European Society of Cardiology Congress 2026
Investor Webcast

August 31, 2026

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European Society of Cardiology Congress 2026

Welcome and Introductions

Vince Anzalone, CFA
Senior Vice President, Investor Relations

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Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, entering into new collaborations and achieving existing projected milestones, rapid technological changes in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

Key Opinion Leader

Gerald F Watts, MD

University of Western Australia, Perth

Gerald Watts trained at Imperial & King's College, London University, and was a scholar at Wolfson College, Oxford University. He is a senior consultant physician, specializing in the rapidly developing field of cardiometabolic medicine, and current chair of the Familial Hypercholesterolemia Australasia Network. He leads the Cardio-metabolic Service in the Departments of Cardiology and Internal Medicine at Royal Perth Hospital and is Winthrop Professor of Cardio-metabolic Medicine in the University of Western Australia.

Research interests include fundamental and applied aspects of lipid disorders and cardiovascular prevention, and improving healthcare delivery for patients with high-risk dyslipidemias, in particular familial hypercholesterolemia and hyperchylomicronemia.

Key Opinion Leader

Børge Nordestgaard, MD

Copenhagen University Hospital, Copenhagen

Børge Nordestgaard is Professor and Chief Physician at Herlev og Gentofte Hospital, Copenhagen University Hospital, University of Copenhagen.

Prof. Nordestgaard has studied and worked in Copenhagen, New York, and London. He has for more than 30 years continued his interest in the pathogenesis, diagnosis and treatment of familial hypercholesterolemia, hyperlipidemia, atherosclerosis and cardiovascular disease, and has written extensively on these conditions. He is chairing the Copenhagen General Population Study and is also a steering committee member of the Copenhagen City Heart Study and of several randomised intervention trials.

Agenda

Topic	Presenter
Introduction	Vince Anzalone, CFA
Overview of Severe Hypertriglyceridemia	Jennifer Hellawell, MD
SHASTA-3 and SHASTA-4 Full Results	Gerald Watts, MD University of Western Australia
SHASTA-3 and SHASTA-4 Discussion	Børge Nordestgaard, MD Copenhagen University Hospital
Commercialization Efforts	Andy Davis, MBA
Key Takeaways	Vince Anzalone, CFA
Q&A	Panel

Bringing RNA Interference to Patients

Arrowhead Pharmaceuticals is a **RNAi therapeutics platform company** with a **broad pipeline** of **wholly owned and partnered** candidates and achieved its **first commercial launch in 2025**

First Commercial Launch in 2025

- **REDEMPLO® approved in US, European Union, Canada, Australia, and China** to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS)
- Potential **Multi-billion-dollar** opportunity across future indications
- Potential for **additional independent and partner launches** in coming years

Broad Pipeline

- **20+ clinical stage programs** with majority wholly owned
- Mix of **early, mid, and late-stage** candidates targeting **rare and high prevalence diseases**
- Growing pipeline with **2-3 new clinical programs planned per year**

Proprietary Platform

- **Targeted RNAi Molecules** platform (**TRiM™**) designed for **deep and durable gene silencing**
- **Fulfilling the promise** of bringing RNAi therapeutics to diseases **outside of the liver**
- Potential to be **best-in-class** across several tissue types

Financial Resources

- **Strong balance sheet** with funding to multiple potential commercial launches
- **Additional non-dilutive capital expected** from Madrigal, Sarepta, Amgen, Takeda, GSK, Novartis, and Royalty Pharma as milestones and royalties are earned

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TRiM™ Platform Enables Delivery to Seven Cell Types

Liver	Lung	Skeletal Muscle	CNS	Adipose	Ocular	Cardio-myocyte
Strong clinical validation	Deep lung clinical validation (RAGE)	Early clinical stage	Early clinical stage	Early clinical validation	Preclinical Stage	Preclinical Stage

Arrowhead is Fulfilling the Promise of Bringing RNAi Throughout the Body

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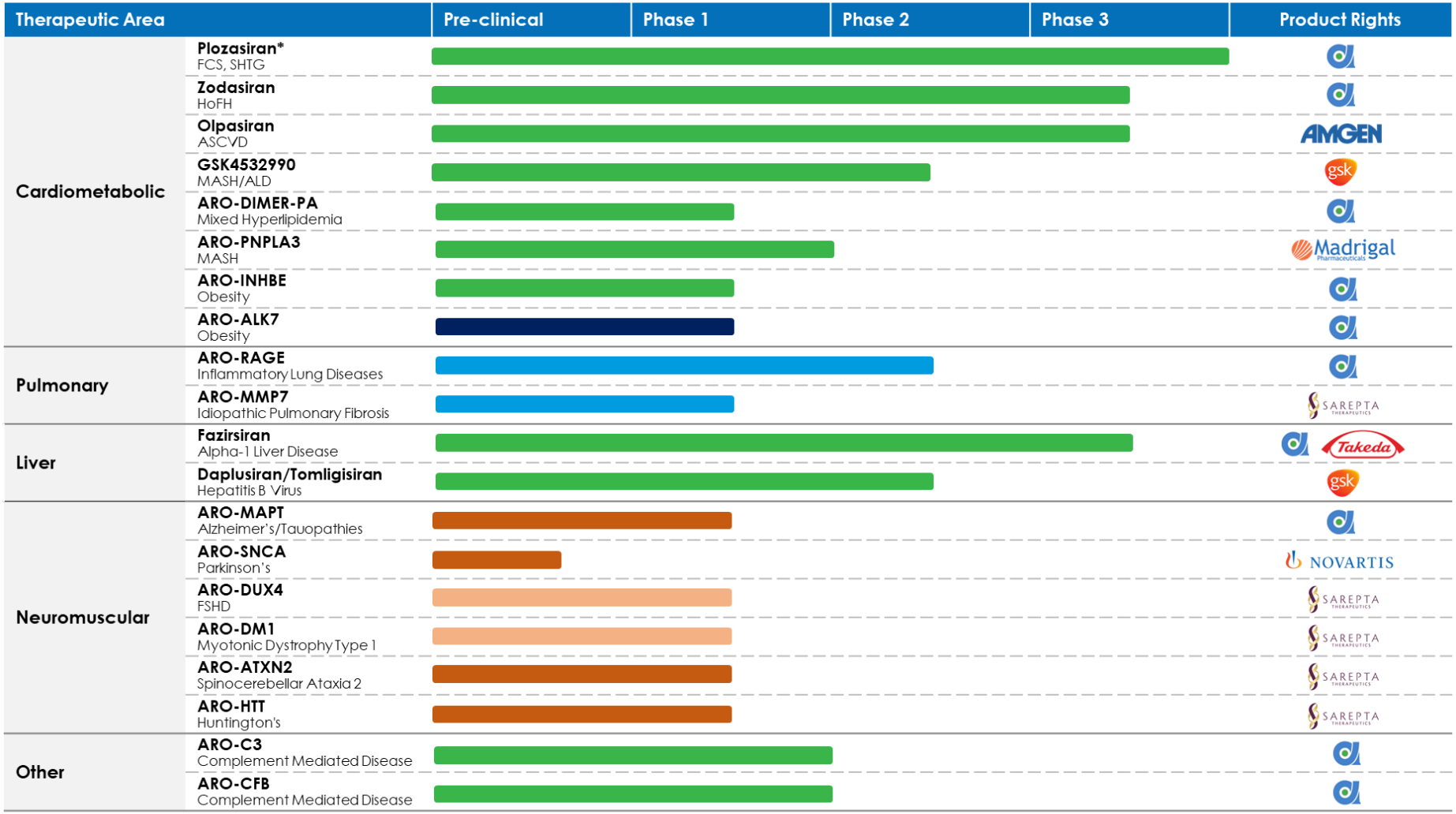
Robust Pipeline with Long-term Growth Opportunities



*Plozasiran is approved as REDEMPLO in U.S. for FCS but has not been approved for SHTG
**Sanofi holds product rights to plozasiran and ARO-DIMER-PA in Greater China only

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Plozasiran Paradigm Shifting SHASTA-3 and SHASTA-4 Results

- Triglyceride **(TG) reductions of ~80%** across the sHTG spectrum, with more than **90% achieving TG levels below risk thresholds** for acute pancreatitis (AP)
- Cumulative **AP events reduced by 78%** with a **100% reduction in the highest-risk** subgroup, patients with TG above 880 mg/dL and a prior history of AP
- **Favorable safety and tolerability profile**, with overall treatment-emergent adverse events similar between plozasiran and placebo groups
- **Accepted in Major Medical Journal,** more details to follow

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Overview of Severe Hypertriglyceridemia

Jennifer Hellawell, MD, FACC
Vice President, Clinical Development

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sHTG Represents a Spectrum of Elevated Triglycerides

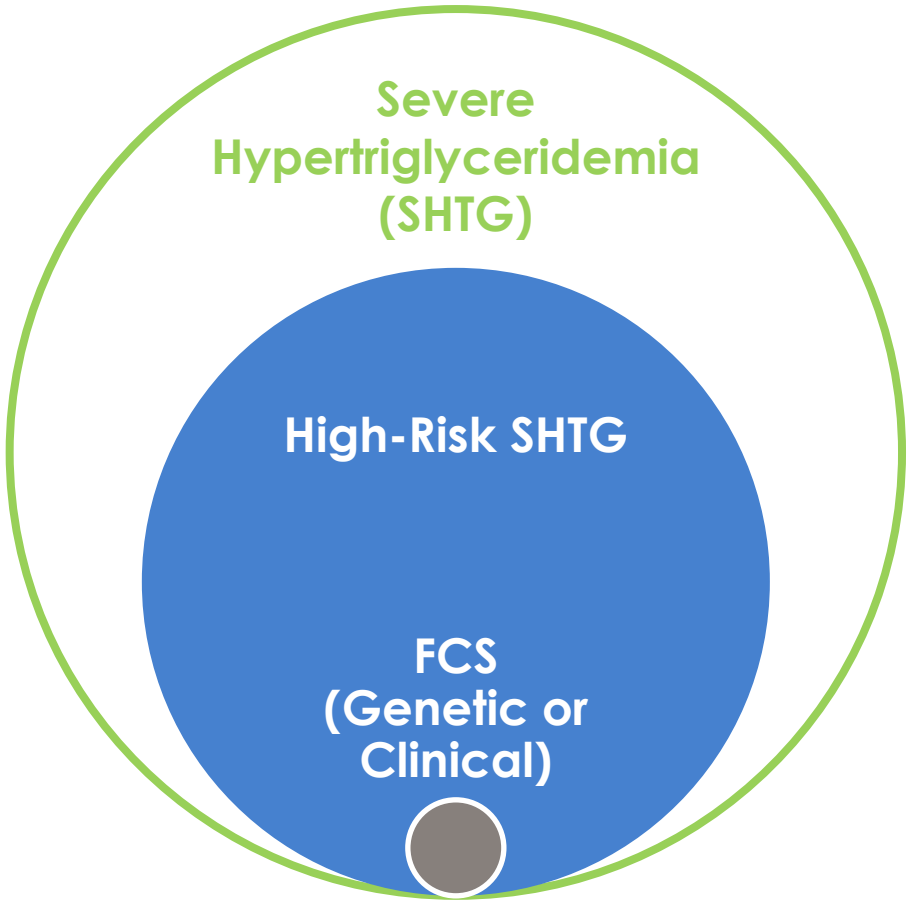


Figure Not to Scale

SHTG

- TGs ≥ 500 mg/dL
- >3+ million people
- Elevated Risk of AP

High-Risk SHTG

- TGs ≥ 880 mg/dL or ≥ 500 mg/dL With Prior AP History
- ~1 million people
- Higher Risk of AP

FCS (Genetic or Clinical)

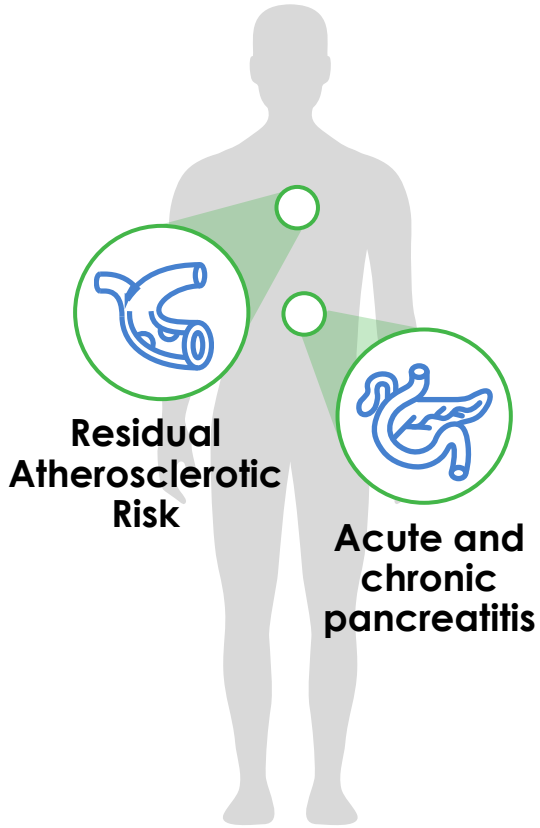
- Persistently Elevated TGs ≥ 880 mg/dL
- Prevalent Prior History of AP
- Potentially 6500+ people
- Extremely High Risk of AP

Source: Nemeth, *Journal of Clinical Medicine* 2022; Rabacchi, *Atherosclerosis* 2015; Company Estimates

sHTG is a Common & Grievous Disease with High Unmet Need

sHTG is a Common and Grievous Disease

- The patient journey usually evolves from hidden genetic and/or metabolic risk factors to sudden acute crises prompting ER visits
- Attacks of acute pancreatitis (AP) can bring excruciating abdominal pain, nausea, vomiting, inability to eat and ICU stays
- After stabilization, these acute crises are followed by intensive chronic lifestyle and medical adjustments, but many patients get lost in transitions of care to the outpatient setting



~ 1 : 100 Prevalence

sHTG Patients at Risk Despite Available Therapies

- Extreme lifestyle modifications (cessation of alcohol consumption, reduced fat and carbohydrates) weight loss, and blood sugar control are the most effective ways to lower TG levels
- Adhering to these regimens is challenging for patients and impairs quality of life
- Conventional therapies, including fibrates, omega-3 fatty acids, and statins only modestly lowers TG levels and do not lower risk of AP

Source: Mach F, et al. *Eur Heart J*. 2025 Nov 7;46(42):4359-4378. Kessler AS, et al. *J Clin Lipidol*. 2025 Jul-Aug;19(4):931-941.

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SHASTA-3 and SHASTA-4 Study Results

Gerald Watts, MD
University of Western Australia, Perth

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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, 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]

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Presented at the European Society of Cardiology (ESC) Congress | August 28-31, 2026 | Munich, Germany

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 factors and secondary causes, such as obesity and type 2 diabetes[3,4]
- Despite lifestyle changes and current lipid-lowering therapies, many patients do not achieve treatment goals (TGs ≤5.65 mmol/L [≤500 mg/dL]) with an elevated risk of AP[5]
- Apolipoprotein C-III (APOC3) is a key regulator of TG-rich lipoprotein metabolism and 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]

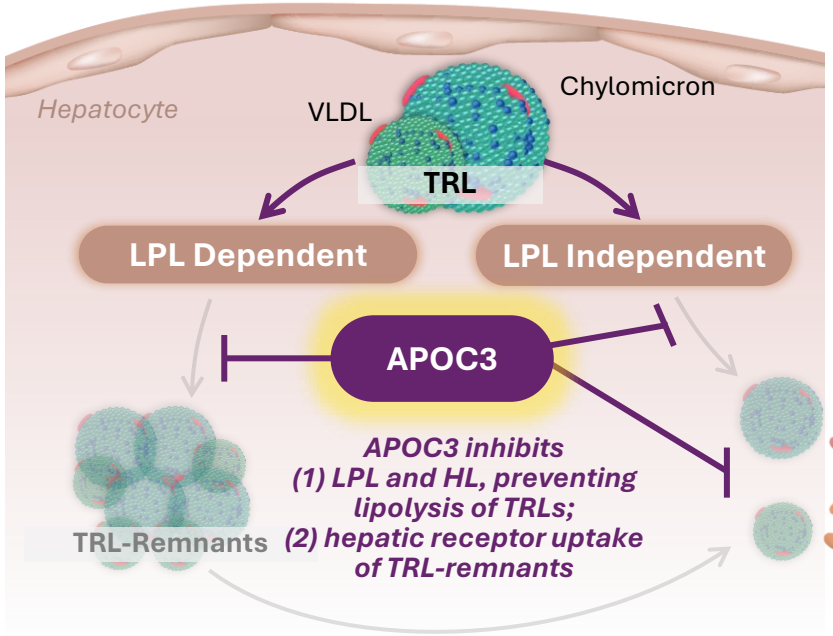
1. Hansen SEJ, et al. *Clin Chem* 2023;69(10):1132–1144. (In eng). DOI: 10.1093/clinchem/hvad094. **2.** Varbo A, Nordestgaard BG. *Eur Heart J* 2021;42(47):4833–4843. DOI: 10.1093/eurheartj/ehab293. **3.** Packard CJ, et al. *Cardiovasc Res* 2024;119(18):2843–2857. (In eng). DOI: 10.1093/cvr/cvad177. **4.** Filtz A, et al. *Am J Prev Cardiol* 2024;18:100648. DOI: https://doi.org/10.1016/j.ajpc.2024.100648. **5.** Berglund L, et al. *J Clin Endocrinol Metab* 2012;97(9):2969–89. (In eng). DOI: 10.1210/jc.2011-3213. **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.

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

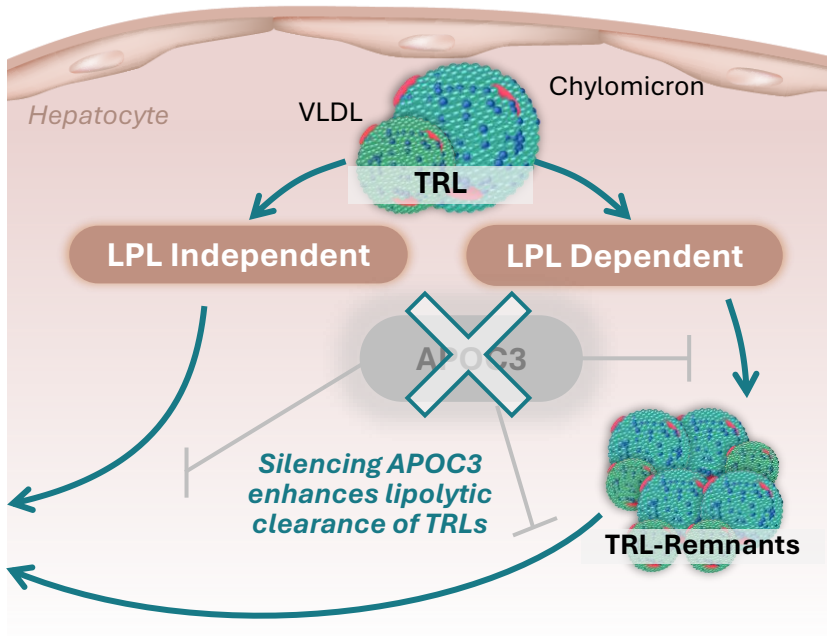
HYPERTRIGLYCERIDEMIA[1,2]

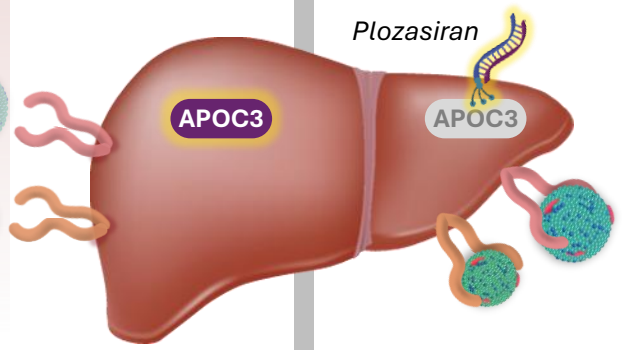
APOC3 inhibits lipolysis and hepatic clearance of TRLs, increasing TGs



PLOZASIRAN[2]

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

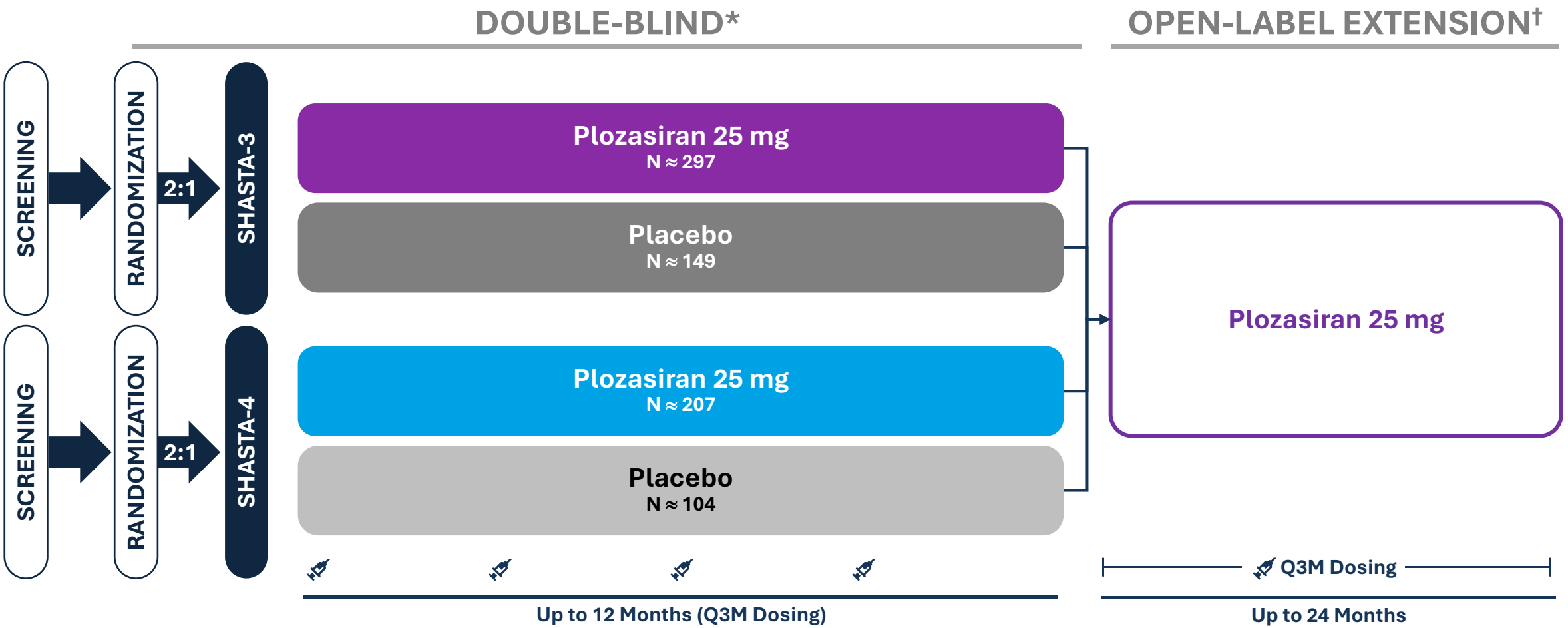




1. Van Zwol W, et al. *J Clin Med*. 2019; 8:1085. **2.** Ballantyne CM, et al. *New Engl J Med*. 2024; Published online: May 28, 2024. DOI: 10.1056/NEJMoa2404143.

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.

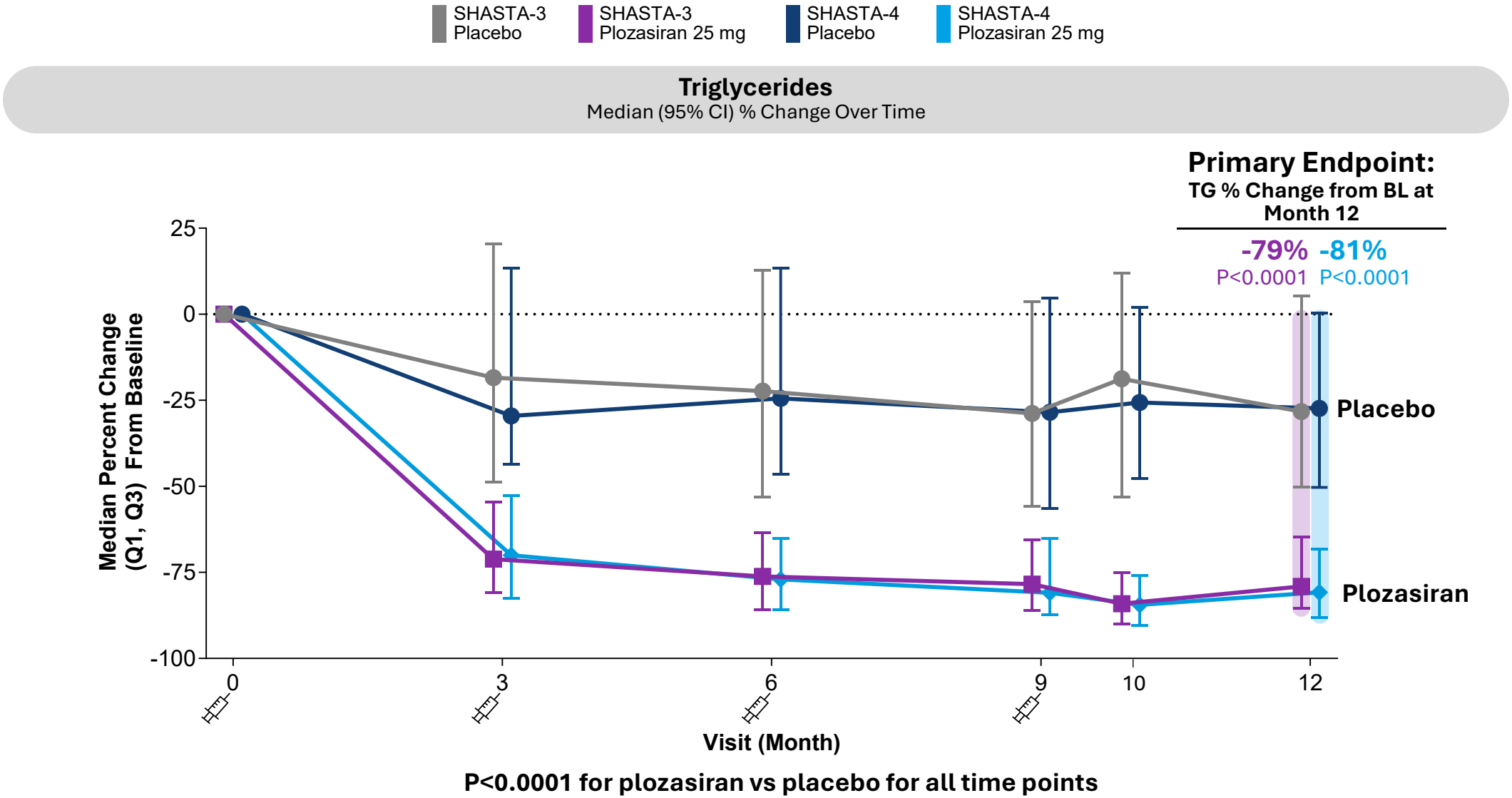
SHASTA 3/4 Baseline Characteristics

Demographics/Characteristic		SHASTA-3		SHASTA-4	
		Placebo (n=149)	Plozasiran (n=297)	Placebo (n=104)	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

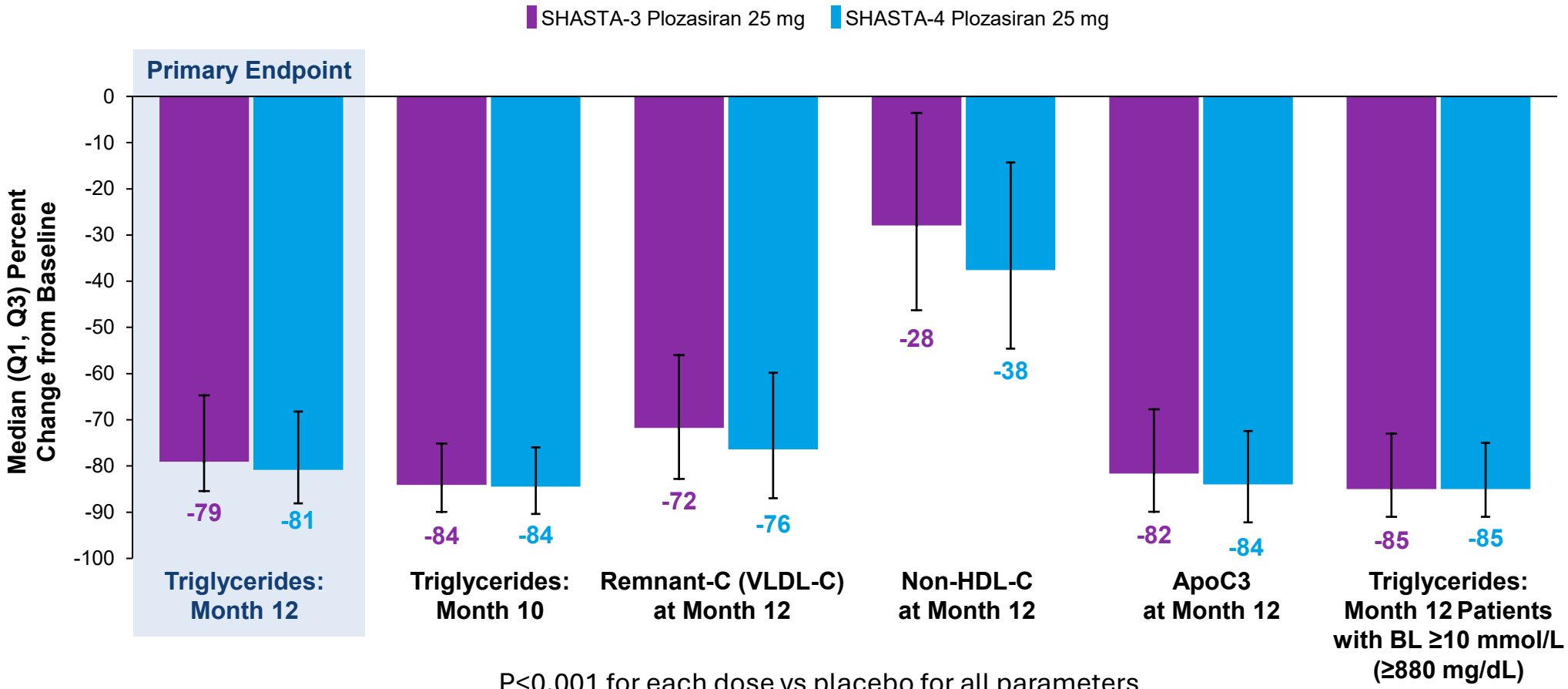


TG Values plotted are median (95% CI). %TG (Q1, Q3): -79% (-65, -85); -81% (-68, -88)

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

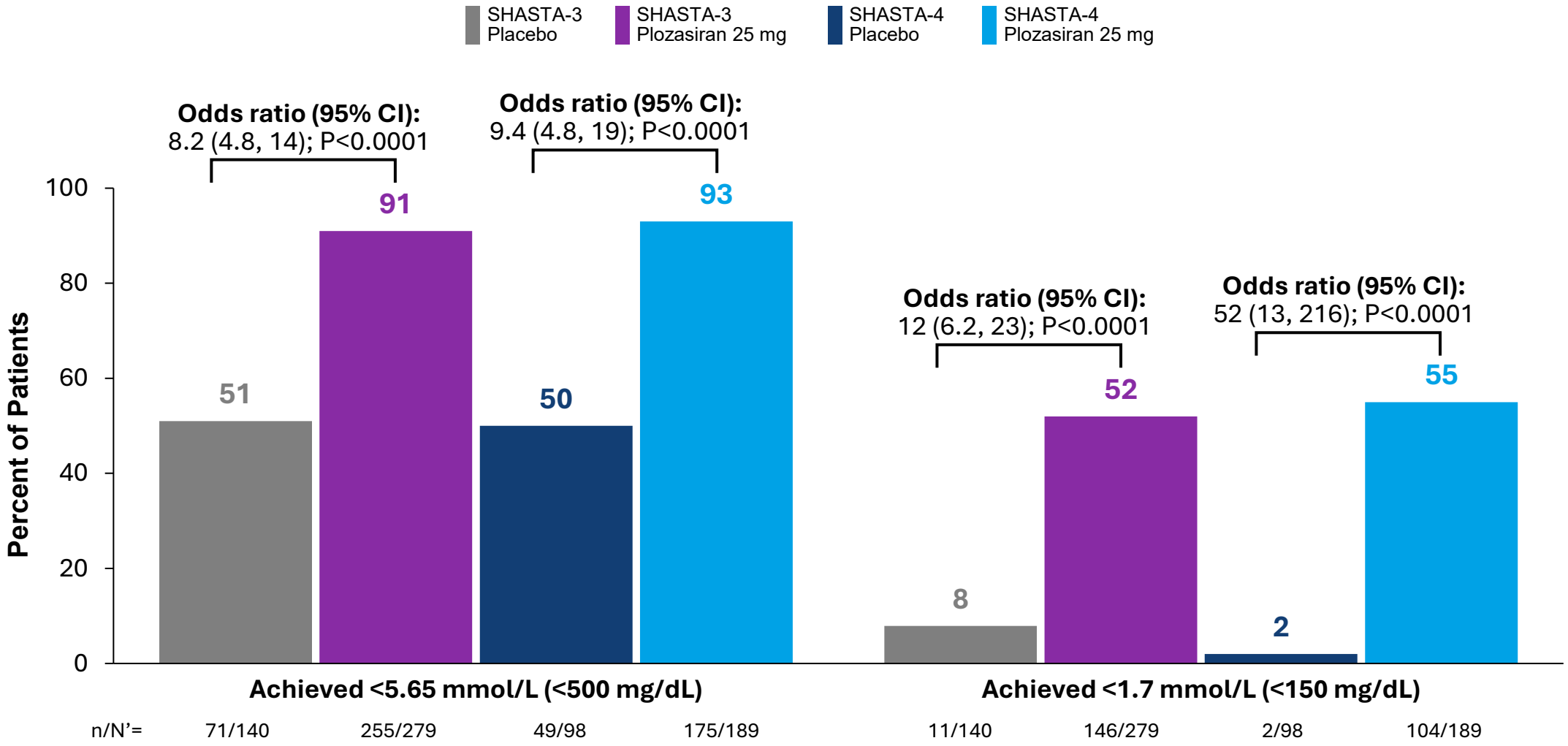


P<0.001 for each dose vs placebo for all parameters

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



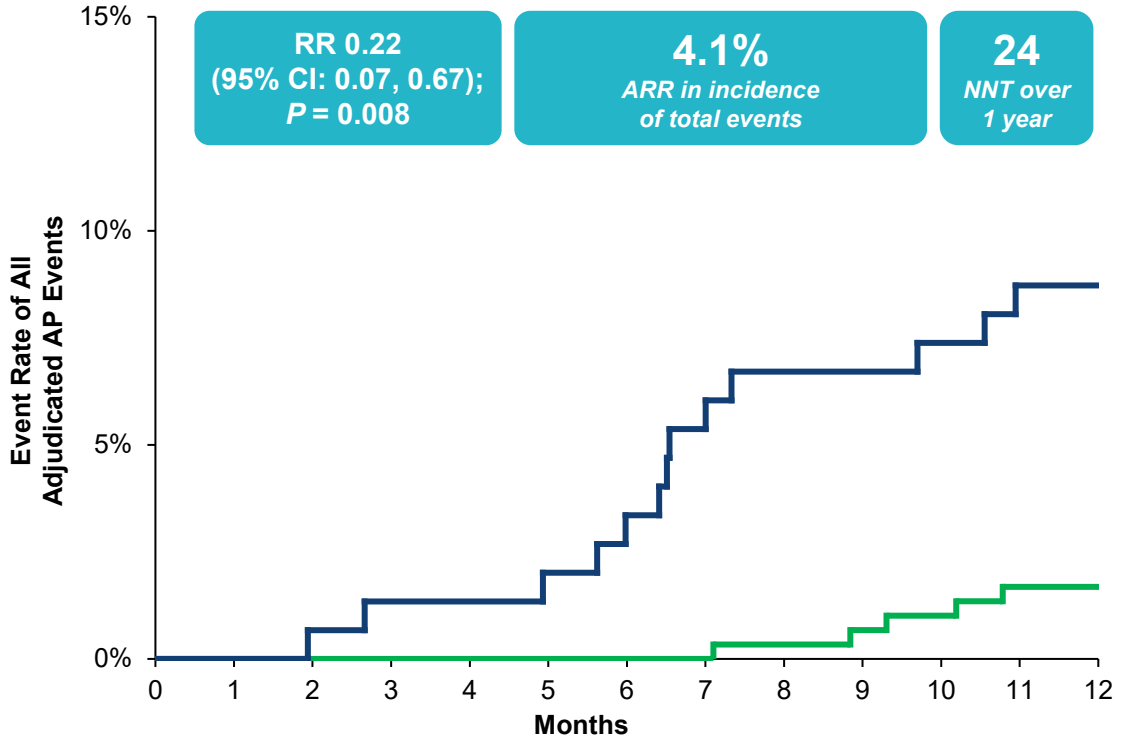
%=100*n/N', where N' is the number of patients available at the specific visit.

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

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

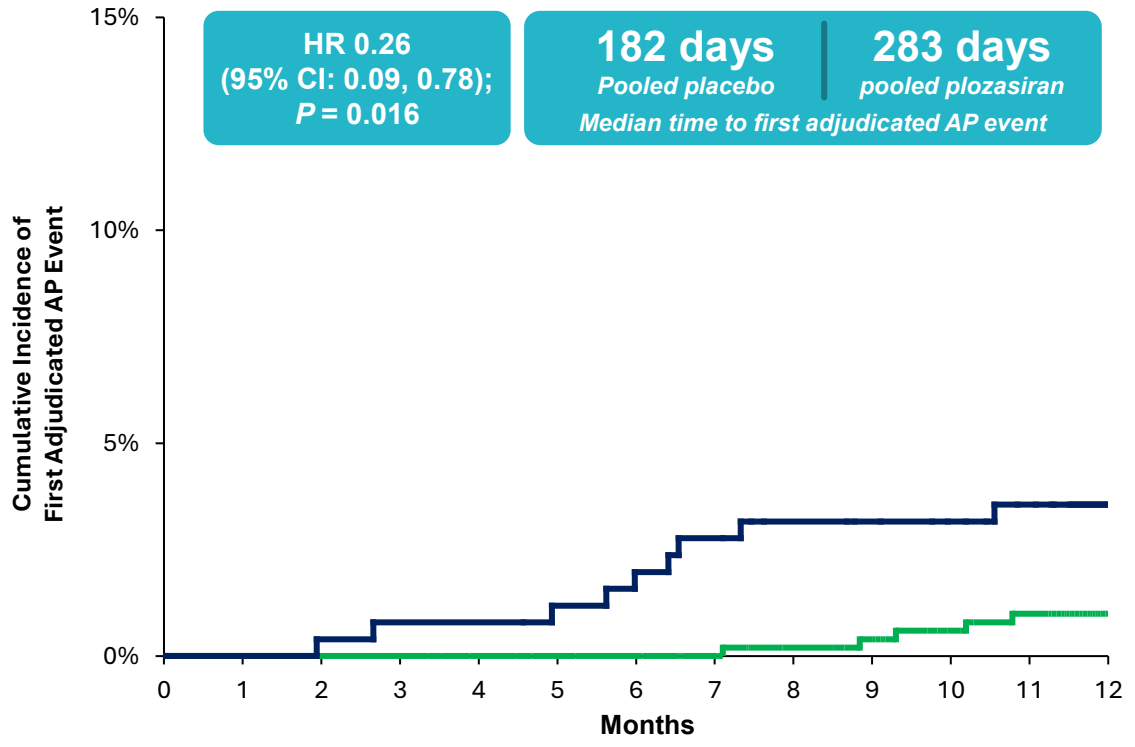
Pooled SHASTA-3/4 Placebo Pooled SHASTA-3/4 Plozasiran 25 mg

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

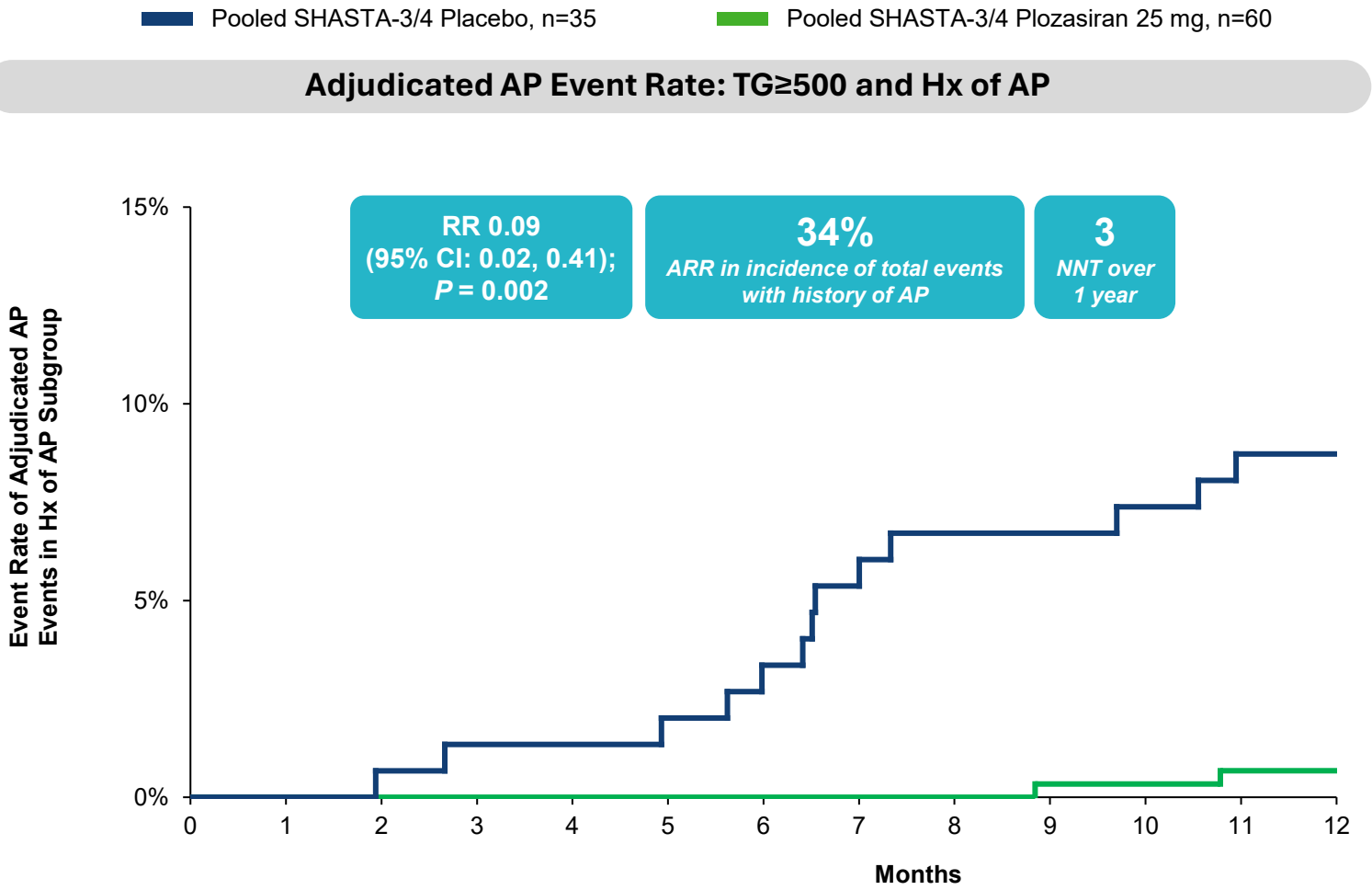


	253	252	251	250	250	248	246	244	239	237	234	230	62
	504	503	502	502	499	497	496	493	488	485	473	468	137

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. *Kaplan Meier curve not shown for this subgroup.

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

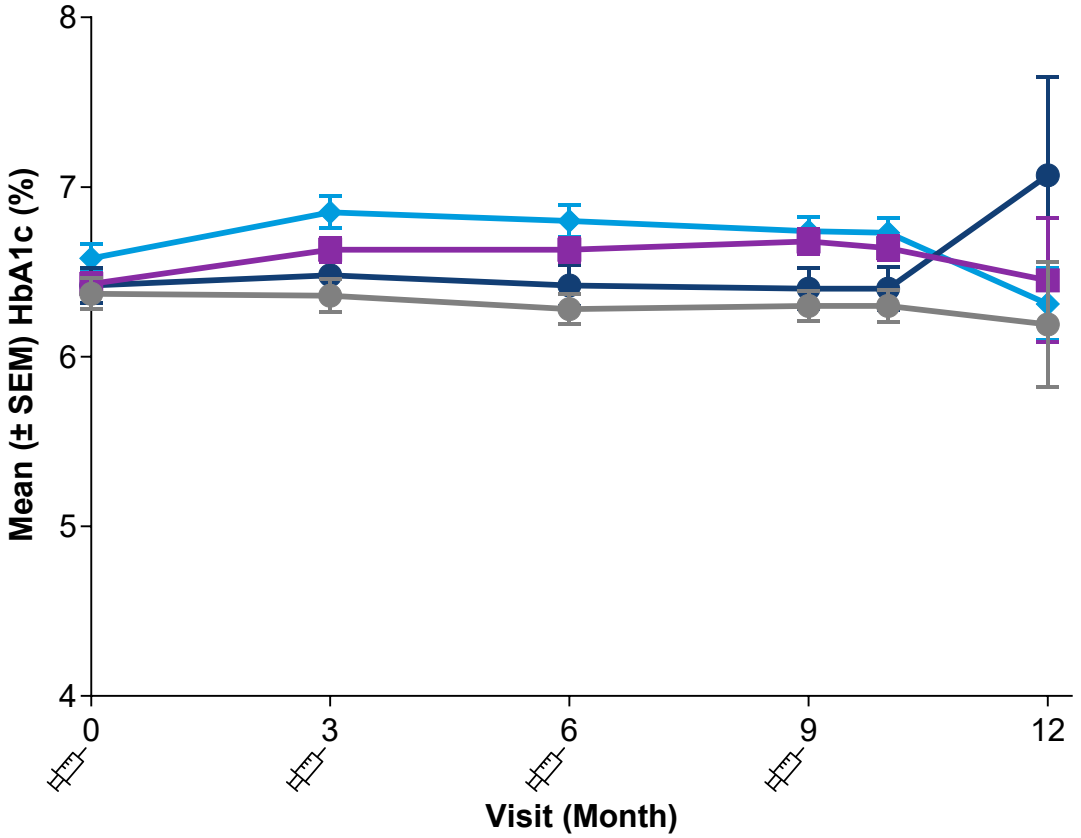
% = 100 x n/N. *SAE is an adverse event that results in death, is life-threatening or requires hospitalization. There were two SAE CV deaths (cardiogenic shock following acute MI and sudden cardiac death in the setting of extensive underlying CV disease) and one death due to chronic myelomonocytic leukemia;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

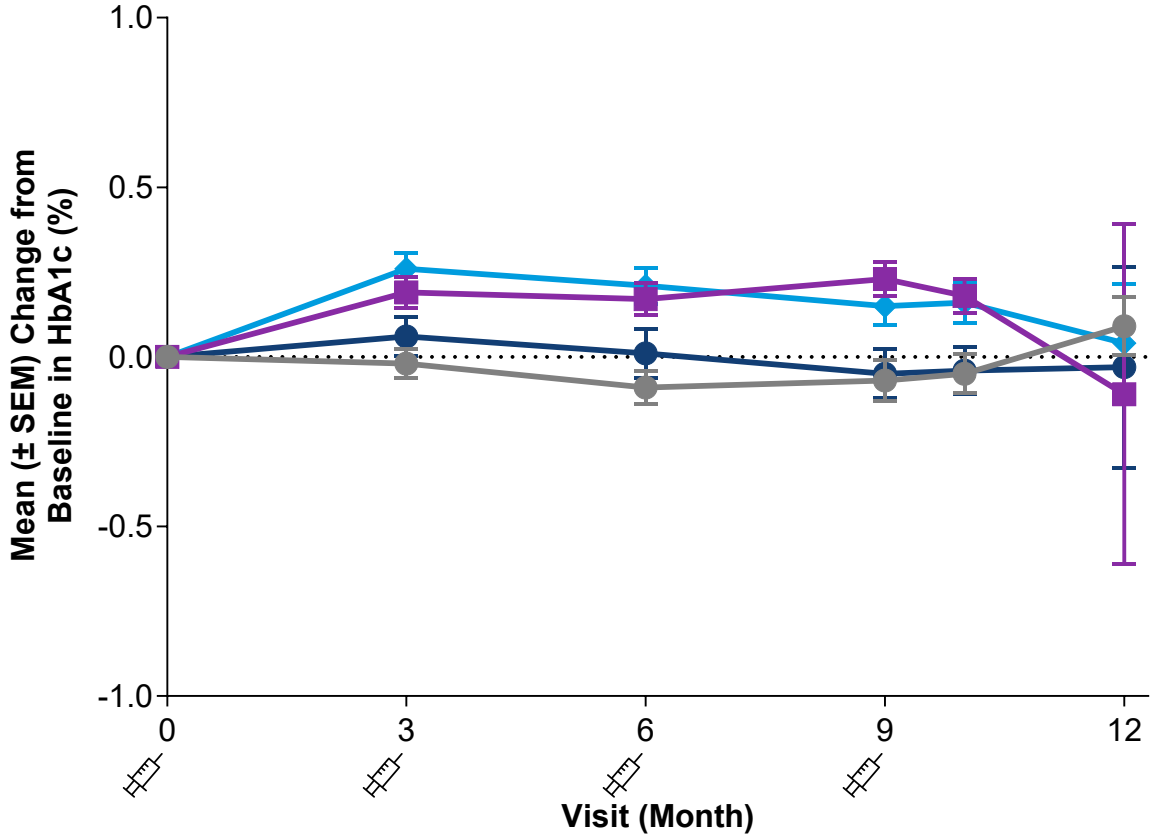
No Worsening of HbA1c Over Time

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 evident at 3 months and sustained over 12 months, with an associated in reduction in risk of AP of ~80%
- >90% of patients treated with plozasiran achieved TGs below 5.6 mmol/L (500 mg/dL) and >50% achieved TGs below 1.7 mmol/L (150 mg/dL)
- Plozasiran reduced the risk of AP across the TG spectrum including the high-risk subgroups; by 91% in all patients with a history of AP and by 100% in the highest risk sub-group, (TG ≥10 mmol/L [880 mg/dL] + 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

- **GF Watts** reports grants and/or honoraria from Amgen, Novartis, Arrowhead, Esperion, Astra Zeneca, Pfizer, Novo Nordisk, Silence Therapeutics, CSL Seqirus, and Sanofi-Regeneron. **CM Ballantyne** reports Grant/Research Support: Abbott Diagnostic, Akcea, Amgen, Arrowhead, Ionis, 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, Illumina, Ionis, Merck, New Amsterdam, Novartis, Novo Nordisk, Roche Diagnostic. **AB Echevarria** reports honoraria for lectures/advisory boards from Novo Nordisk, Novartis, Amgen, Sanofi, Eli Lilly, Daiichi Sankyo, Sobi, Ultragenyx, and the Spanish Society of Arteriosclerosis; payment for expert testimony from Menarini; travel support from Ferrer, Ultragenyx, Chiesi; Member of the board of directors of the Spanish Society of Arteriosclerosis (until 2024).**RS Rosenson** reports grant/research support from (all paid to institution, not individual): Amgen, Arrowhead, Novartis, Eli Lilly, Regeneron; consulting fees from Amgen, Arrowhead, CRISPR Therapeutics, Eli Lilly, Lipigon, Novartis, Precision Biosciences, Regeneron, Ultragenyx, Verve; non-promotional speaking fee from Amgen and Kowa; other support from MediMergent, LLC (significant); and is an UpToDate, Inc. stock shareholder (significant). **S Subramanian** reports grants from Arrowhead and Eli Lilly; consulting/advisory fees from Ionis and Abbott Diabetes Care; participation on a Data Safety Monitoring Board for Ionis and New Amsterdam Pharma **N Lepor** reports research grants from Arrowhead, Ionis, Amgen, Novartis, AstraZeneca, Merck, Novo Nordisk, Kardigan, Genentech, Boehringer Ingelheim, Bayer (all paid to institution, not individual) and speaker fees from Ionis, Amgen, AstraZeneca, Novo Nordisk, Bayer, Regeneron. **A Bajaj** reports research grants from Arrowhead, Amgen, Ionis, New Amsterdam Pharma, Eli Lilly, Novartis, Alexion (all paid to institution, not individual); honoraria/speaker fees from Chiesi, Arrowhead, Ionis; Board Member for National Lipid Association, National Triglyceride Association. **J Goldberg** received research funding from NHLDI, and reports being a consultant for Akcea-Ionis, and Arrowhead Pharmaceuticals. **A Gallo** received funding from Amgen, Arrowhead, Bio89, Ionis, and Sanofi-Regeneron. A.G. has also received honoraria for board, conferences or congresses from Akcea, Amarin, Amgen, AstraZeneca, Chiesi, Lilly, MSD, Novartis, Sanofi-Regeneron, Servier, Viatris, and Ultragenyx. **R Scott** reports travel support for continuing medical education from Christchurch Hospital. **M Saxena** reports research grants/aid from NIHR, MSD, Recor Medical, Ablative Solutions all paid to institution, not individual); advisory/consulting/speaker fees from AstraZeneca, Arrowhead, Alnylam, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Novartis, Mineralys Therapeutics, Sanofi, Vifor Pharma, Recor Medical, Marea Therapeutics, Menarini, MSD, IQVIA, PPD; travel support from AstraZeneca, Mineralys, Novartis; Board/committee membership: British & Irish Hypertension Society Executive Committee member (Honorary) and CV Research Specialty Lead North London NIHR (funding to institution) **A Baass** received research grants from Akcea, Amgen, Astra Zeneca, Fondation Leducq, Fondation Yvan Morin, Merck Frosst, and Sanofi and has participated in clinical research protocols from Acasti Pharma Inc., Akcea, Amgen, Arrowhead Pharmaceuticals, Astra Zeneca, Ionis Pharmaceuticals, Inc., Isis Pharmaceuticals, The Medicines Company, Merck Frosst, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., and Sanofi. A.M. has served on advisory boards and received honoraria for symposia from Akcea, Amgen, and Sanofi. **R Fu, L Aiyer, J Hellawell,** and **J Hamilton** are all current employees of Arrowhead Pharmaceuticals. **D Gaudet** reports grants and/or honoraria from Alnylam, Amgen, Arrowhead, AstraZeneca, Boehringer-Ingelheim, CRISPR Therapeutics, Dalcor Pharma, Eli Lilly, Esperion, Ionis, Kowa, Novartis, Pfizer, Regeneron, Sanofi, Ultragenyx and Verve Therapeutics. **J Smith, V Blaha, JL Diaz Dalco, J Li** report no conflicts of interest.

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SHASTA-3 and SHASTA-4 Discussion

Børge Nordestgaard, MD
Copenhagen University Hospital

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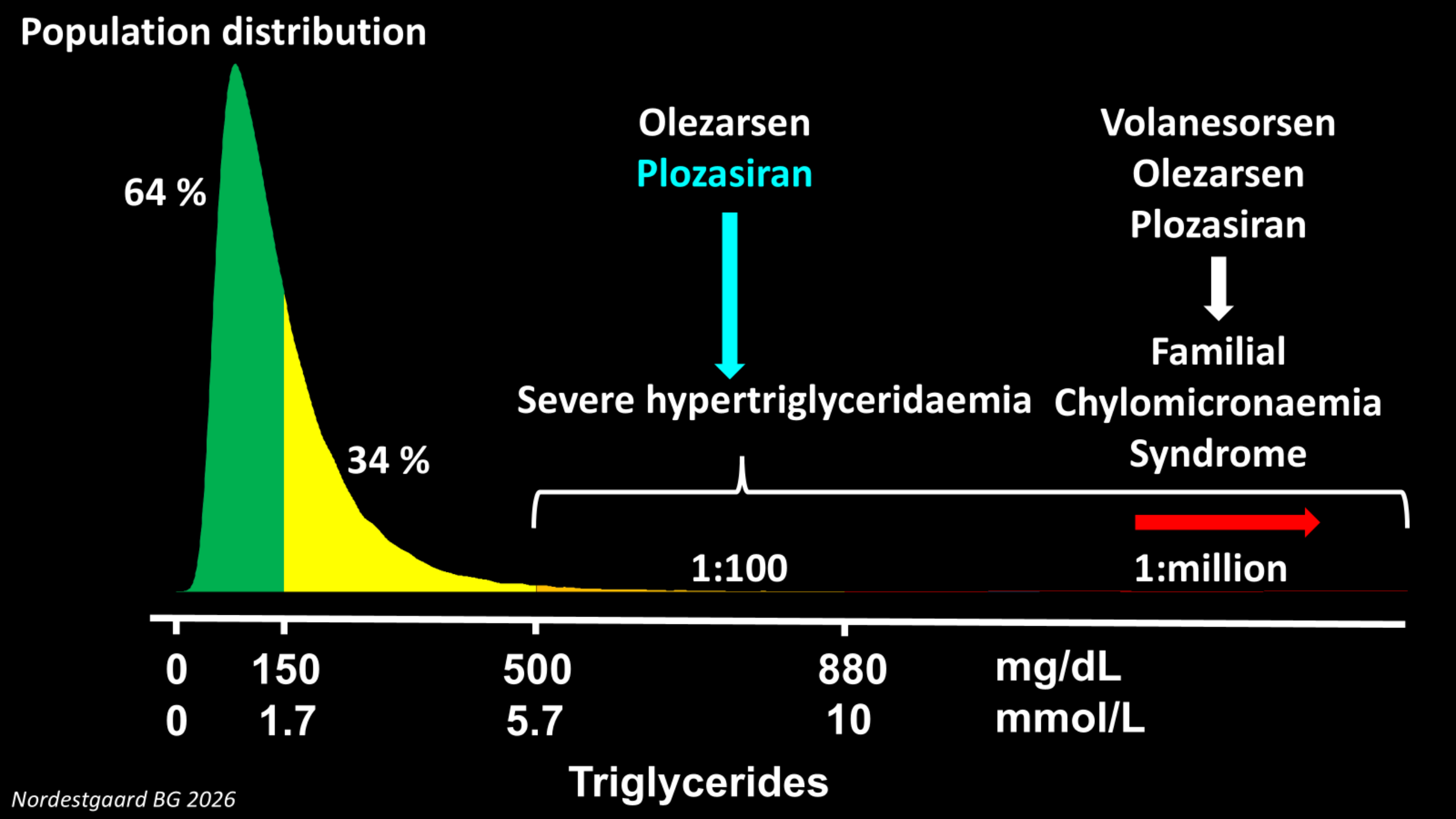
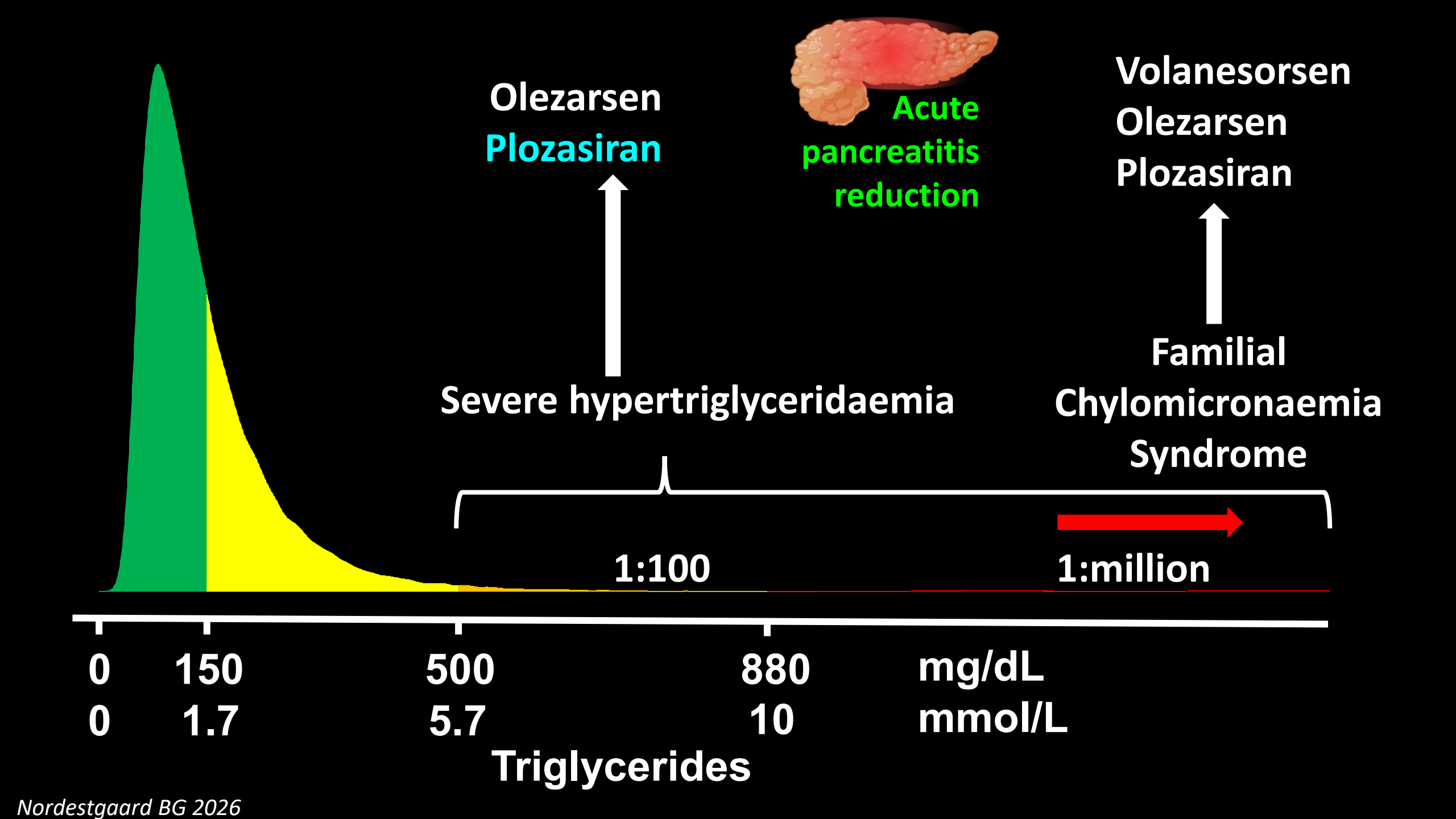
Discussant review - SHASTA-3/4

Børge G Nordestgaard
Copenhagen University Hospital
University of Copenhagen


Population distribution
64 %
34 %
Olezarsen
Plozasiran
Severe hypertriglyceridaemia
Volanesorsen
Olezarsen
Plozasiran
Familial
Chylomicronaemia
Syndrome
1:100
1:million
0
150
500
880
mg/dL
0
1.7
5.7
10
mmol/L
Triglycerides
Nordestgaard BG 2026

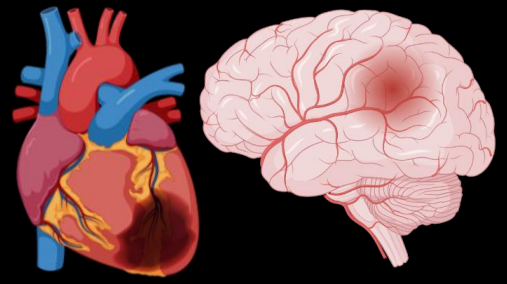


Nordestgaard BG 2026

Side effects

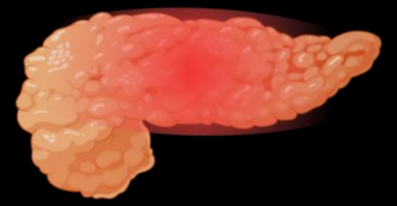
- Worsening glycemic control (14% vs. 9%)
- Low drug discontinuation
- More follow-up needed

SHASTA-3 and SHASTA-4 baseline :
N=757 with severe hypertriglyceridaemia ≥ 5.7 mmol/L (500 mg/dL)



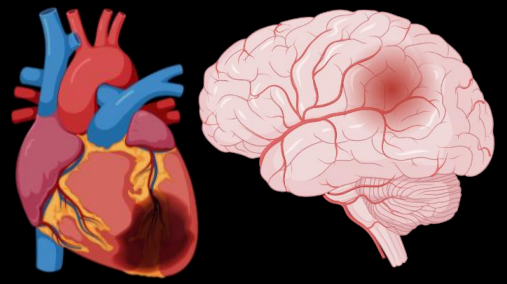
32% ASCVD

59% diabetes



21% acute pancreatitis (AP)

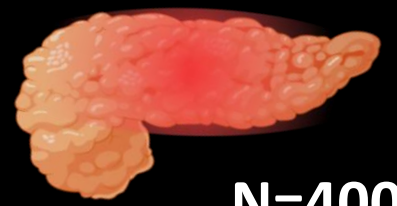
3.4 million individuals without ASCVD/AP nationwide in Denmark 2008-21:
N=29,000 with severe hypertriglyceridaemia ≥ 5.7 mmol/L (500 mg/dL)



N=2000 ASCVD **x5**

Incidence per 1000 person-years

18 **x9** 2



N=400
acute pancreatitis

Nordestgaard BG 2026 unpublished

Clinical implication

A huge unmet medical need:
Severe hypertriglyceridaemia causing acute pancreatitis and ASCVD

Now we have efficient therapies:
ApoC3 inhibition to lower triglycerides and acute pancreatitis

Focus on preventing ASCVD needed

Nordestgaard BG 2026

European Society of Cardiology Congress 2026

Plozasiran Commercialization Efforts

Andy Davis, MBA
Senior Vice President, Cardiometabolic Franchise

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Multiple Groups of Patients with Elevated TGs Have Been Studied in Plozasiran Clinical Trials

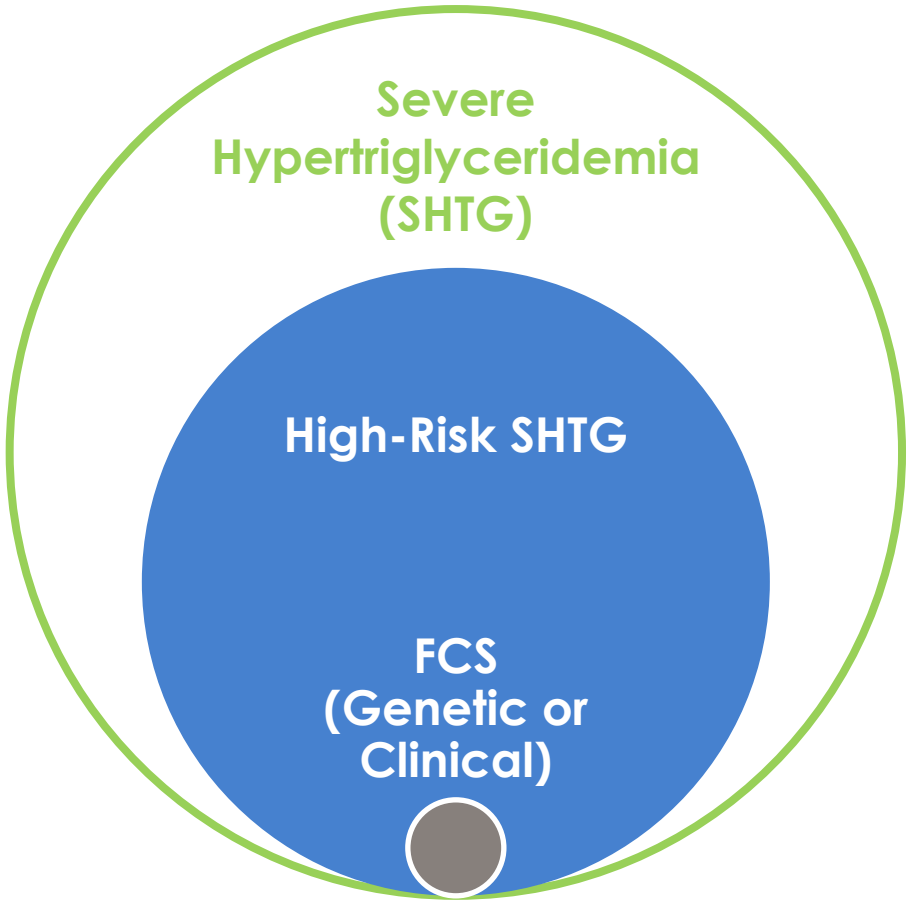

Figure Not to Scale

US Market Size Estimates

SHTG

- TGs ≥ 500 mg/dL
- >3+ million people
- Elevated Risk of AP

High-Risk SHTG

- TGs ≥ 880 mg/dL or ≥ 500 mg/dL With Prior AP History
- ~1 million people
- Higher Risk of AP

FCS (Genetic or Clinical)

- Persistently Elevated TGs ≥ 880 mg/dL
- Prevalent Prior History of AP
- Potentially 6500+ people
- Extremely High Risk of AP

Source: Nemeth, *Journal of Clinical Medicine* 2022; Rabacchi, *Atherosclerosis* 2015; Company Estimates

The Value Proposition of Plozasiran Across These Patient Groups Has Been Consistent and Regarded as Best-in-Class

TG Reduction

- **Deep:** Reduction of ~80% compared to baseline[1]
- **Sustained:** Maintained throughout the treatment period

Goal Attainment

- **Over 90%** of plozasiran-treated patients reached levels **less than 500 mg/dL**[2]

AP Risk Reduction

- **Statistically significant reduction** in risk of developing acute pancreatitis

Safety Profile

Favorable safety profile

- **No** hypersensitivity
- **No** clinically meaningful change in platelets
- **No** meaningful elevation in liver enzymes or liver fat[3]
- Change in HbA1c **consistent with APOC3i** class[4]

Dosing Simplicity

- **Convenient 25-mg dose** every three-months
- **No** titration required

Delivering on What is Important to Patients, Physicians, and Payers

1. -27% placebo; 2. At month 12; 3.Relative to placebo; 4.Watts et al. EHJ 2026 and Tryngolza USPI

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Our Initial Launch Focus Will Be The High-Risk sHTG Segment

Estimated US Adult Population (M)	500 – 880 mg/dL	≥ 880 mg/dL	
No Prior History of AP	~2.6M	~0.7M	3.3
Prior History of AP	~0.1M	~0.1M	0.2
	2.7	0.8	3.5

Potential Clinical FCS

- Recurrent hospitalizations for severe abdominal pain without other explainable cause; OR Family history of hypertriglyceridemia-induced pancreatitis
- Recurrent episodes of acute pancreatitis not caused by alcohol or cholelithiasis; OR childhood pancreatitis

The Shaded Quadrants Represent the Highest Clinical Urgency and Payer Willingness to Pay

Source: Company estimates

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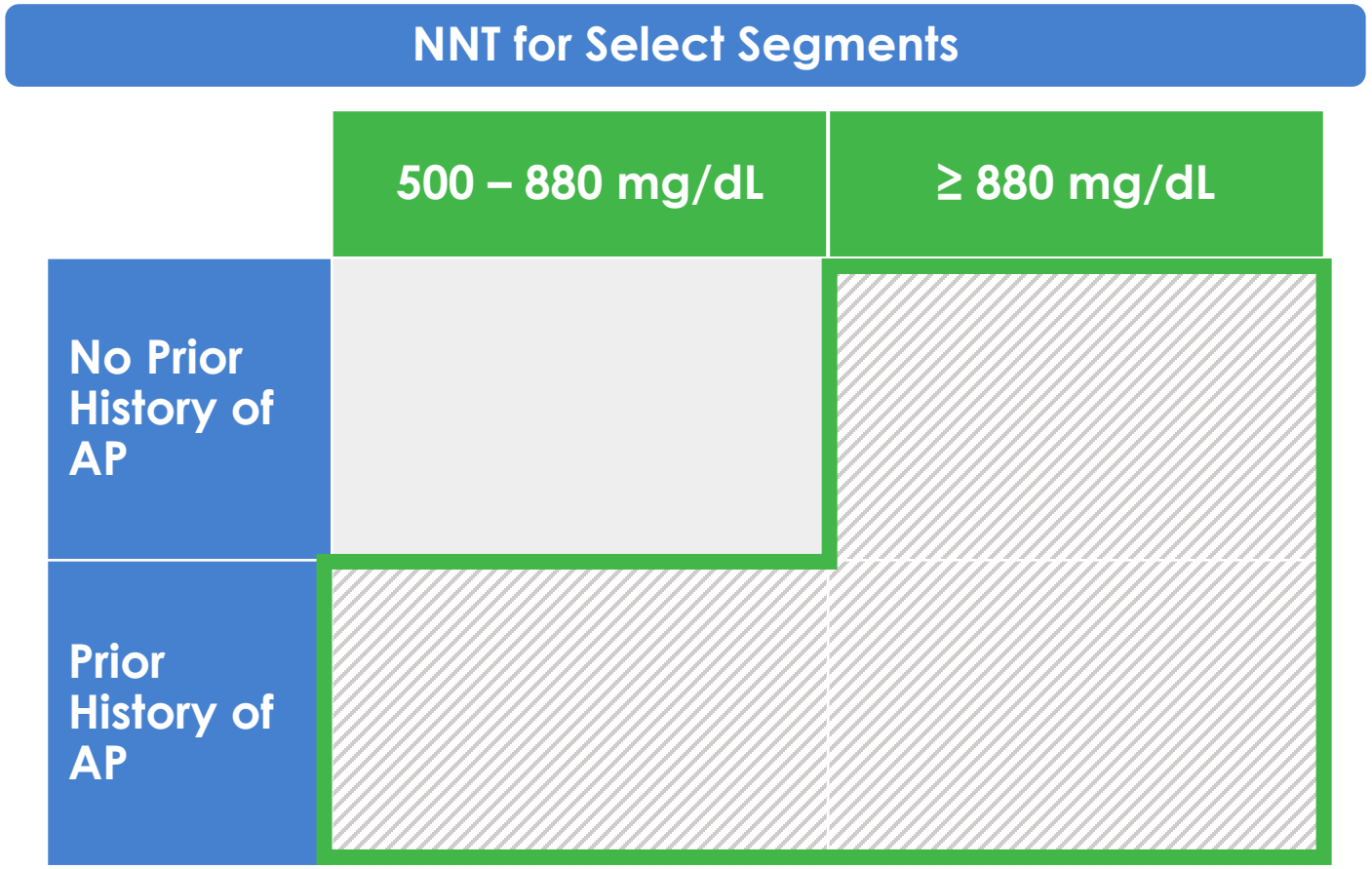
The Number Needed to Treat (NNT) with Plozasiran in the High-Risk Segment is Compelling and Supports This Launch Focus



In the High-risk Segments, You Need to Treat 3–9 Patients for 1 Year with Plozasiran to Prevent 1 AP Event

*Source: Arrowhead Data on File

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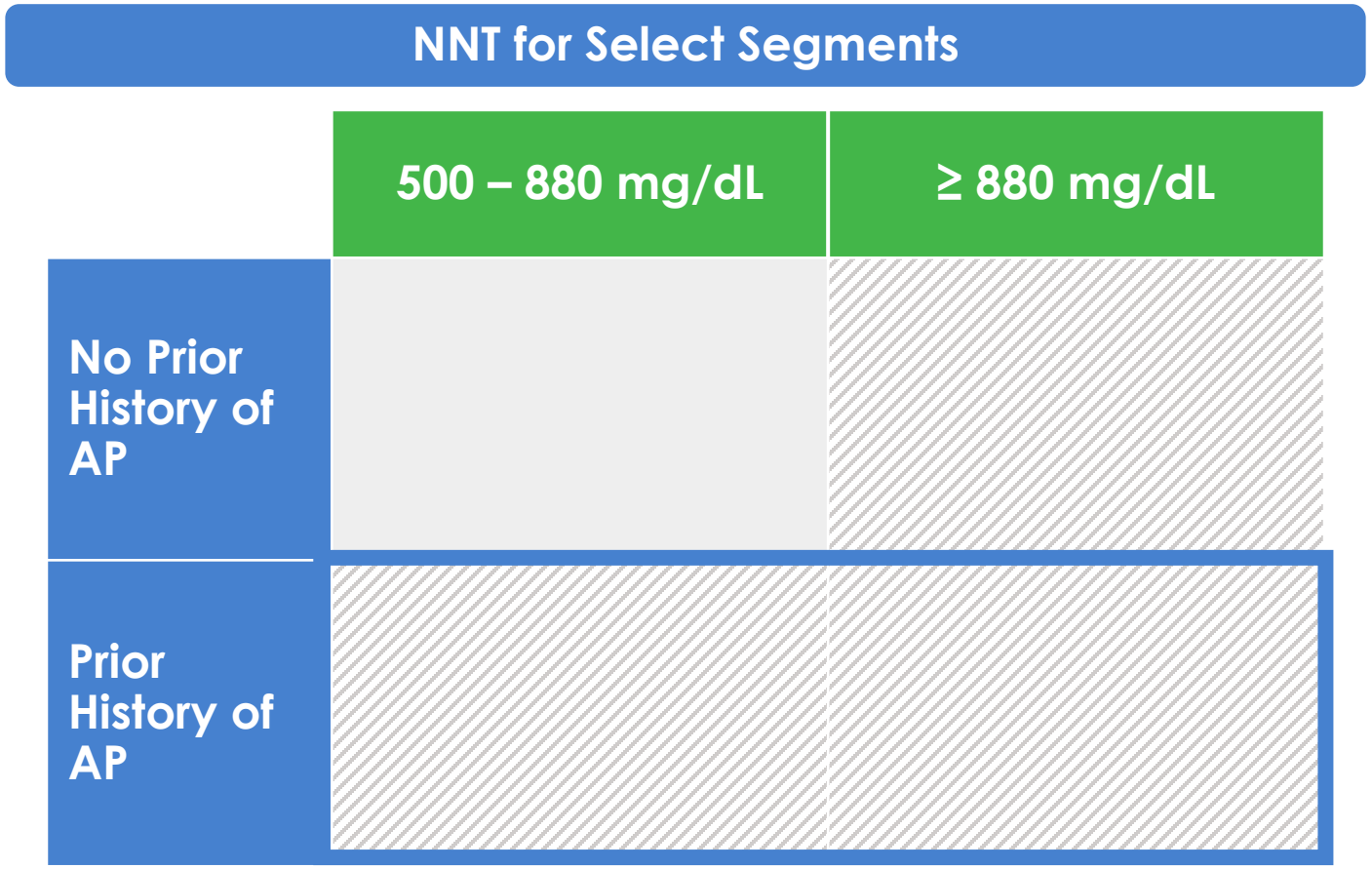
The Number Needed to Treat (NNT) with Plozasiran in the High-Risk Segment is Compelling and Supports This Launch Focus



In the High-risk Segments, You Need to Treat 3–9 Patients for 1 Year with Plozasiran to Prevent 1 AP Event

*Source: Arrowhead Data on File

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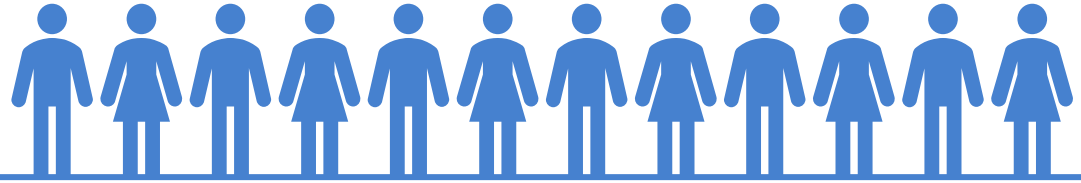
We Are Targeting Over 20,000 Healthcare Professionals in the U.S. at Launch



~1M High-Risk SHTG patients in the U.S.

HCPs Identified
Across 4 Specialties Who Primarily Treat SHTG

- **LIPIDOLOGISTS**
- **ENDOCRINOLOGISTS**
- **PREVENTIVE CARDIOLOGISTS**
- **INTERNAL MEDICINE/PRIMARY CARE**

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Our Commercialization Efforts Are Already Very Advanced

Key Launch Readiness Activities

Medical	Commercial	Patient Services	Regulatory	Day 1 Launch
Medical Education and Communication strategy developed and executing	Marketing and Market Access strategy developed and executing compliantly on key go-to-market activities	Expansion and optimization of distribution and patient services well underway	Regulatory interactions planned in the near future	Patient, provider, and payer Day 1 readiness
✓	✓	✓	○	○

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European Society of Cardiology Congress 2026

Key Takeaways

Vince Anzalone, CFA
Senior Vice President, Investor Relations

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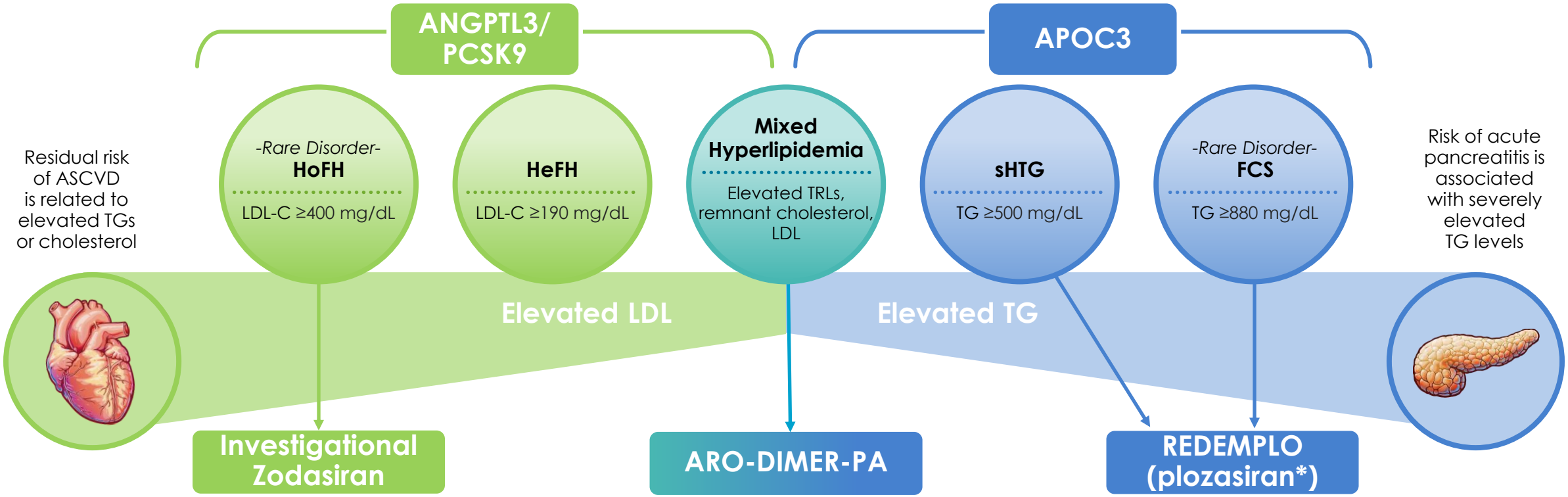
Key Takeaways

- Plozasiran demonstrates an **attractive profile and consistent safety and tolerability**
- **Compelling value proposition** for physicians, patients, and payers with a low number needed to treat (NNT) to prevent 1 AP event in one year of treatment
  - **NNT of 24** in overall sHTG study population
  - **NNT of 3** in patients with a prior history of AP
- **sNDA** on schedule for 2026 with **priority review voucher** potentially accelerating review
- **Launch readiness** efforts well underway
  - If approved, sHTG represents a **potential $3-4 billion** opportunity

What's Next in Arrowhead's Cardiometabolic Pipeline

Lipid Disorders, Including FCS, sHTG, Mixed Hyperlipidemia, and HoFH, Are Characterized by a Spectrum of **Elevated Levels of TGs and/or Cholesterol**[1-12]

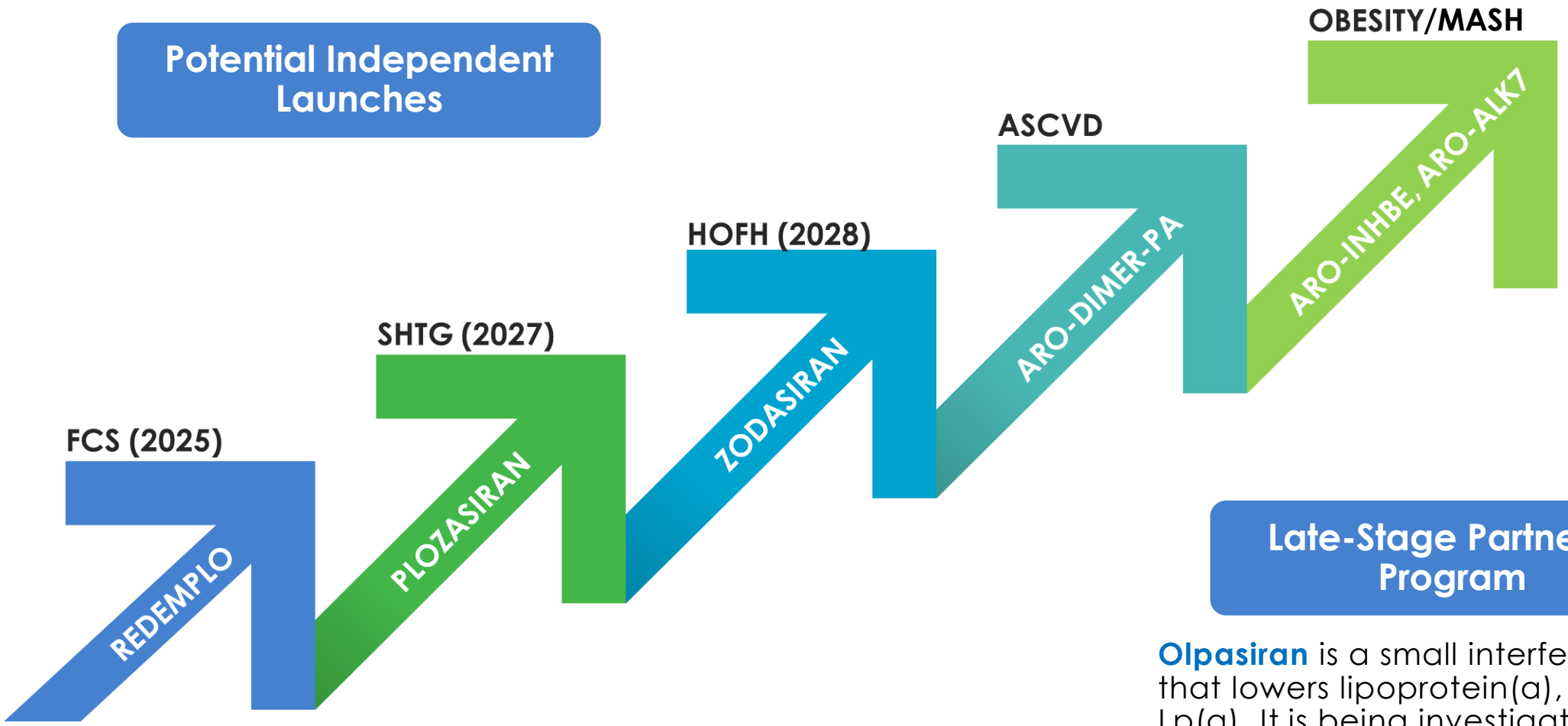


ASCVD, atherosclerotic cardiovascular disease; FCS, familial chylomicronemia syndrome; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; sHTG, severe hypertriglyceridemia; TG, triglyceride; TRL, triglyceride-rich lipoprotein.

*REDEMPLO (plozasiran) is approved to reduce TGs in FCS in US, EU, Canada, Australia, and China, but investigational plozasiran has not been reviewed or approved to treat sHTG in any countries

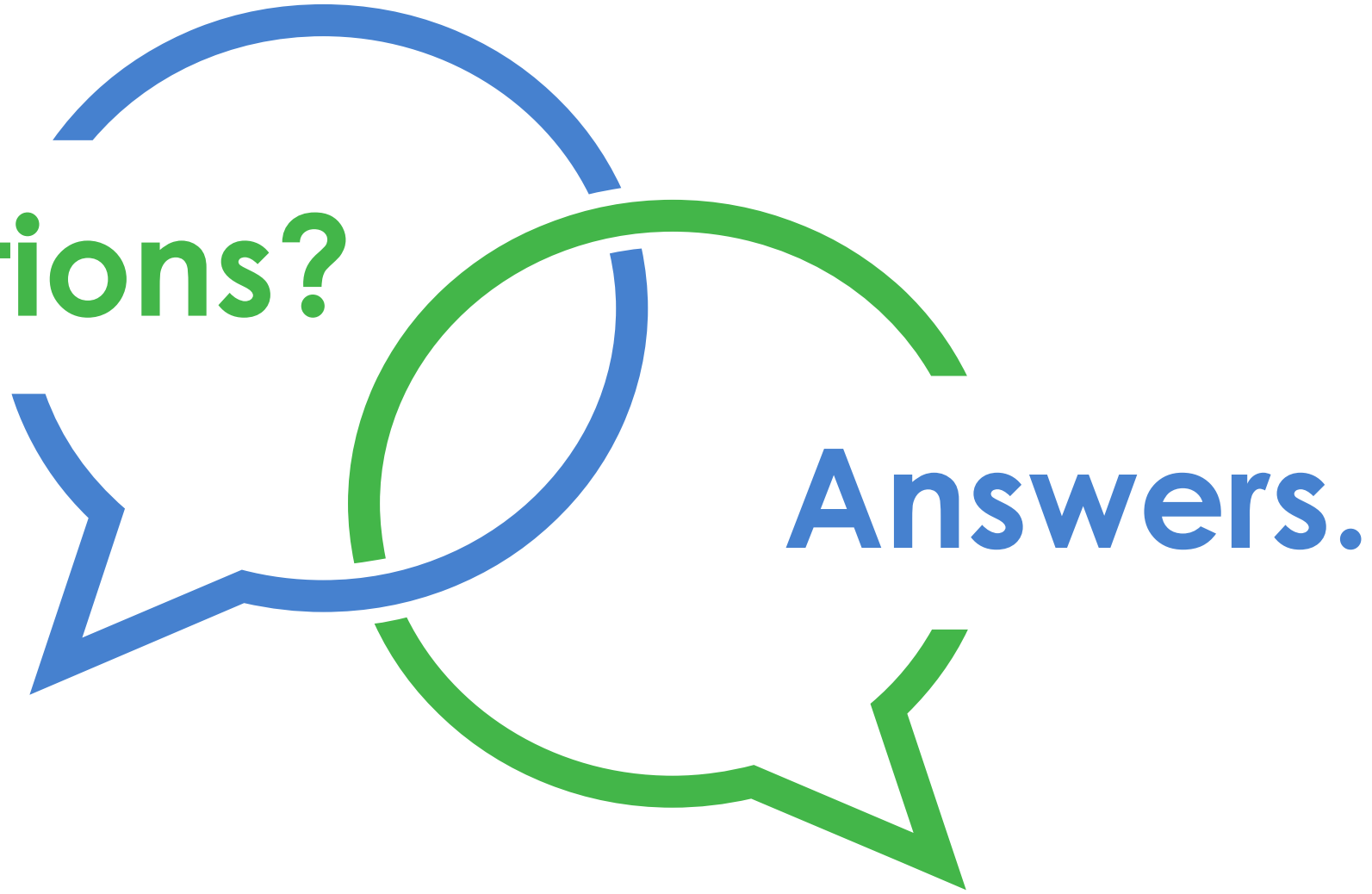
1. Malick WA, et al. *J Am Coll Cardiol*. 2023;81(16):1646-1658. 2. Larouche M, et al. *Curr Atheroscler Rep*. 2023;25(12):1101-1111. 3. Nordestgaard BG, et al. *Lancet*. 2014;384(9943):626-635. 4. Mach F, et al. *Eur Heart J*. 2020;41(1):111-188. 5. Lloyd-Jones DM, et al. *J Am Coll Cardiol*. 2022;80(14):1366-1418. 6. McGowan MP, et al. *J Am Heart Assoc*. 2019;8(24):e013225. 7. Yang Z, et al. *Front Cardiovasc Med*. 2022;9:913977. 8. Romandini A, et al. *Pharmaceuticals* (Basel). 2023;16(2):176. 9. Virani SS, et al. *J Am Coll Cardiol*. 2021;78(9):960-993. 10. Gaudet D, et al. *N Engl J Med*. 2014;371(23):2200-2206. 11. Berberich AJ, et al. *Endocr Rev*. 2022;43(4):611-653.

Multiple Potential Commercial Launches in Cardiometabolic



Olpasiran is a small interfering RNA (siRNA) that lowers lipoprotein(a), also known as Lp(a). It is being investigated by Amgen in Phase 3 studies for the treatment of atherosclerotic cardiovascular disease

Questions?



Answers.