adjusted treatment effects. Longer-term studies are needed to establish optimal dosing and further characterize safety, tolerability, and durability of treatment effects, as well as potential cardiovascular benefit.

Safety and Tolerability

In the single escalating dose cohorts, treatment-emergent adverse events (TEAEs) were reported in all 21 ARO-DIMER-PA-treated participants and nine of 10 placebo-treated participants. Most participants had a maximum TEAE severity of Grade 1 or Grade 2. No serious adverse events, deaths, or Grade 4 or Grade 5 TEAEs were reported. One participant in the 400 mg cohort experienced Grade 3 syncope six hours after administration.

Injection-site erythema was the most commonly reported adverse event, occurring in 20 of 21 ARO-DIMER-PA-treated participants and no placebo-treated participants. Other reported events included headache and pyrexia. Hyperglycemia was reported in three ARO-DIMER-PA-treated participants, although no clinically meaningful changes in HbA1c were observed. HbA1c follow-up measurements were reported at 12 weeks for placebo and the 25 mg, 50 mg, 100 mg, and 200 mg groups, and at eight weeks for one participant in the 400 mg group. One participant in the 200 mg cohort had an investigator-reported aminotransferase elevation. No clear pattern of hepatotoxicity was observed, and no cases met Hy's law criteria. No clinically meaningful platelet changes were observed. Occasional transient elevations in high-sensitivity C-reactive protein occurred around dosing, with no apparent sustained elevation over time.

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 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 the PALISADE Study

The PALISADE study (NCT05089084) is a Phase 3 placebo-controlled study to evaluate the efficacy and safety of plozasiran in adults with genetically confirmed or clinically diagnosed FCS. The primary endpoint of the study is percent change from baseline in fasting TG versus placebo at Month 10. A total of 75 patients distributed across 39 different sites in 18 countries were randomized to receive 25 mg plozasiran, 50 mg plozasiran, or matching placebo once every three months. Participants who completed the randomized period were eligible to continue in a 2-part extension period, where all participants receive plozasiran.

About Familial Chylomicronemia Syndrome

Familial chylomicronemia syndrome (FCS) is a severe and rare genetic disease often caused by various monogenic mutations. FCS leads to extremely high triglyceride (TG) levels, typically over 880 mg/dL. Such severe elevations can lead to various serious signs and symptoms including acute and potentially fatal pancreatitis, chronic abdominal pain, diabetes, hepatic steatosis, and cognitive issues. Currently, the therapeutic options that can adequately treat FCS are limited.

About ARO-DIMER-PA and the Phase 1/2a Study

ARO-DIMER-PA is an investigational, liver-targeted, dual-functional siRNA therapeutic designed to silence expression of both PCSK9 and APOC3 in hepatocytes. Enabled by Arrowhead's proprietary Targeted RNAi Molecule (TRiM™) platform, it is designed to address complementary pathways involved in LDL cholesterol and triglyceride-rich lipoprotein metabolism with a single molecule.

ARO-DIMER-PA-1001 (NCT07223658) is a placebo-controlled, dose-escalation Phase 1/2a study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and lipid effects of single and multiple doses of ARO-DIMER-PA in adults with mixed hyperlipidemia. The study includes single-ascending-dose and multiple-ascending-dose parts, with participants enrolled at 11 sites in Australia, New Zealand, and Georgia. The findings presented at AHA are interim single-dose results.

About Mixed Hyperlipidemia

Mixed hyperlipidemia is characterized by elevated LDL cholesterol and triglyceride-rich lipoproteins, both of which contribute to atherosclerotic cardiovascular disease risk. Treatment often requires multiple therapies to address these lipid pathways. ARO-DIMER-PA is being evaluated as a potential single-agent approach to reducing both LDL cholesterol and triglycerides. Cardiovascular outcome benefit has not been established for ARO-DIMER-PA.

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.

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