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Scientific Sessions

TRIGLYCERIDE LOWERING AND ACUTE PANCREATITIS RISK REDUCTION WITH PLOZASIRAN IN SHTG: A POOLED ANALYSIS OF SHASTA-3 AND SHASTA-4

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American Heart Association.

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DISCLOSURES

CM Ballantyne reports Grant/Research Support: Abbott Diagnostic, Akcea, Amgen, Arrowhead, lonis, Merck, New Amsterdam, Novartis, Novo Nordisk, Roche Diagnostic, NIH, AHA, ADA (all paid to institution, not individual) and Consultant: 89Bio, Abbott Diagnostics, Amarin, Amgen, Arrowhead, AstraZeneca, Denka Seiken, Eli Lilly, Esperion, Genentech, lllumina, lonis, Merck, New Amsterdam, Novartis, Novo Nordisk, Roche Diagnostic.

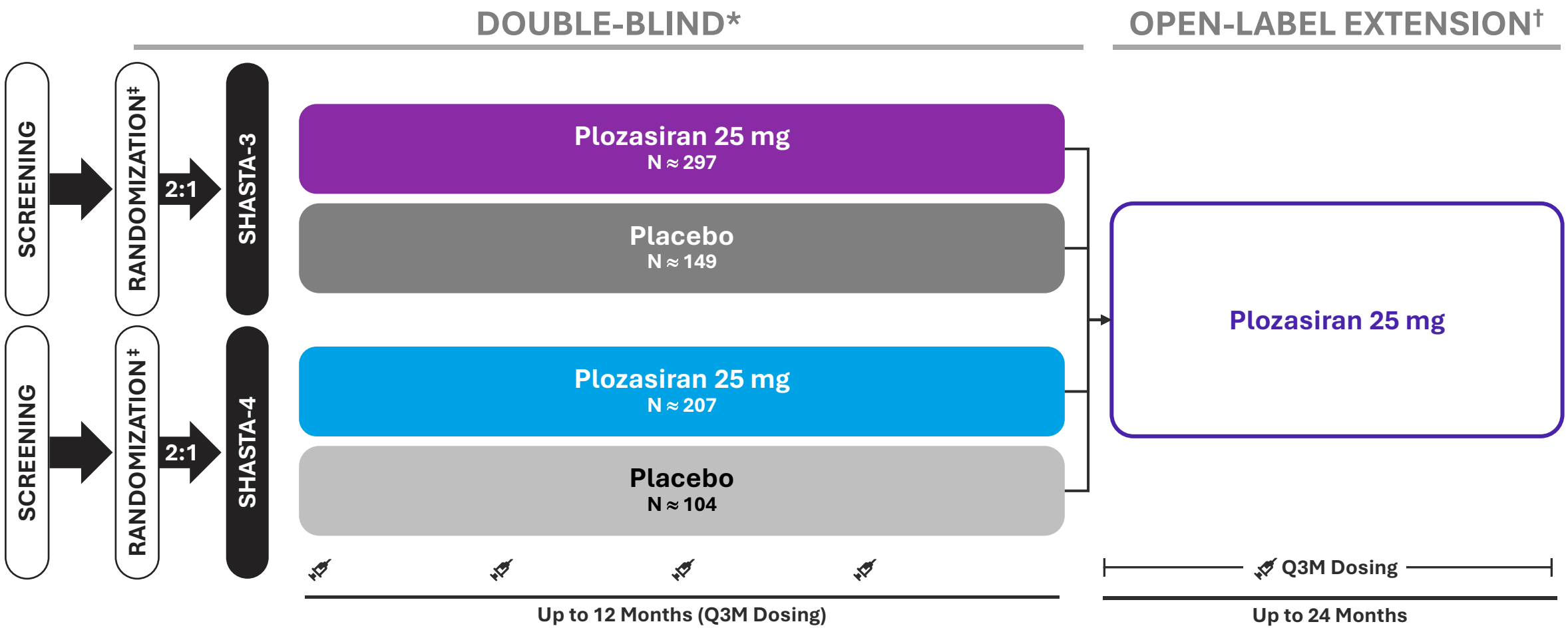
BACKGROUND: SEVERE HYPERTRIGLYCERIDEMIA

- AP risk in sHTG increases with the severity of TG elevation, while a prior history of AP further increases the risk of subsequent AP events[1-4]
- Reflecting these 2 established risk factors, randomization to Plozasiran, in the phase 3 SHASTA-3 and SHASTA-4 studies was stratified by screening TG level and history of AP within the previous 5 years[5-6]
- The primary efficacy and safety results of SHASTA-3 and SHASTA-4 have been reported[7]
- Building on the risk-based stratification of these studies, the present analysis examined the individual and combined effects of TG level and prior AP history on AP risk over 12 months and evaluated the effect of Plozasiran across these risk strata.

1. Hansen SEJ, et al. *Clin Chem* 2023;69(10):1132–1144. (In eng). **2.** Varbo A, Nordestgaard BG. *Eur Heart J* 2021;42(47):4833–4843. **3.** Packard CJ, et al. *Cardiovasc Res* 2024;119(18):2843–2857. (In eng). **4.** Filtz A, et al. *Am J Prev Cardiol* 2024;18:100648. **5.** Berglund L, et al. *J Clin Endocrinol Metab* 2012;97(9):2969–89. (In eng). **6.** US Food and Drug Administration. FDA Approves Drug to Reduce Triglycerides in Adults with Familial Chylomicronemia Syndrome. Available at https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-reduce-triglycerides-adults-familial-chylomicronemia-syndrome. Accessed Nov 23, 2025. **7.** Watts GF et al. New Eng. J. Med; 2026

AP, acute pancreatitis; **APOC3**, apolipoprotein C3; **sHTG**, severe hypertriglyceridemia; **TG,** triglycerides.

METHODS: STUDY SCHEMA



*A subset of patients enrolled in SHASTA-3 underwent serial MRI-PDFF in a substudy to assess change in liver fat content. MRI-PDFF was conducted at screening and Month 12 at sites where MRI-PDFF testing is available. ABPM was a substudy of SHASTA-4 and was conducted for the evaluation of changes in systolic and diastolic blood pressures in a total of up to 60 patients. †All patients will have the option to participate in an open-label extension study comprised of patients from both studies. Patients who opt out of the OLE will have an additional 3-month follow-up visit at Month 15. ‡The randomization was stratified based on TG levels (≥880 mg/dL vs <880 mg/dL) and prior history of AP, within 5 years of screening. Adapted from Watts GF, et al. *New Engl J Med*. 2026.

ABPM, ambulatory blood pressure monitoring; **MRI-PDFF**, magnetic resonance imaging-proton density fat fraction; **OLE**, open-label extension; **Q3M**, every 3 months.

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SHASTA 3/4 BASELINE CHARACTERISTICS

Demographics/Characteristic		SHASTA-3/4 Pooled		
		Placebo (n=254)	Plozasiran (n=503)	Total (N=757)
Age (years), mean (SD)		52 (12)	53 (12)	52 (12)
Sex at birth, Male, n (%)		192 (76)	406 (81)	598 (79)
Race, n (%)	White	197 (78)	406 (81)	603 (80)
	Asian	47 (19)	71 (14)	118 (16)
	Black or African American	3 (1.2)	16 (3.2)	19 (2.5)
Ethnicity, Hispanic, n (%)		54 (21)	96 (19)	150 (20)
BMI (kg/m^2), mean (SD)		31 (5.0)	31 (5.1)	31 (5.1)
History of cardiovascular disease, n (%)		73 (29)	171 (34)	244 (32)
History of diabetes mellitus[a], n (%)		139 (55)	303 (60)	442 (58)
History of AP, n (%)		58 (23)	102 (20)	160 (21)
Triglycerides (mg/dL)[b]	Mean (SD)	872 (589)	885 (575)	881 (579)
	Median (Q1, Q3)	678 (546, 1023)	694 (540, 1038)	688 (545, 1032)
	≥880 mg/dL, n (%)	82 (32)	168 (33)	250 (33)
HbA1c (%), mean (SD)		6.4 (1.1)	6.5 (1.1)	6.5 (1.1)
TG-lowering therapy, n (%)	Fibrates	150 (59)	311 (62)	461 (61)
	Omega-3 fatty acid	65 (26)	133 (26)	198 (26)
Lipid-lowering therapy, n (%)	Statin	173 (68)	352 (70)	525 (69)
	Ezetimibe	58 (23)	116 (23)	174 (23)
	≥2 therapies	173 (68)	331 (66)	504 (67)

[a]Diabetic patients are defined as having HbA1c ≥6.5% or fasting glucose 7 mmol/L (≥126 mg/dL) or with medical history of 'diabetes' or receiving diabetic medications at baseline. [b]For fasting TG concentrations, baseline is defined as the average (i.e., geometric mean) of Day 1 pre-dose assessment, and the last fasting TG concentration collected during the screening period.

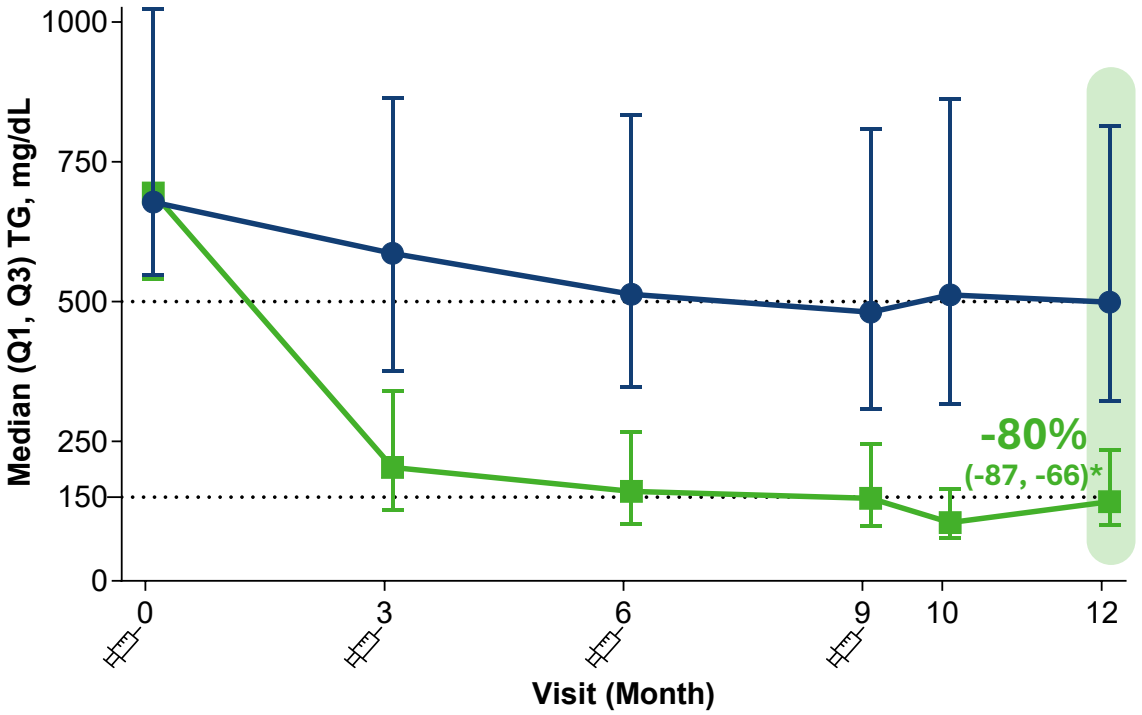
AP, acute pancreatitis; **BMI**, body mass index; **HbA1c**, glycosylated hemoglobin; **Q1, Q3,** interquartile range; **SD**, standard deviation; **TG**, triglycerides.

PLOZASIRAN SHOWED SUSTAINED REDUCTIONS IN TG LEVELS IN SHTG IN SHASTA-3 AND 4

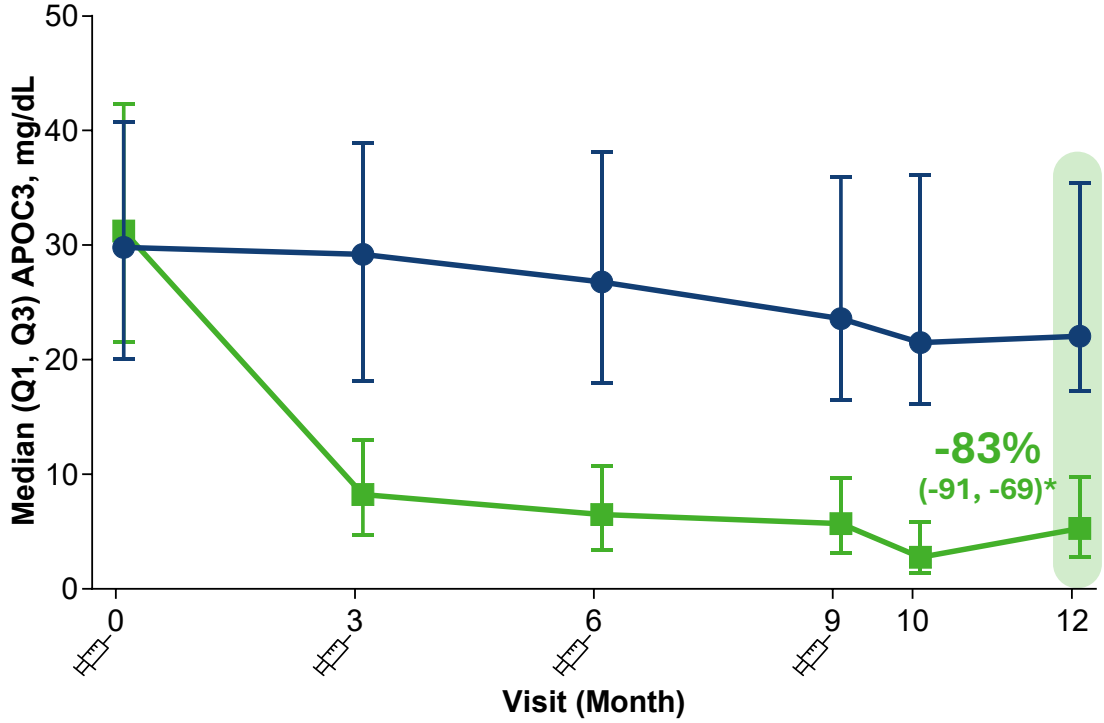
SHASTA-3/4 Pooled Placebo

SHASTA-3/4 Pooled Plozasiran

Triglycerides
Median (Q1, Q3) Absolute Value Over Time



APOC3
Median (Q1. Q3) Absolute Value Over Time



>90% of patients achieved TG<500 mg/dL | **50% of patients achieved TG<150 mg/dL**

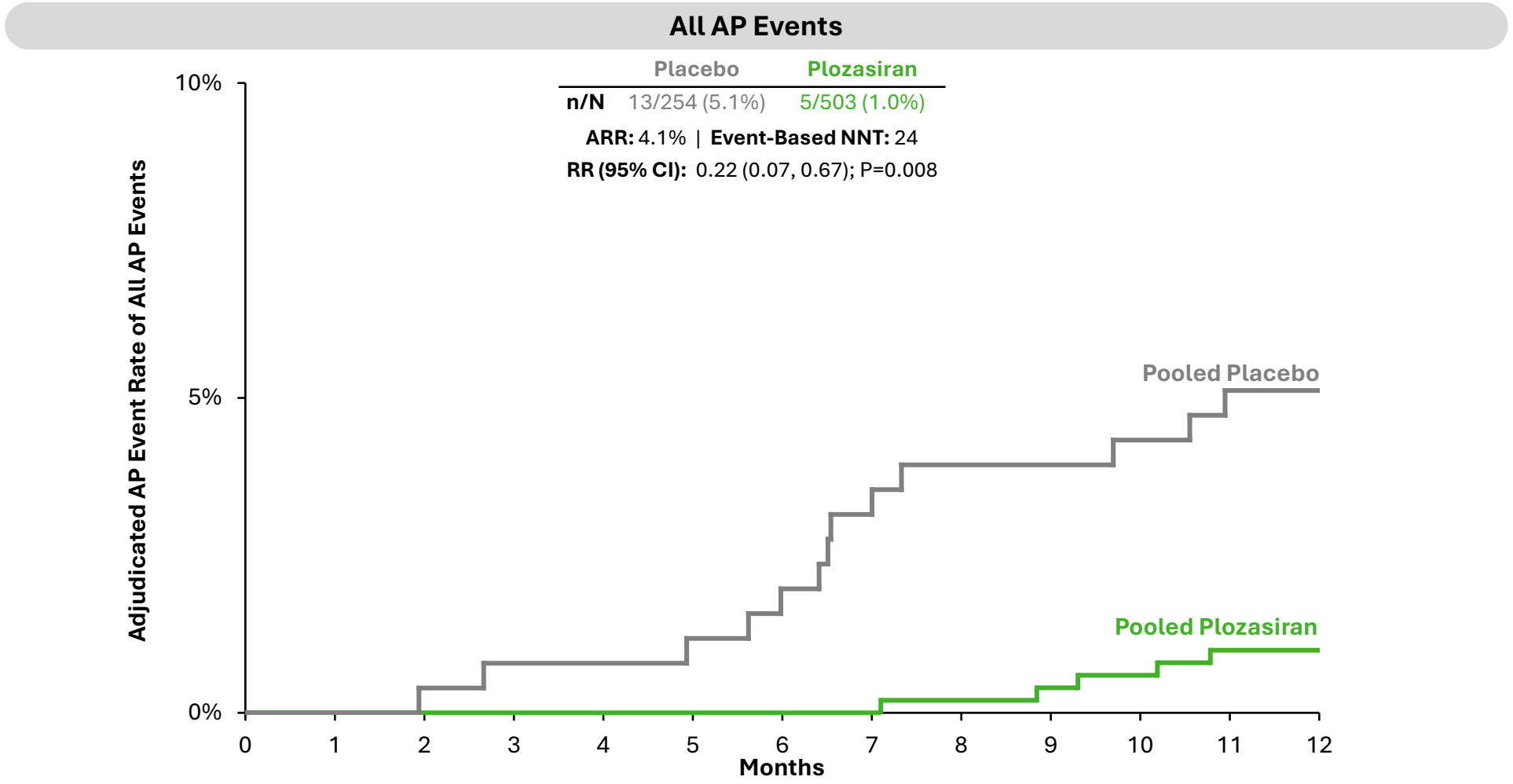
P<0.0001 for plozasiran vs placebo for all time points

*Median percent change from baseline (Q1, Q3). Watts GF, et al. *New Engl J Med*. 2026.

BL, baseline; **CI**, confidence interval; **Q1, Q3**, interquartile range; **sHTG**, severe hypertriglyceridemia; **TG**, triglycerides.

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ALL ADJUDICATED AP EVENTS ACROSS THE TG SPECTRUM



Positively adjudicated AP events included documented, probable, and possible AP; ARR is the difference in event rates between treatment and control groups. NNT is the reciprocal of ARR and represents the number of patients who must be treated over a specified period to prevent one additional adverse event. Panel: All 4 Quadrants. Watts GF, et al. *New Engl J Med*. 2026.

AP, acute pancreatitis; **ARR**, absolute risk reduction; **CI**, confidence interval; **NNT**, number needed to treat; **RR**, risk ratio; **TG**, triglyceride.

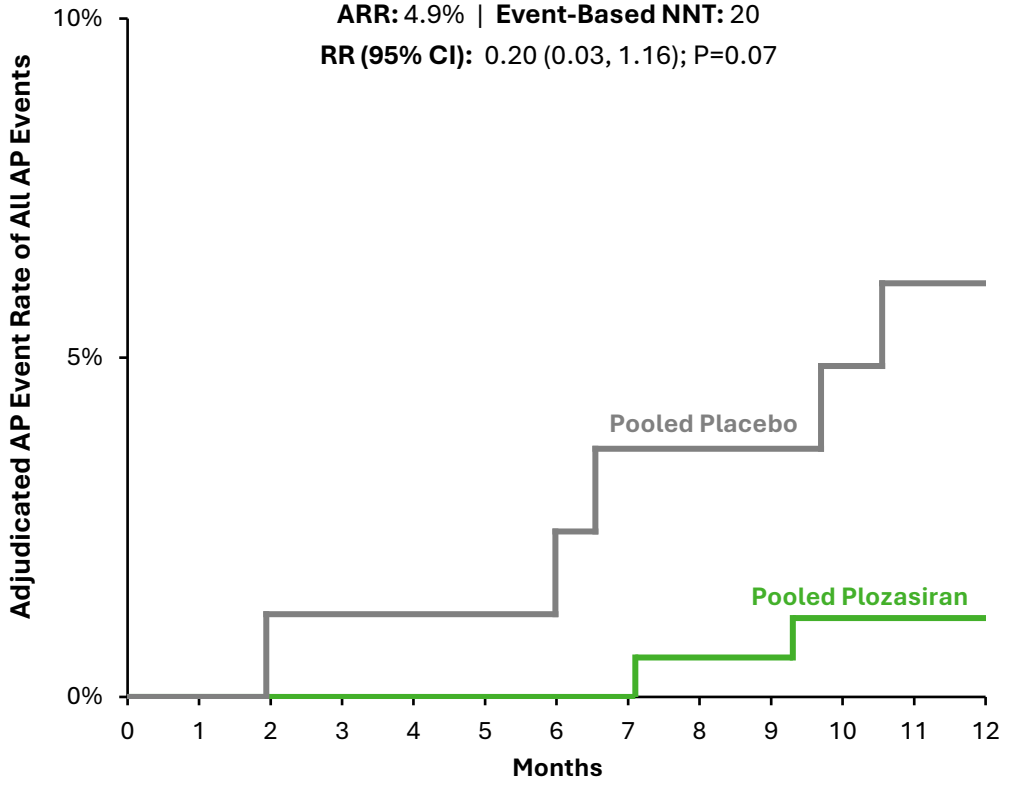
SUBGROUP ANALYSIS OF ALL ADJUDICATED AP EVENTS BY TG STRATA

TG levels ≥880 mg/dL ± history of AP

	Placebo	Plozasiran
n/N	5/82 (6.1%)	2/168 (1.2%)

ARR: 4.9% | **Event-Based NNT:** 20

RR (95% CI): 0.20 (0.03, 1.16); P=0.07

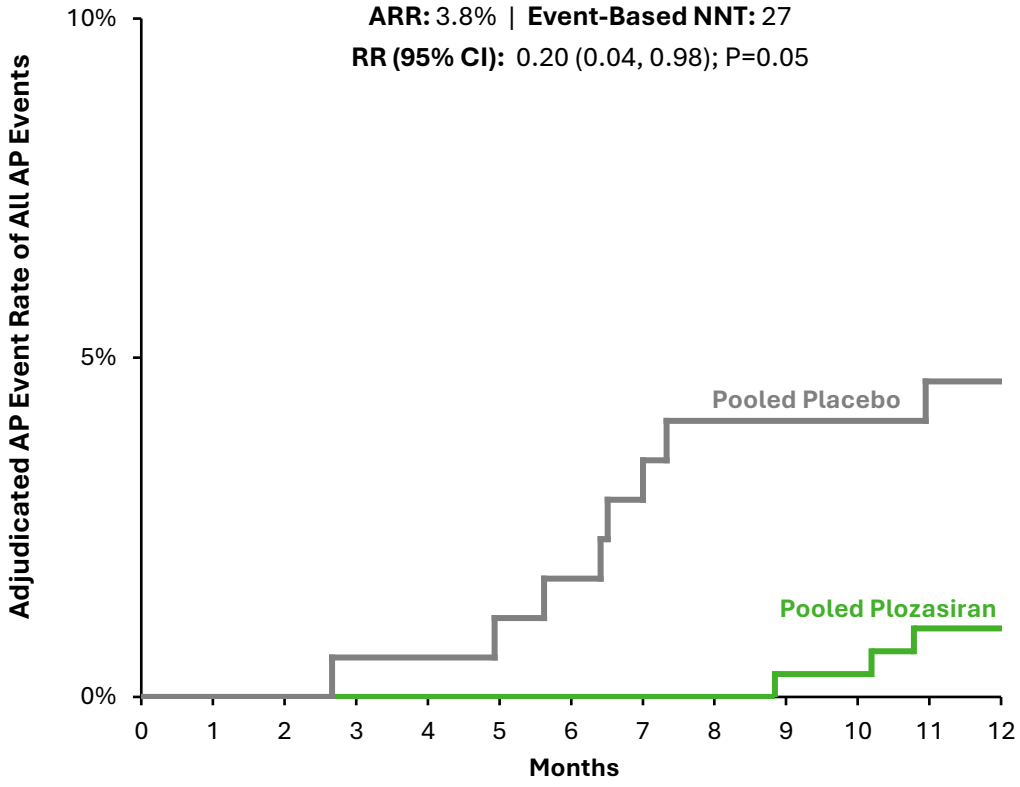


TG levels 500-880 mg/dL ± history of AP

	Placebo	Plozasiran
n/N	8/172 (4.7%)	3/335 (0.9%)

ARR: 3.8% | **Event-Based NNT:** 27

RR (95% CI): 0.20 (0.04, 0.98); P=0.05



Positively adjudicated AP events included documented, probable, and possible AP; ARR is the difference in event rates between treatment and control groups. NNT is the reciprocal of ARR and represents the number of patients who must be treated over a specified period to prevent one additional adverse event. Left Panel: Right Hemisphere Quadrants; Right Panel: Left Hemisphere Quadrants

AP, acute pancreatitis; **ARR**, absolute risk reduction; **CI**, confidence interval; **NNT**, number needed to treat; **RR**, risk ratio; **TG**, triglyceride.

AP EVENTS OCCURRED ACROSS TG SPECTRUM INCLUDING IN PATIENTS WITH OR WITHOUT PRIOR AP

This Analysis Evaluated the Relative and Combined Importance of TG Levels and Recent AP History in Predicting AP Events Over 12 Months

	TG 500–880 mg/dL	TG ≥880 mg/dL	
No History of AP	**1 | 1** *N = 464*	**2 | 2** *N = 198*	**No Prior AP Hemisphere:** **3 | 3** *N = 662*
History of AP	**7 | 10** *N = 43*	**4 | 5** *N = 52*	**Prior AP Hemisphere:** **11 | 15** *N = 95*
	TG 500–880 Hemisphere: **8 | 11** *N = 507*	**TG ≥880 Hemisphere:** **6 | 7** *N = 250*	**TOTAL:** **14 | 18** *N = 757*

TG ≥880 mg/dL and/or history of AP
13 | 17; *N = 293*

AP events include documented, probable, and possible positively adjudicated events.

AP, acute pancreatitis.

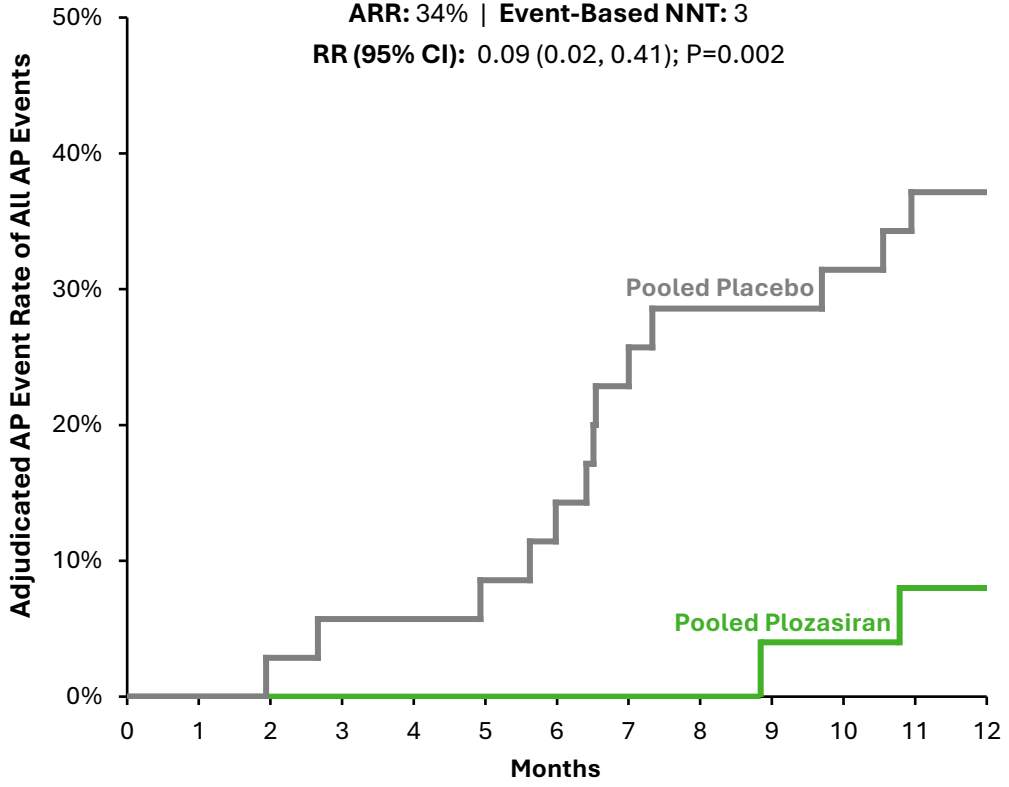
SUBGROUP ANALYSIS OF ALL ADJUDICATED AP EVENTS BY HISTORY OF AP

History of AP + TG levels ≥500

	Placebo	Plozasiran
n/N	13/35 (37.1%)	2/60 (3.3%)

ARR: 34% | **Event-Based NNT:** 3

RR (95% CI): 0.09 (0.02, 0.41); P=0.002

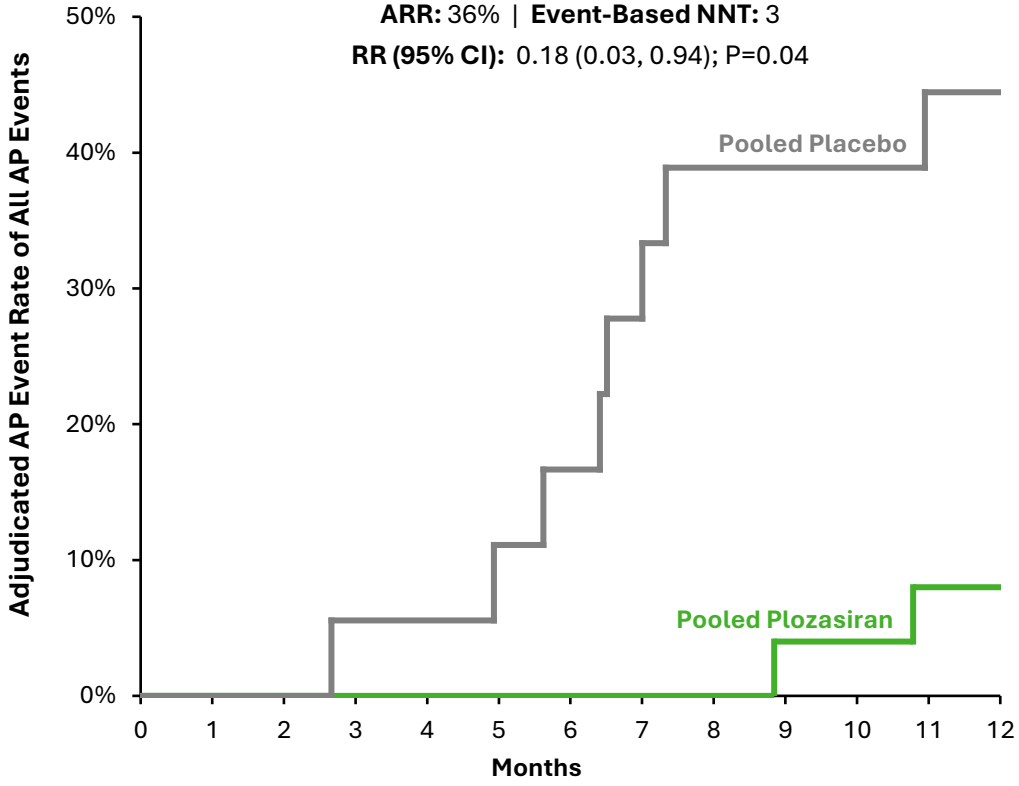


History of AP + TG levels 500–880 mg/dL

	Placebo	Plozasiran
n/N	8/18 (44.4%)	2/25 (8.0%)

ARR: 36% | **Event-Based NNT:** 3

RR (95% CI): 0.18 (0.03, 0.94); P=0.04



Positively adjudicated AP events included documented, probable, and possible AP; ARR is the difference in event rates between treatment and control groups. NNT is the reciprocal of ARR and represents the number of patients who must be treated over a specified period to prevent one additional adverse event. Left Panel: Lower Hemisphere Quadrants; Right Panel: Lower Left Quadrant

AP, acute pancreatitis; **ARR**, absolute risk reduction; **CI**, confidence interval; **NNT**, number needed to treat; **RR**, risk ratio; **TG**, triglyceride.

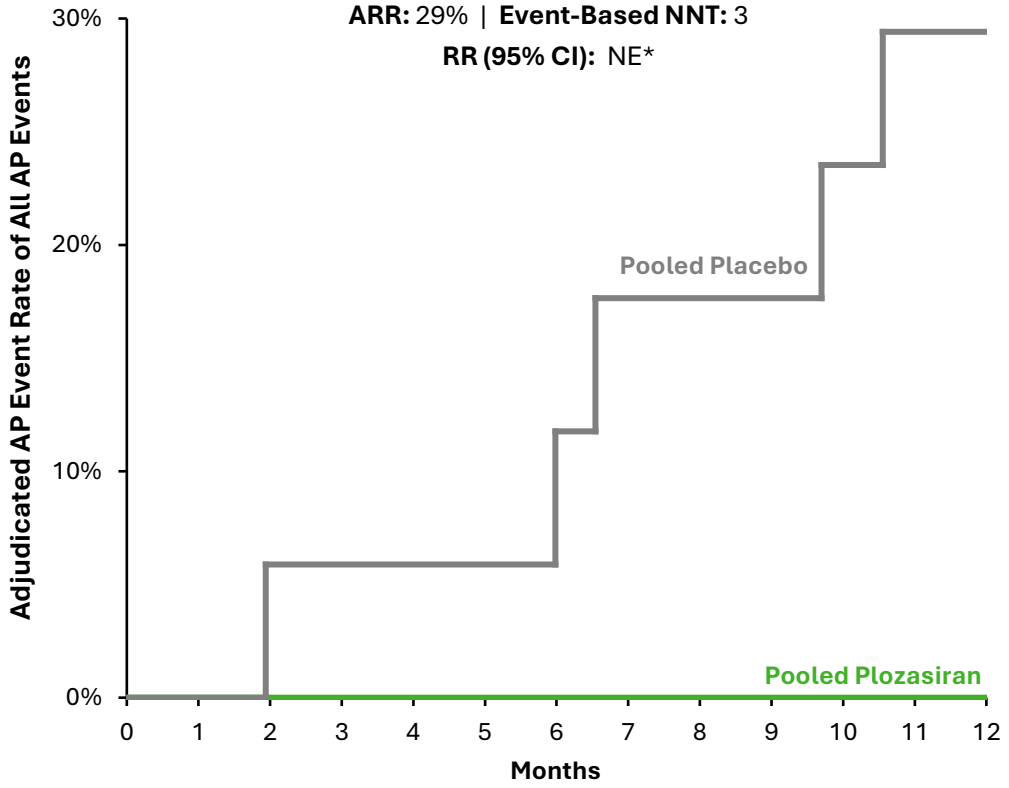
SUBGROUP ANALYSIS OF ALL ADJUDICATED AP EVENTS BY ALL HIGH-RISK FACTORS

TG ≥880 mg/dL + history of AP

	Placebo	Plozasiran
n/N	5/17 (29.4%)	0/35 (0%)

ARR: 29% | **Event-Based NNT:** 3

RR (95% CI): NE*

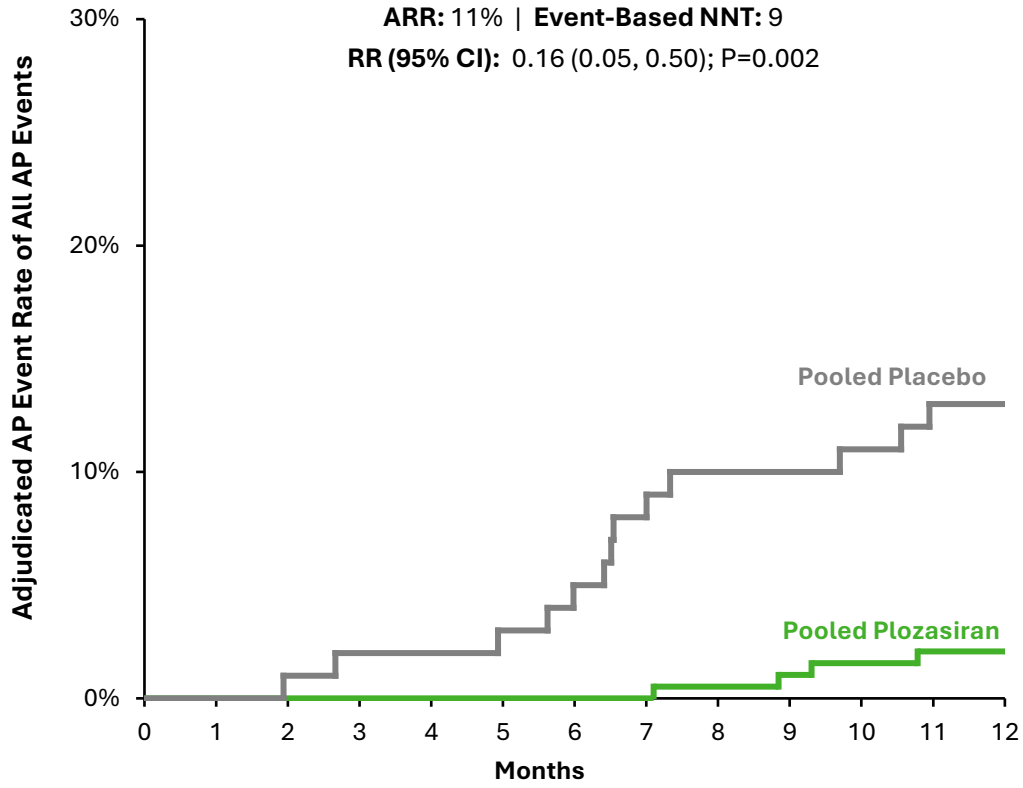


TG ≥880 mg/dL and/or history of AP

	Placebo	Plozasiran
n/N	13/100 (13.0%)	4/193 (2.1%)

ARR: 11% | **Event-Based NNT:** 9

RR (95% CI): 0.16 (0.05, 0.50); P=0.002



*NE, not estimable due to no events in plozasiran group.

Positively adjudicated AP events included documented, probable, and possible AP; ARR is the difference in event rates between treatment and control groups. NNT is the reciprocal of ARR and represents the number of patients who must be treated over a specified period to prevent one additional adverse event. Left panel: Lower Right Quadrant: Very Highest Risk Subgroup; Right Panel: Reverse L-Shaped Quadrants.

SUMMARY OF ADVERSE EVENTS

	SHASTA-3/4		
	Pooled Placebo (n=252)	Pooled Plozasiran (n=504)	Total (N=756)
All TEAEs, n (%)	184 (73)	368 (73)	552 (73)
Most common TEAEs ≥5%			
Worsening glycemic control	22 (8.7)	72 (14)	94 (12)
Diarrhea	8 (3.2)	28 (5.6)	36 (4.8)
Abdominal pain	17 (6.7)	13 (2.6)	30 (4.0)
Serious TEAEs, n (%)	24 (10)	42 (8.3)	66 (8.7)
Any TEAEs by maximum severity, n (%)			
Mild	50 (20)	91 (18)	141 (19)
Moderate	106 (42)	227 (45)	333 (44)
Severe	26 (10)	42 (8.3)	68 (9.0)
SAEs*	0 (0.0)	3 (0.6)	3 (0.4)
TEAEs leading to study drug discontinuation, n (%)	2 (0.8)	7 (1.4)	9 (1.2)
Injection site reaction, n (%)	5 (2.0)	16 (3.2)	21 (2.8)
Hypersensitivity, n (%)	1 (0.4)	1 (0.2)	2 (0.3)
Platelet count decreased, n (%)	4 (1.6)	2 (0.4)	6 (0.8)
Hepatic laboratory measures, n (%)			
ALT or AST ≥ 3X ULN at any post-baseline visit	4 (1.6)	5 (1.0)	9 (1.2)
ALT or AST ≥ 5X ULN at any post-baseline visit	2 (0.8)	2 (0.4)	4 (0.5)

	SHASTA-3		
Liver fat using MRI-PDFF (%), mean (SD)	**Placebo (n=13)**	**Plozasiran (n=23)**	**Total (n=36)**
Baseline, mean (SD)	16.2 (8.3)	14.0 (8.0)	14.8 (8.1)
Month 12, mean (SD)	15.6 (9.5)	15.0 (9.8)	15.2 (9.5)
Change from baseline, mean (SD)	-0.5 (7.3)	1.0 (8.9)	0.5 (8.3)

- TEAEs leading to discontinuation remained low (1.2%)
- AEs were generally similar between groups
- No cases of anaphylaxis or systemic hypersensitivity
- Worsening glycemic control occurred in 14% and 9% of patients in the plozasiran and placebo groups
  - No additional worsening of HbA1c over time
- No clinically meaningful:
  - Changes in platelet counts observed
  - Elevations in ALT or AST relative to placebo
    - No cases met Hy's law criteria
- No statistically significant (p=0.70) treatment-emergent increase in HFF

% = 100 x n/N. *SAE is an adverse event that results in death, is life-threatening or requires hospitalization. There were two SAE CV deaths (cardiogenic shock following acute MI and sudden cardiac death in the setting of extensive underlying CV disease) and one death due to chronic myelomonocytic leukemia; all were attributable to pre-existing CV or hematologic disease and were assessed as unrelated to study treatment. Note: Patients with multiple events are counted only once within a category. Glycemic control–related TEAEs, included diabetes mellitus inadequate control, diabetes mellitus, type 2 diabetes mellitus, hyperglycemia, blood glucose increased, HbA1c increased, glucose tolerance impaired, glucose urine present/glycosuria, and insulin resistance, Injection site: reaction TEAEs included pain, erythema, reactions, bruising, discomfort, hypersensitivity, inflammation, pruritis, and administration site: erythema, pain, reaction by system organ class and preferred term. Adapted from Watts GF, et al. *New Engl J Med*. 2026.

ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **HFF**, hepatic fat fraction; **MRI-PDFF,** magnetic resonance imaging-proton density fat fraction; **SD**, standard deviation; **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event; **ULN**, upper limit of normal.

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CONCLUSIONS

- Plozasiran administered every 3 months produced sustained TG reductions of ~ 80%, with >90% of patients achieving TG < 500 mg/dL and >50% achieving TG < 150 mg/dL
- Plozasiran was associated with ~80% lower rate of AP events versus placebo, with reductions also observed across prespecified high-risk subgroups
- AP events occurred across the spectrum of TG. Although AP risk was higher with TG ≥880 mg/dl than with TG 500 to 880 mg/dL, a history of AP within the previous 5 years identified patients at greatest risk of subsequent AP
- Most AP events occurred in patients with a prior history of AP, with substantial risk observed at both TG 500 to 880 mg/dL and TG ≥880 mg/dL; the NNT with Plozasiran was 3 in both subgroups
- Plozasiran was generally well tolerated, with no new safety signals identified
- These findings suggest that AP prevention in sHTG should consider both TG level and prior AP history. Patients with prior AP remain at high risk of recurrence across the sHTG spectrum, including at TG 500 to 880 mg/dL, and may particularly benefit from achieving and maintaining lower TG levels

AP, acute pancreatitis; **ARR**, absolute risk reduction; **CI**, confidence interval; **NNT**, number needed to treat; **sHTG**, severe hypertriglyceridemia; **TG**, triglyceride.

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TRIGLYCERIDE LOWERING AND ACUTE PANCREATITIS RISK REDUCTION WITH PLOZASIRAN IN SHTG: A POOLED ANALYSIS OF SHASTA-3 AND SHASTA-4

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