Plozasiran for Severe Hypertriglyceridemia and Risk of Pancreatitis: The SHASTA-3 and SHASTA-4 Pivotal Trial 12-Month Results

Gerald F. Watts, DSc, MD, PhD[1]; Christie M. Ballantyne, MD[2]; Agustin Blanco Echevarria, MD, PhD[3]; Jamie Smith, MD[4]; Robert S. Rosenson, MD[5]; Savitha Subramanian MD[6]; James Trippi, MD[7]; Norman Lepor, MD[8]; Archna Bajaj, MD[9]; Vladimir Blaha, MD, PhD[10]; Russell Scott, MD, PhD[11]; Alexis Baass, MD[12]; Ira J. Goldberg, MD[13]; Antonio Gallo, MD, PhD[14]; Jose Luis Diaz Diaz, MD, PhD[15]; Manish Saxena, MBBS, MSc, FESC[16]; Jianping Li, MD[17]; Ran Fu, PhD[18]; Lalitha Aiyer, MD, MS, MBA[18]; Jennifer Hellawell, MD[18]; James Hamilton, MD, MBA[18]; Daniel Gaudet, MD, PhD[19]

[1]School of Medicine, University of Western Australia, and the Department of Cardiology, Royal Perth Hospital—Perth, Australia; [2]Baylor College of Medicine and the Texas Heart Institute—Houston, Texas; [3]Hospital Universitario 12 de Octubre, Madrid, Spain; [4]Torbay and South Devon NHS Foundation Trust - Torbay Hospital (Department of Diabetes and Endocrinology), Torquay, UK; [5]Metabolism and Lipids Program, Mount Sinai Fuster Heart Hospital, Icahn School of Medicine, Mount Sinai, NY, USA; [6]University of Washington, Seattle, Washington; [7]Ascension St. Vincent Heart Center, Indianapolis, Indiana; [8]National Heart Institute, Beverly Hills, CA, USA; [9]University of Pennsylvania, Philadelphia; [10]Third Department of Internal Medicine–Metabolism and Gerontology, Faculty of Medicine, Hradec Králové, University Hospital Hradec Králové and Charles University, Czech Republic; [11]New Zealand Clinical Research, Christchurch, New Zealand; [12]Institute de recherches cliniques de Montréal, Canada; [13]NYU Langone Health, New York, NY, USA; [14]APHP Hôpital Universitaire Pitié Salpêtrière, France; 15Complejo Hospitalario Universitario de A Coruña, Galicia, Spain; [16]Barts Health NHS Trust and Queen Mary University London, UK; [17]Peking University First Hospital, China; [18]Arrowhead Pharmaceuticals, Pasadena, CA, USA; [19]Université de Montréal and ECOGENE 21, Montréal Canada

Background: Severe Hypertriglyceridemia (sHTG)

- sHTG (triglycerides ≥5.65 mmol/L [≥500 mg/dL]) affects approximately 1% of the population and increases the risk of acute pancreatitis (AP)[1,2]
- sHTG is a heterogeneous disorder driven by polygenic susceptibility and secondary factors, including obesity, type 2 diabetes, overnutrition, alcohol use, and medications[3,4]
- Despite lifestyle modification and available lipid-lowering therapies, many patients do not achieve TGs ≤5.65 mmol/L (≤500 mg/dL) and remain at elevated AP risk[5]
- Apolipoprotein C-III (APOC3) is a key regulator of TG-rich lipoprotein metabolism and clearance and represents a validated therapeutic target[3]
- Plozasiran, a hepatocyte-targeted siRNA that reduces hepatic APOC3 synthesis, was evaluated in adults with sHTG in the phase 3 SHASTA-3 and SHASTA-4 trials[6]

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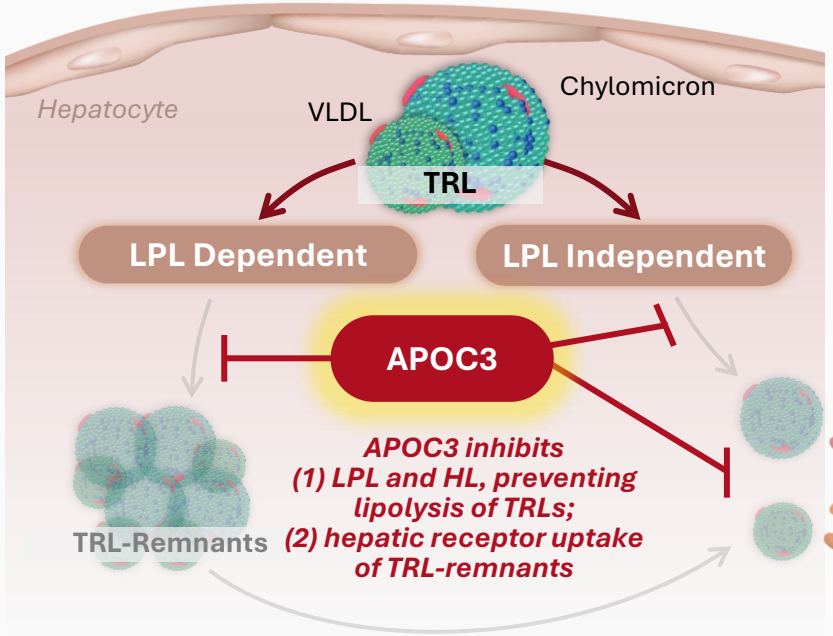
AP, acute pancreatitis; **APOC3**, apolipoprotein C3; **sHTG**, severe hypertriglyceridemia; **TG,** triglycerides.

Background: Plozasiran is an Investigational siRNA Therapeutic Targeting APOC3, a Key Regulator of TG and TRL Metabolism

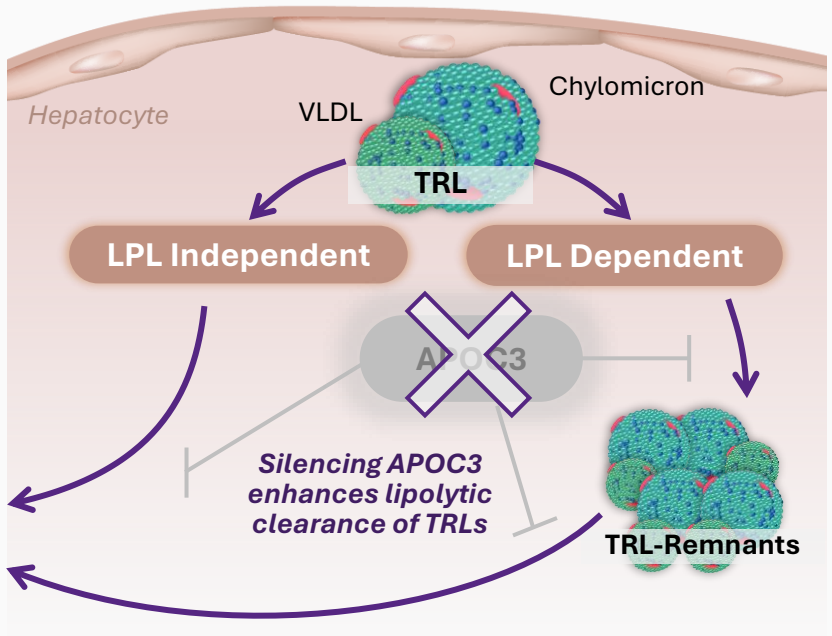
HYPERTRIGLYCERIDEMIA[1,2]

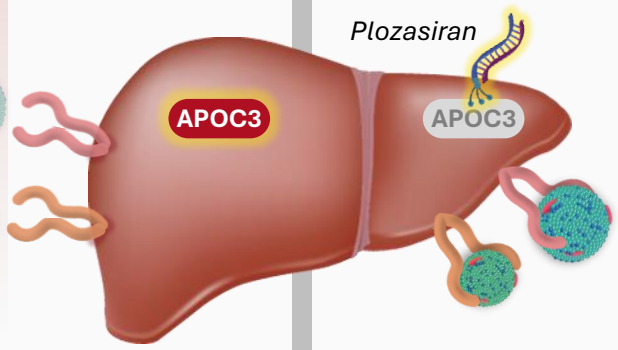
APOC3 inhibits lipolysis and hepatic clearance of TRLs, increasing TGs



PLOZASIRAN[2]

Silencing of APOC3 enhances lipolysis and hepatic clearance of TRLs, reducing TGs

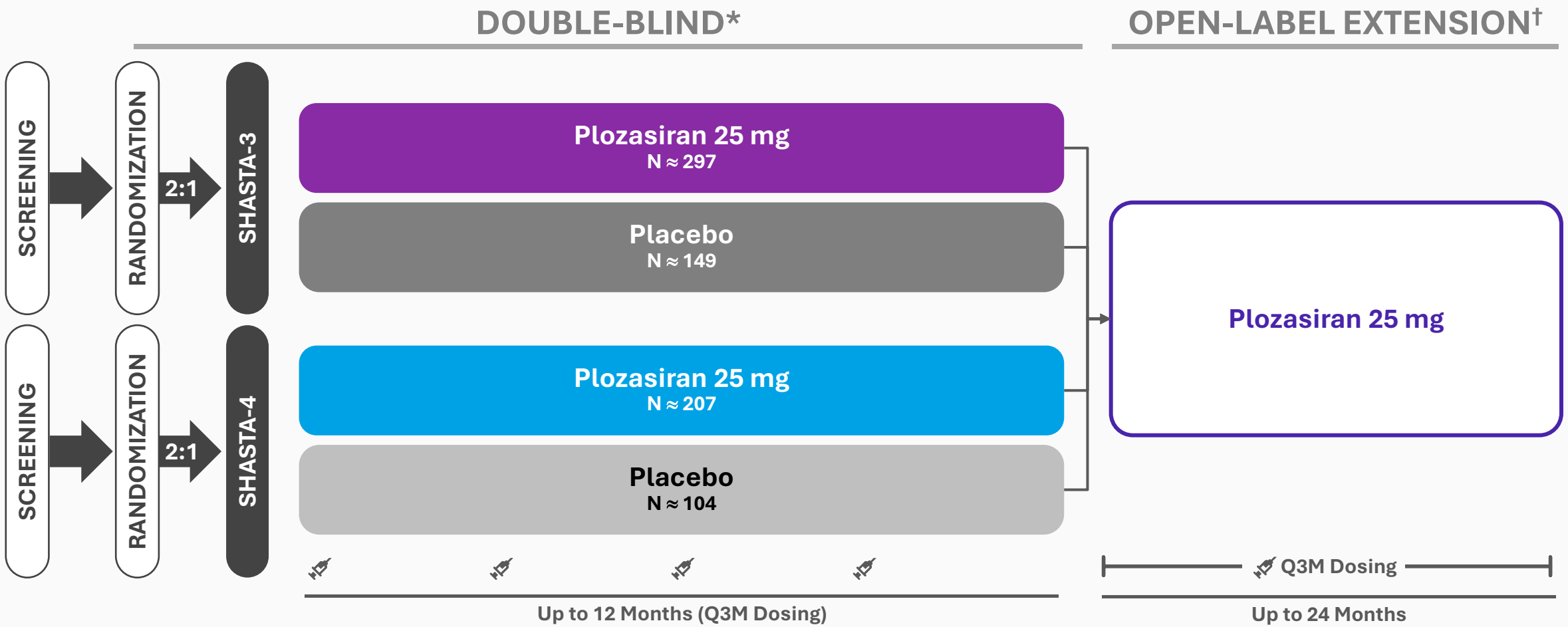




1. Van Zwol W, et al. *J Clin Med*. 2019; 8:1085. **2.** Ballantyne CM, et al. *New Engl J Med*. 2024; Published online: May 28, 2024. DOI: 10.1056/NEJMoa2404143.

APOC3, apolipoprotein C3; **HL**, hepatic lipase; **LPL**, lipoprotein lipase; **siRNA**, small interfering RNA; **TG,** triglycerides; **TRL**, triglyceride rich lipoproteins; **VLDL**, very low-density lipoprotein.

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.

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

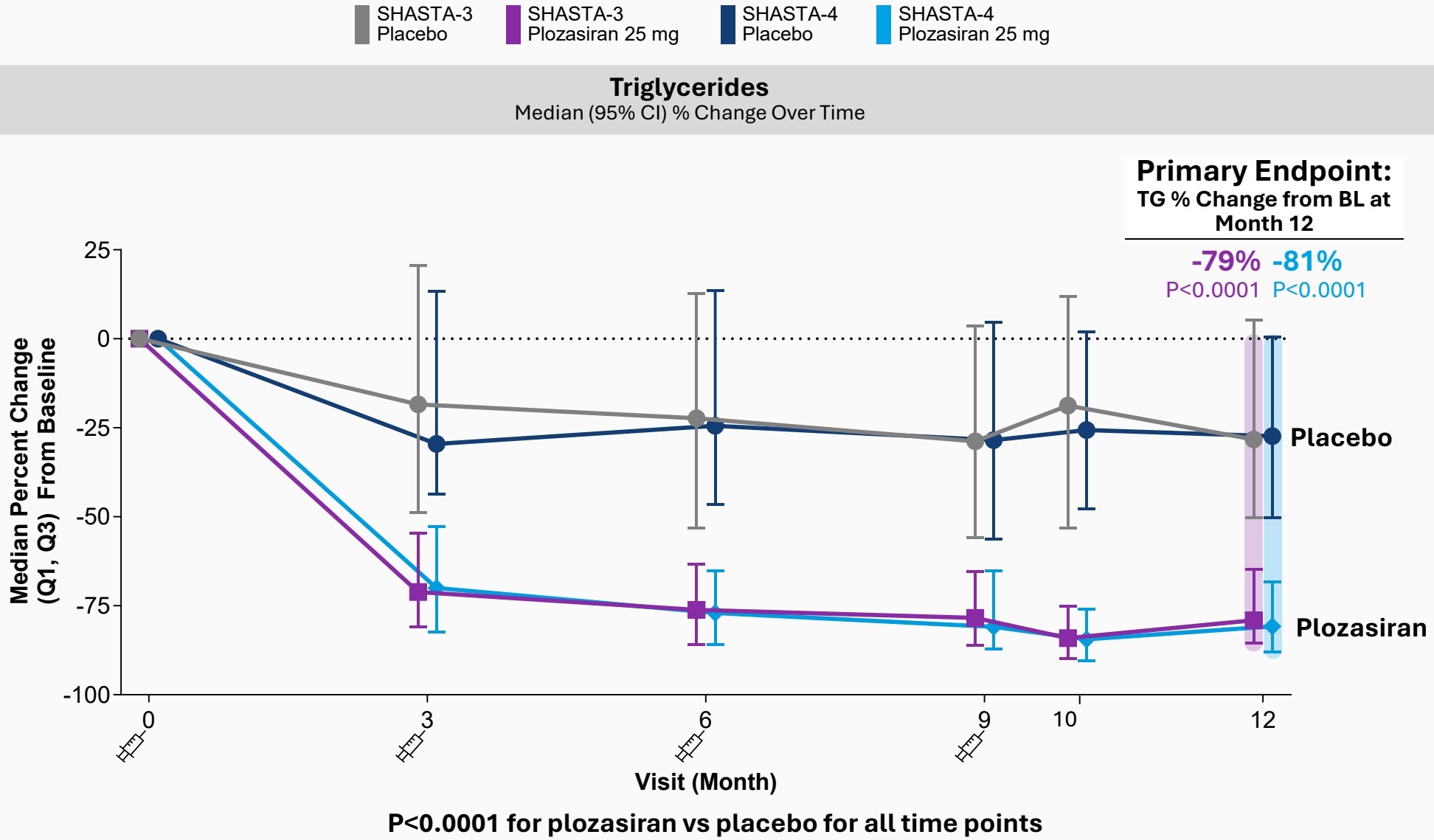
SHASTA 3/4 Baseline Characteristics

Demographics/Characteristic		SHASTA-3 Placebo (n=149)	SHASTA-3 Plozasiran (n=297)	SHASTA-4 Placebo (n=104)	SHASTA-4 Plozasiran (n=207)
Age (years), mean (SD)		51 (12)	52 (12)	53 (12)	53 (11)
Sex at birth, n (%), Male		122 (82)	247 (83)	69 (66)	160 (77)
Race, n (%)	White	109 (73)	223 (75)	87 (84)	184 (89)
	Asian	38 (26)	62 (21)	9 (8.7)	9 (4.3)
	Black or African American	0	3 (1.0)	3 (2.9)	13 (6.3)
Ethnicity, Hispanic, n (%)		33 (22)	57 (19)	21 (20)	39 (19)
BMI (kg/m^2), mean (SD)		30 (4.8)	31 (5.3)	31 (5.4)	32 (4.9)
History of cardiovascular disease, n (%)		37 (25)	104 (35)	35 (34)	68 (33)
History of diabetes mellitus, n (%)		81 (54)	174 (59)	57 (55)	130 (63)
History of AP, n (%)		37 (25)	57 (19)	21 (20)	45 (22)
Triglycerides (mmol/L)[a]	Mean (SD)	9.3 (5.8)	9.4 (5.7)	10.6 (7.7)	10.8 (7.4)
	Median (Q1, Q3)	7.6 (6.2, 11.1)	7.5 (6.1, 10.8)	8.0 (6.3, 12.2)	8.3 (6.4, 12.5)
	≥ 10 mmol/L, n (%)	44 (30)	91 (31)	38 (37)	77 (37)
HbA1c (%)[b], mean (SD)		6.4 (1.1)	6.4 (1.1)	6.4 (1.1)	6.6 (1.2)
TG-lowering therapy, n (%)	Fibrates	94 (63)	185 (62)	55 (53)	127 (61)
	Omega-3 fatty acid	30 (20)	79 (27)	35 (34)	54 (26)
Lipid-lowering therapy, n (%)	Statin	95 (64)	204 (69)	78 (75)	148 (72)
	Ezetimibe	37 (25)	73 (25)	20 (19)	44 (21)
	≥2 therapies	97 (65)	194 (65)	75 (72)	138 (67)

*Data are reported as mean (±SD) unless otherwise noted. [a]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. [b]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.

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

Plozasiran Showed Sustained TG Reductions in SHASTA-3 and 4

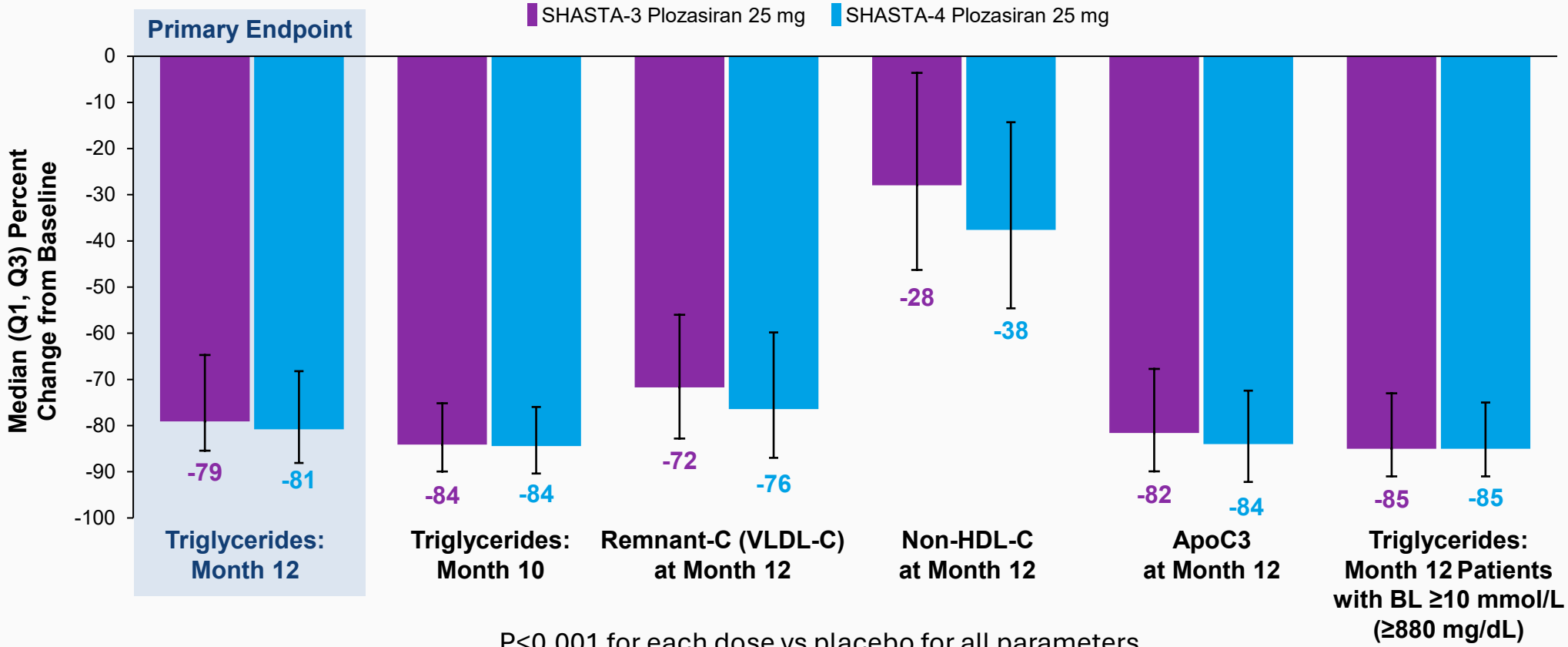


TG Values plotted are median (95% CI). %TG (Q1, Q3): -79% (-65, -85); -81% (-68, -88)

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

Plozasiran Lowered TGs and Other Lipid Parameters Including Remnant-C and Non-HDL-C

% Change in TGs from BL at Month 10 and 12 and Among Patients with BL TG ≥10 mmol/L (≥880 mg/dL) at Month 12
% Change in Remnant-C (VLDL-C), Non-HDL-C, and ApoC3 from BL at Month 12

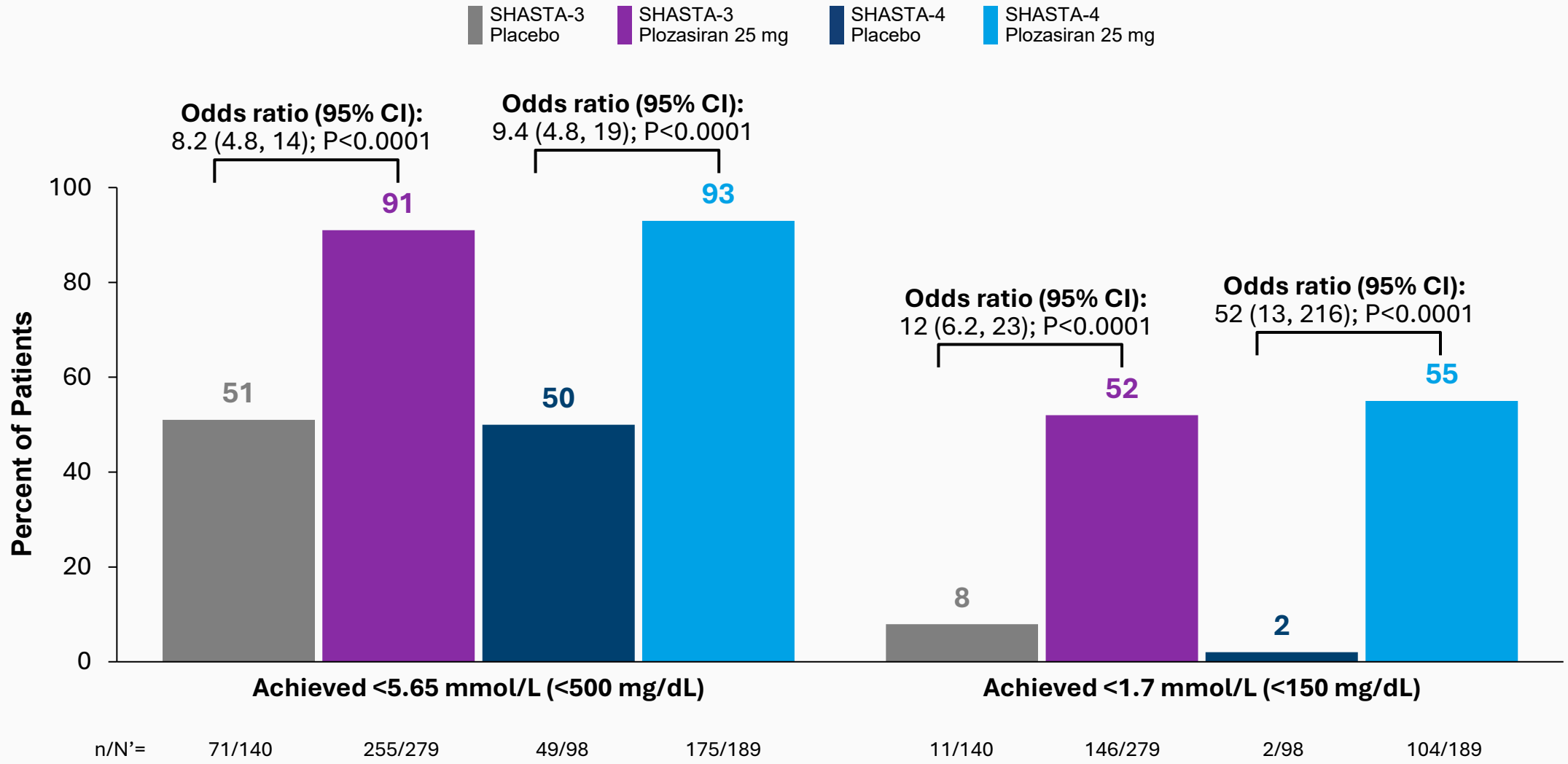


P<0.001 for each dose vs placebo for all parameters

Data are shown as median. Error bars are Q1, Q3.

ApoC3, apolipoprotein C3; **BL**, baseline; **non-HDL-C**, non-high-density lipoprotein cholesterol; **Q1, Q3,** interquartile range; **remnant-C**, remnant cholesterol; **TG**, triglycerides; **VLDL-C**, very low-density lipoprotein cholesterol

Plozasiran Lowered TG Levels Below Clinically Relevant Thresholds at 12 Months



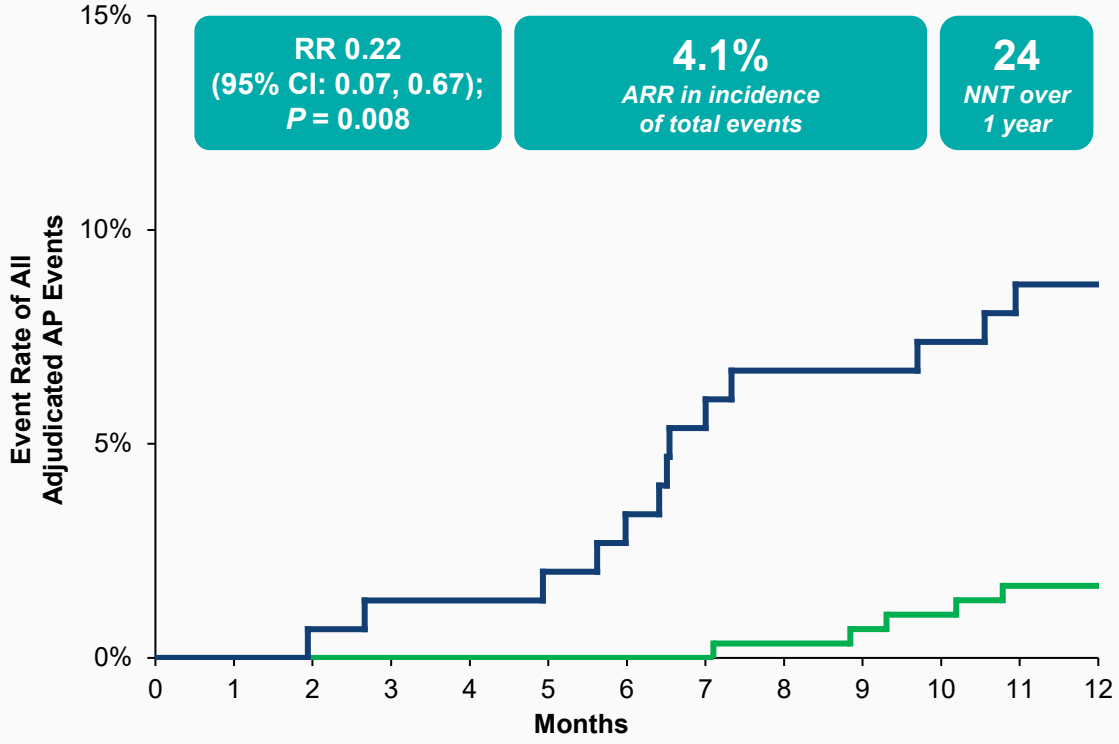
%=100*n/N', where N' is the number of patients available at the specific visit.

CI, confidence interval; **TG**, triglycerides.

Plozasiran Reduced AP Event Frequency and Time to First AP Event in the Broad sHTG Population

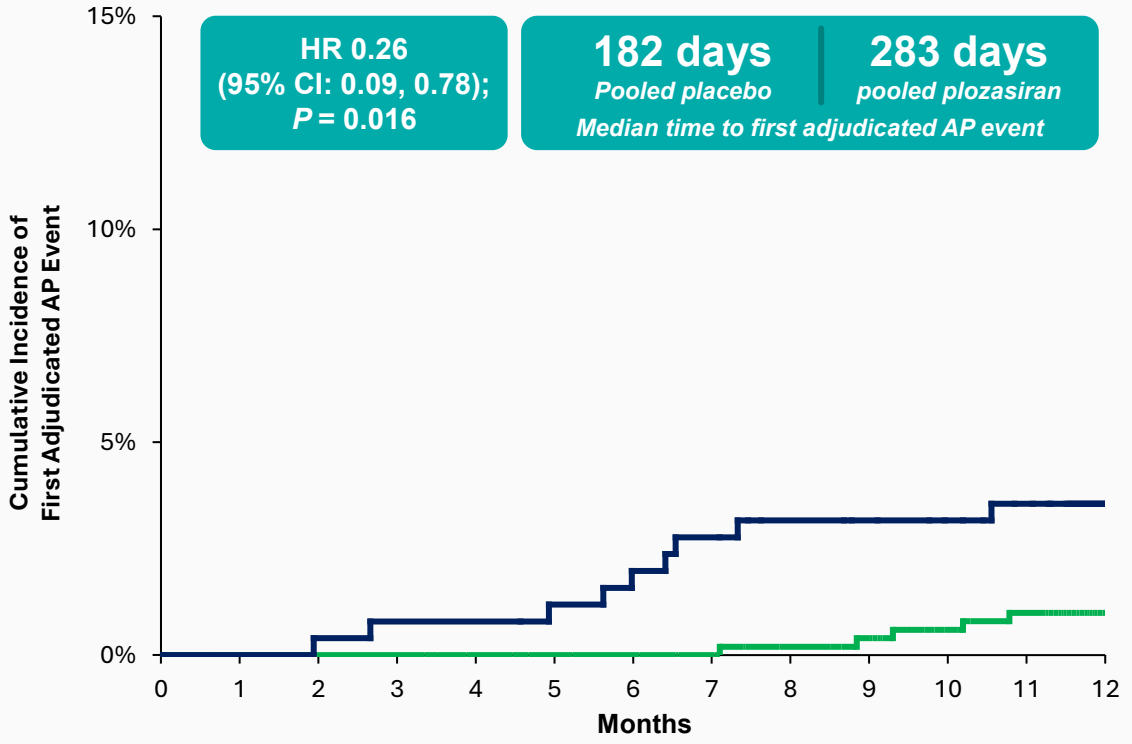
Pooled SHASTA-3/4 Placebo Pooled SHASTA-3/4 Plozasiran 25 mg

Adjudicated AP Event Rate: Total AP Events



No. at Risk													
Pooled Placebo	253	252	251	250	250	248	246	244	239	237	234	230	62
Pooled Plozasiran	504	503	502	502	499	497	496	493	488	485	473	468	137

Time to First AP Event

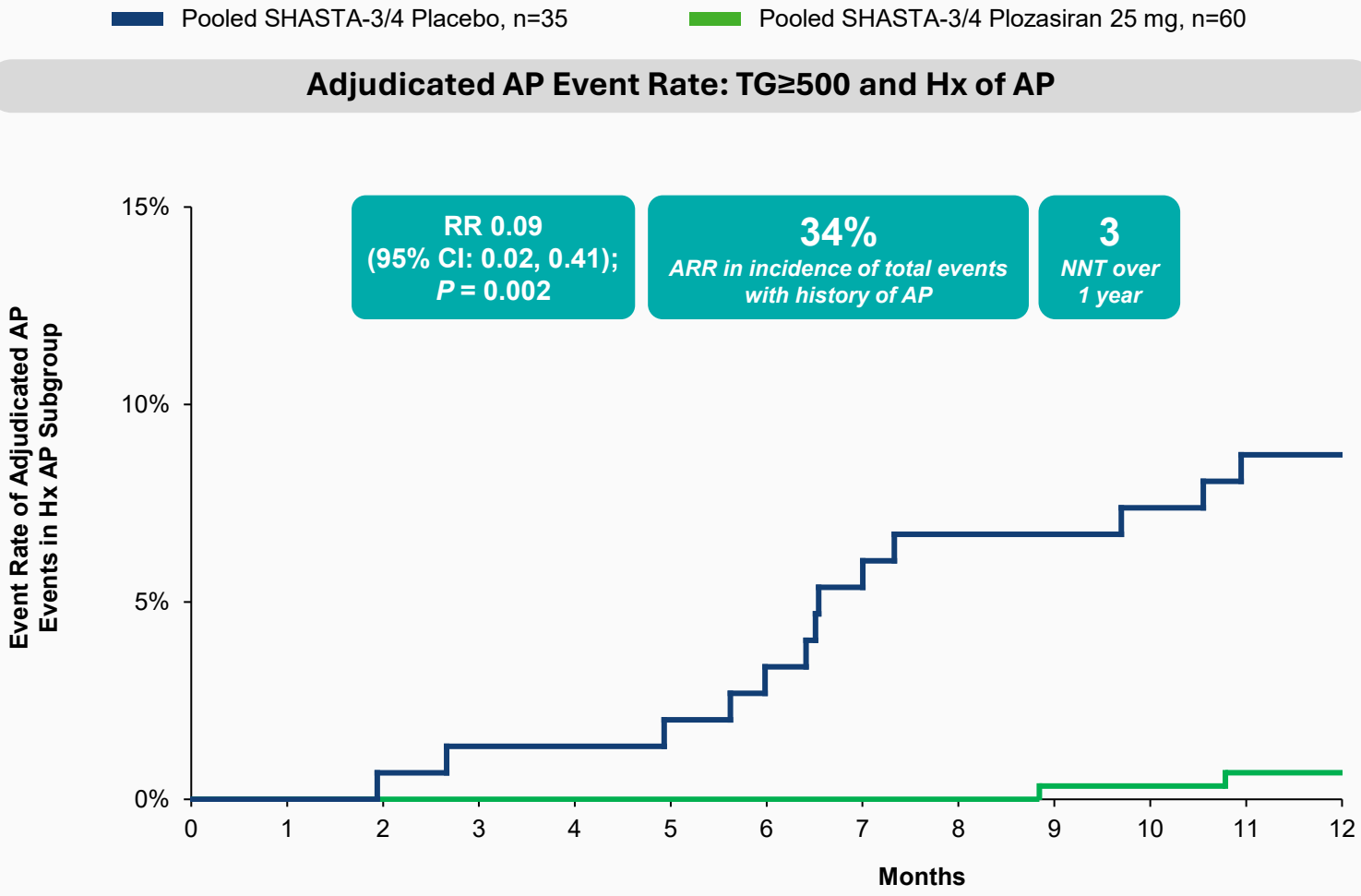


	253	252	251	250	250	248	246	244	239	237	234	230	62
	504	503	502	502	499	497	496	493	488	485	473	468	137

Positively adjudicated AP events included documented, probable, and possible AP; Absolute risk reduction (ARR) is the difference in event rates between treatment and control groups. Number needed to treat (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.

ARR, absolute risk reduction; **AP**, acute pancreatitis; **CI**, confidence intervals; **HR**, hazard ratio; **NNT**, number needed to treat; **RR**, risk ratio; **TG**, triglycerides.

Plozasiran Reduced Frequency of AP Events in High-Risk Subgroups (TG ≥500+Hx AP)



In highest risk subgroup, TG ≥10 mmol/L (880 mg/dL) with a Hx of AP Plozasiran reduced AP event rate by 100%*

Positively adjudicated AP events included documented, probable, and possible AP. *Data not shown..

ARR, absolute risk reduction; **AP**, acute pancreatitis; **CI**, confidence intervals; **HR**, hazard ratio; **Hx**, history; **NNT**, number needed to treat; **RR**, risk ratio; **TG**, triglycerides.

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 clinically meaningful changes in platelet counts observed
- No meaningful 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

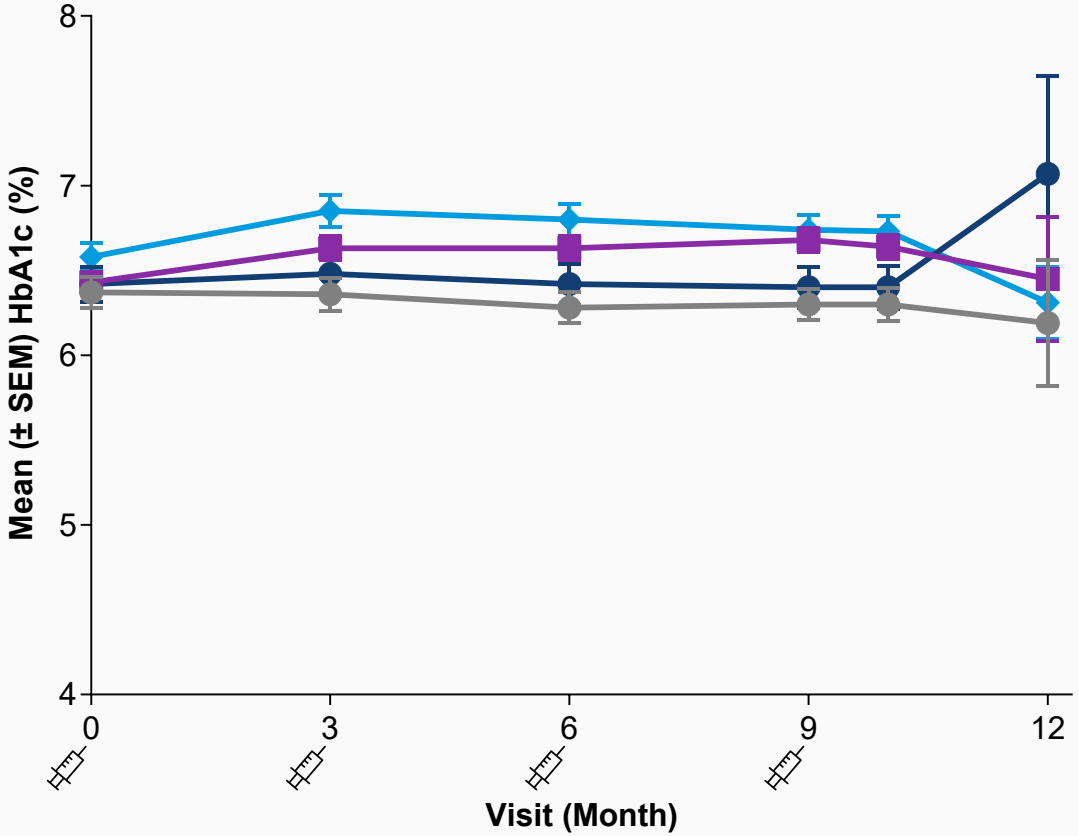
% = 100 x n/N. *SAE is an adverse event that results in death, is life-threatening or requires hospitalization. There were two SAE CV deaths (cardiogenic shock following acute MI and sudden cardiac death in the setting of extensive underlying CV disease) and one death due to chronic myelomonocytic leukemia; 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.

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.

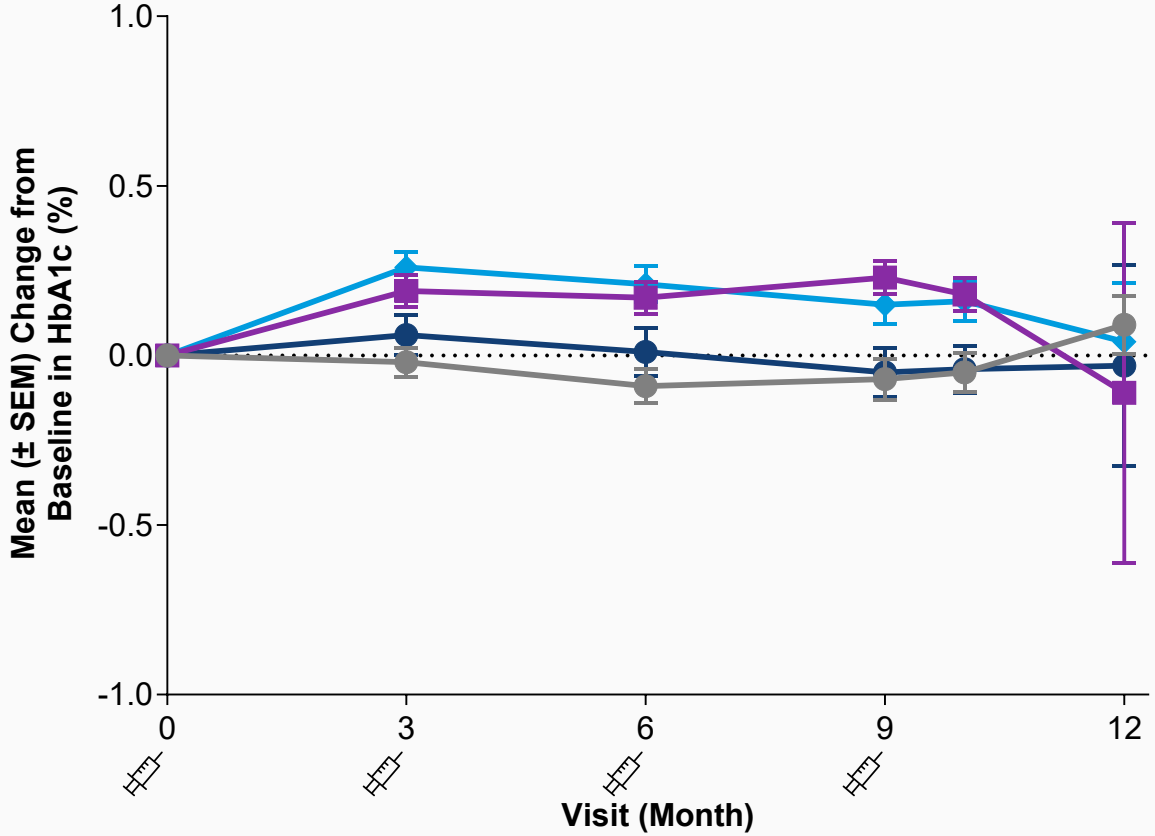
No Worsening of HbA1c Over Time

SHASTA-3 Placebo
SHASTA-3 Plozasiran 25 mg
SHASTA-4 Placebo
SHASTA-4 Plozasiran 25 mg

Glycemic Control: HbA1c (All Patients)
Mean (±SEM) Absolute Value Over Time



Glycemic Control: HbA1c (All Patients)
Mean (±SEM) Absolute Change from Baseline



HbA1c, glycosylated hemoglobin; **SEM**, standard error of mean.

Conclusions

- Plozasiran administered every 3 months reduced TG and AP events in patients with sHTG on conventional background therapy and diet
- TG reductions of ~80% were sustained across the dosing cycle, evident as early as 3 months, and resulted in ~80% AP risk reduction with plozasiran
- >90% of patients treated with plozasiran achieved TGs below thresholds of 5.6 mmol/L (500 mg/dL) and >50% achieved TGs below 1.7 mmol/L (150 mg/dL)
- Plozasiran reduced risk of AP across the TG spectrum including in high-risk subgroups; by 91% in history of AP subgroup (TG ≥500+Hx AP) and by 100% in highest risk sub-group, [TG ≥10 mmol/L (880 mg/dL) with a history of AP]
- No new safety signals identified, consistent with prior experience
- The findings support the value of APOC3-targeted therapy with plozasiran for preventing AP in sHTG

Disclosures

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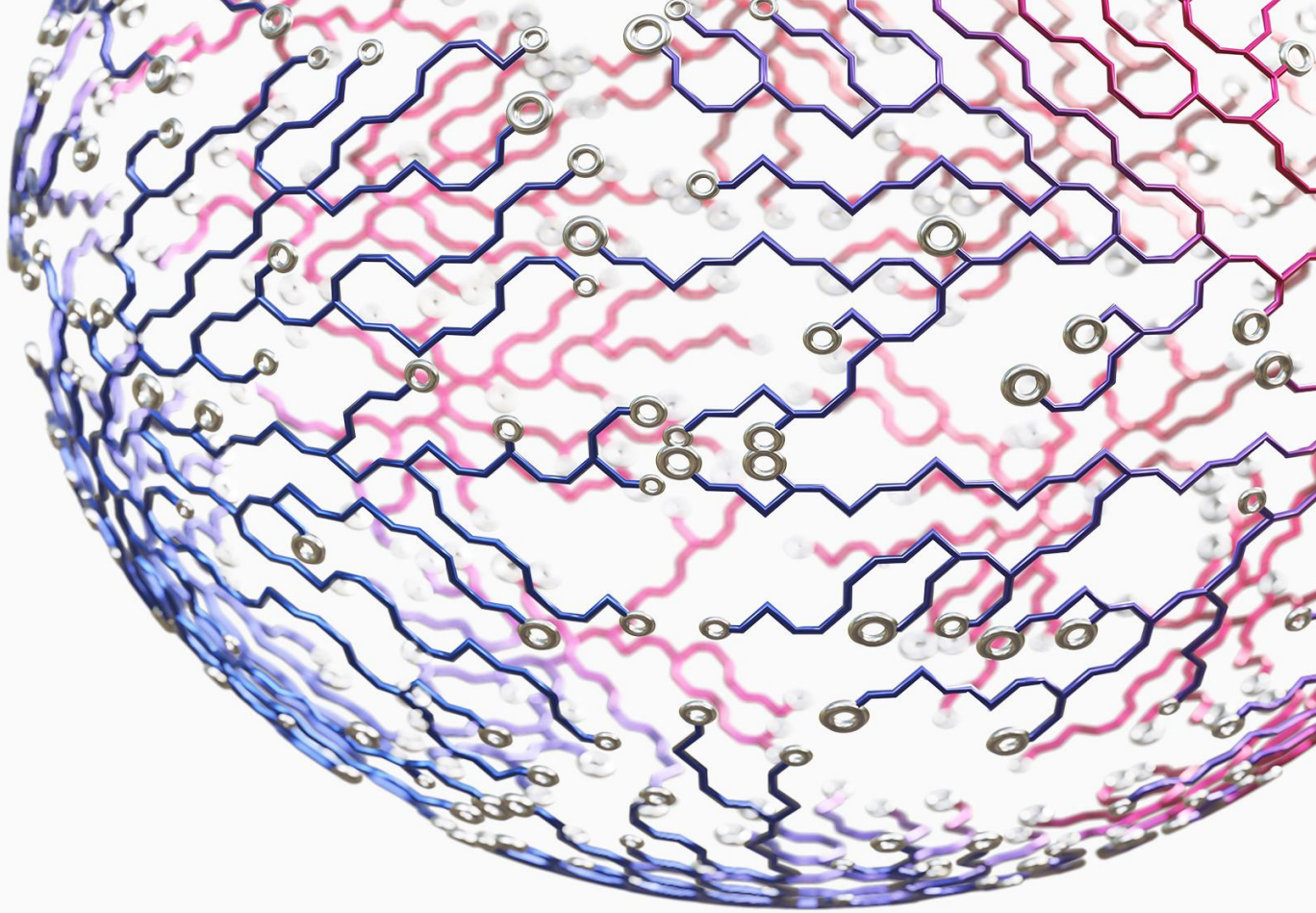

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