

PALISADE

Plozasiran Phase 3 Results Investor Call
European Society of Cardiology 2024

September 3, 2024

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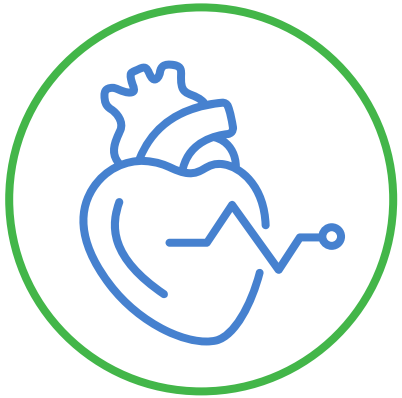
Plozasiran PALISADE Phase 3 Results – September 3, 2024



Introductions

Vince Anzalone, CFA
Vice President, Finance and IR

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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.

Agenda

Topic	Presenter
Introductions	**Vince Anzalone,** CFA, VP, Finance and IR
Delivering on the Promise of RNAi	**Chris Anzalone,** PhD, CEO
Clinical Plan & Impressive Results to Date	**Bruce Given,** MD, Chief Medical Scientist
ESC 2024 Encore Presentation	**Gerald F. Watts,** DSc, MD, PhD, Winthrop Professor of Cardio-metabolic Medicine at the University of Western Australia
Commercial Readiness	**Andy Davis**, SVP, Head of Global Cardiometabolic Franchise
Concluding Remarks	**Chris Anzalone,** PhD, CEO
Q&A	Panel

Cardiometabolic Opinion Leader

Gerald F. Watts, DSc DM PhD FRCP FRACP FCSANZ

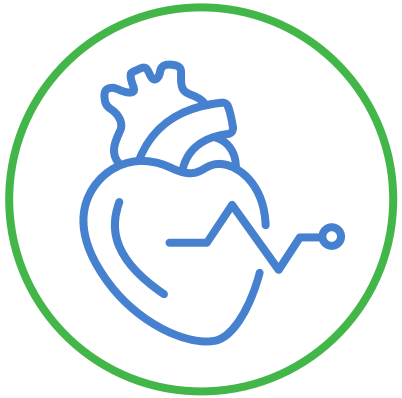


Winthrop Professor of Cardio-metabolic Medicine

University of Western Australia, Perth

Dr. 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 cardio-metabolic 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. He has supervised several Masters, MD and PhD students and post-doctoral research fellows, and holds several research grants, with multiple collaborations.

Plozasiran PALISADE Phase 3 Results – September 3, 2024



Delivering on the Promise of RNAi

Chris Anzalone, Ph.D.
President and CEO

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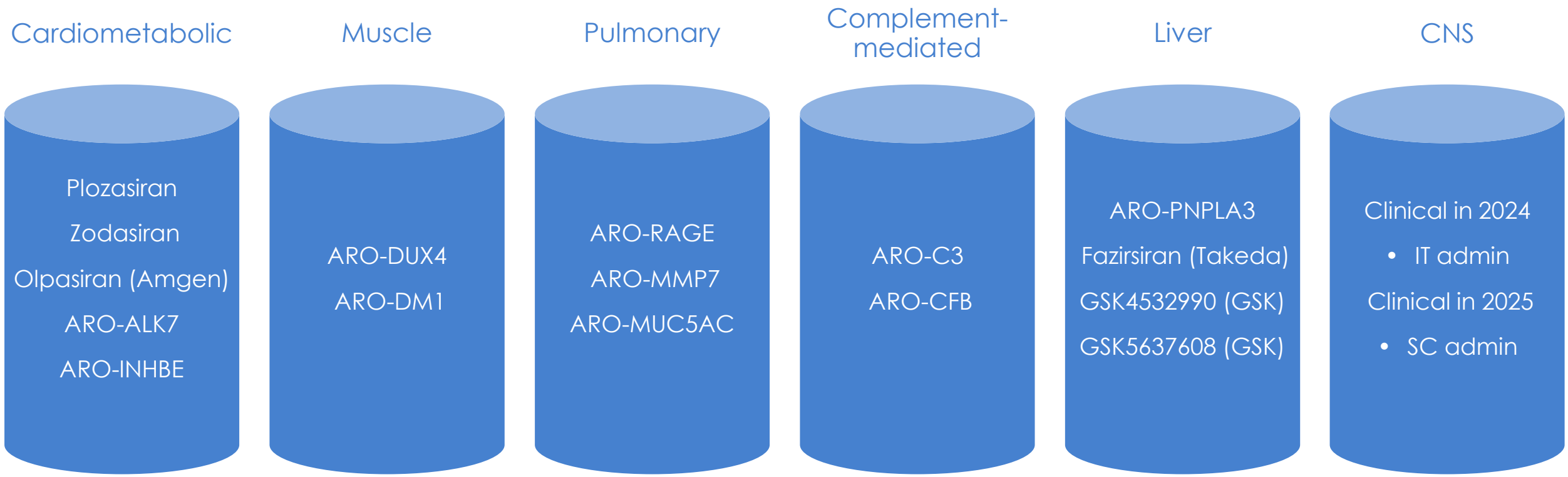
Who We Are

Arrowhead is developing RNAi therapeutics to treat a broad range of conditions across several verticals



Cardiometabolic is the key near-term focus for Arrowhead

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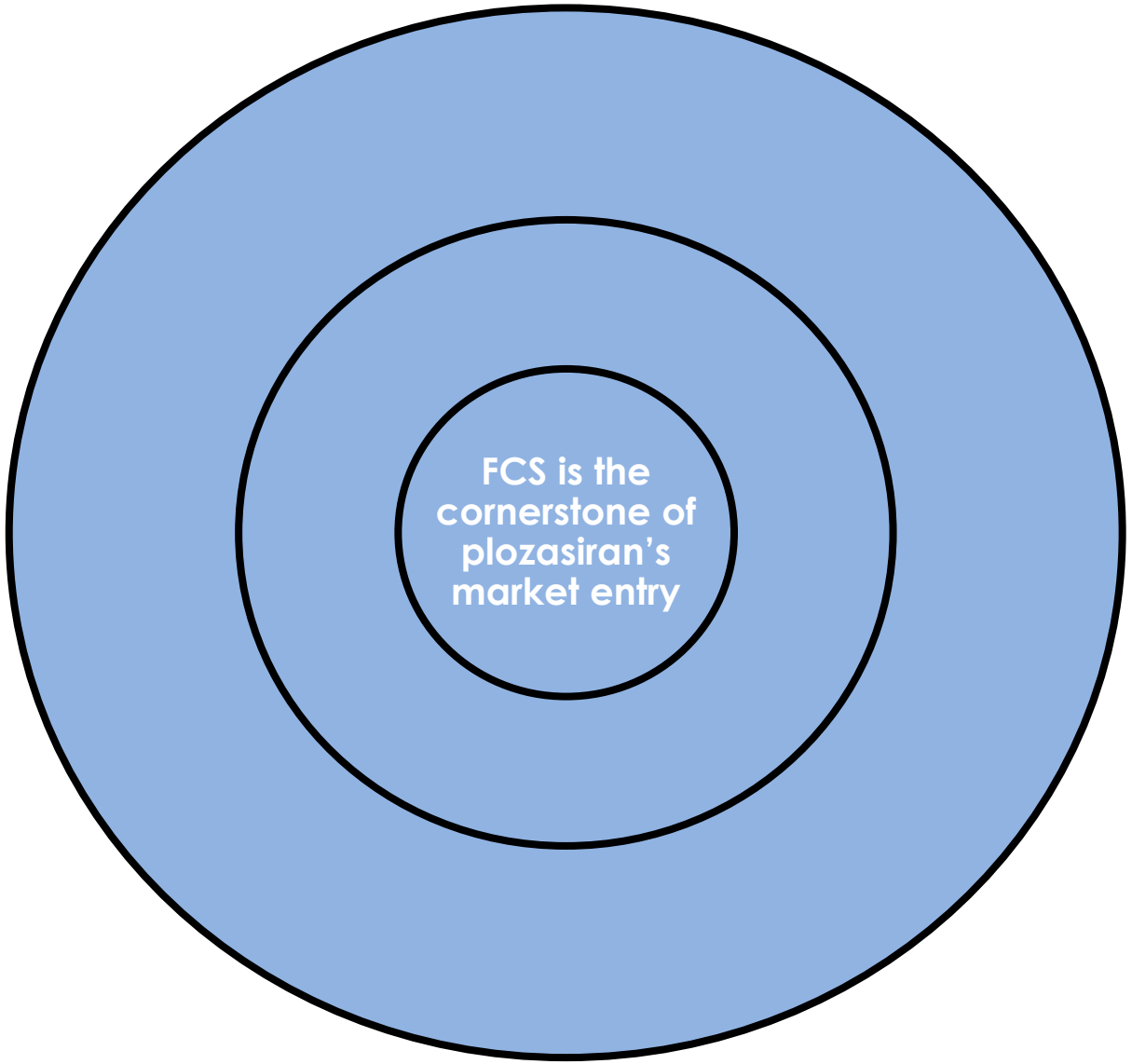
Cardiometabolic, Plozasiran, and FCS



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Plozasiran Could be a Pipeline within a Drug

It starts with FCS: patients deserve a powerful, reliable, and convenient therapy

- Dramatic triglyceride lowering
- Reduction in acute pancreatitis
- Convenient 4 doses/year schedule
- Favorable safety profile

…and, Arrowhead is studying additional populations to learn whether more patients may also benefit from plozasiran

~3 million people in the US with severe hypertriglyceridemia (TGs > 500 mg/dl)

~20 million people in the US with TGs 150 - 500 mg/dl

Enables a staged commercial approach if studies warrant label expansion

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Comprehensive Clinical Plan and Impressive Results to Date

Bruce Given, M.D.
Chief Medical Scientist

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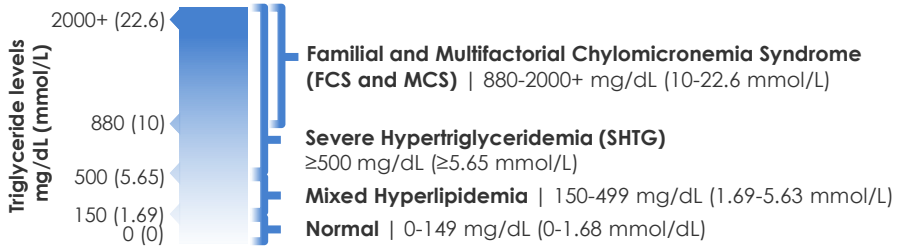
The Role of APOC3 in Lipid Disorders

Elevated Triglyceride Levels and Associated Disorders

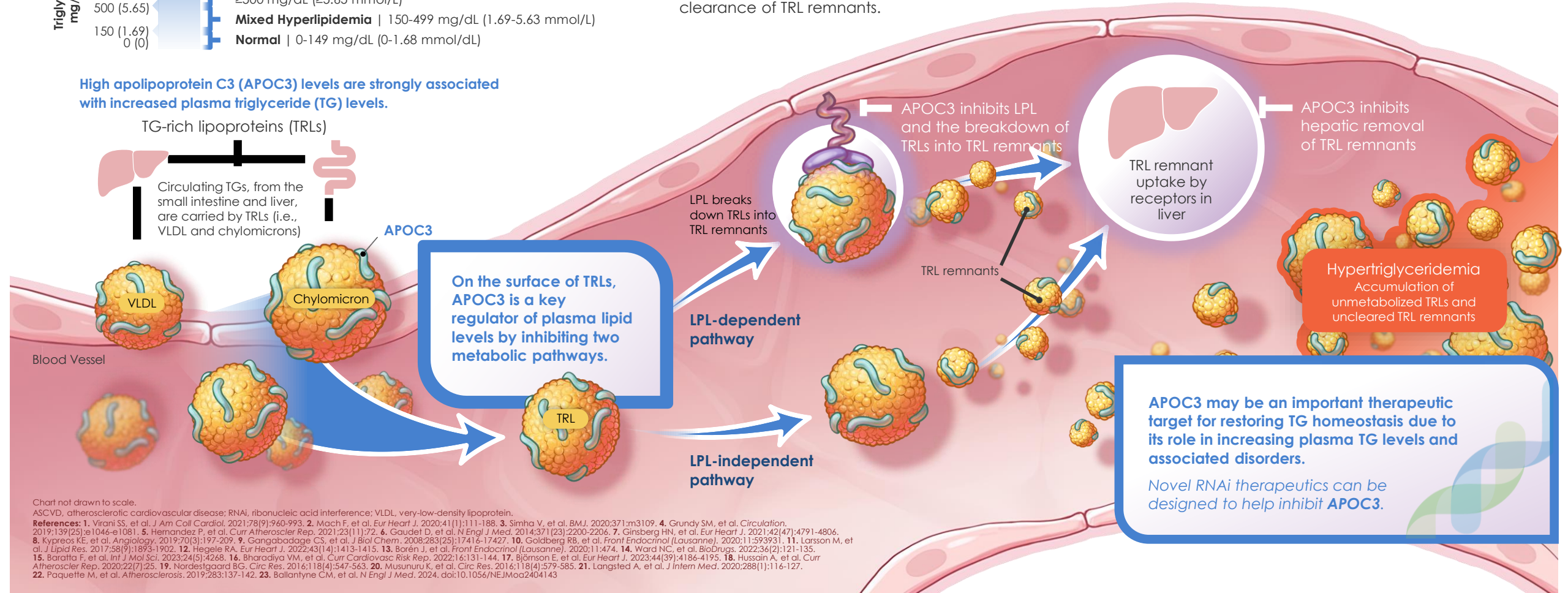


Numerous epidemiological studies have shown an association between higher TG-rich lipoproteins (TRLs) and increased risk of ASCVD events. A growing number of genome-wide association and Mendelian randomization studies also support a causal role for TRLs in atherosclerosis.

Patients with more severely elevated TGs, as seen in SHTG and persistent chylomicronemia (MCS and FCS), experience significant morbidity (e.g., pancreatitis) and negative impacts on daily living.

APOC3 increases plasma TG levels by inhibiting breakdown of TRLs by lipoprotein lipase (LPL) and hepatic clearance of TRL remnants.

High apolipoprotein C3 (APOC3) levels are strongly associated with increased plasma triglyceride (TG) levels.



APOC3 may be an important therapeutic target for restoring TG homeostasis due to its role in increasing plasma TG levels and associated disorders.

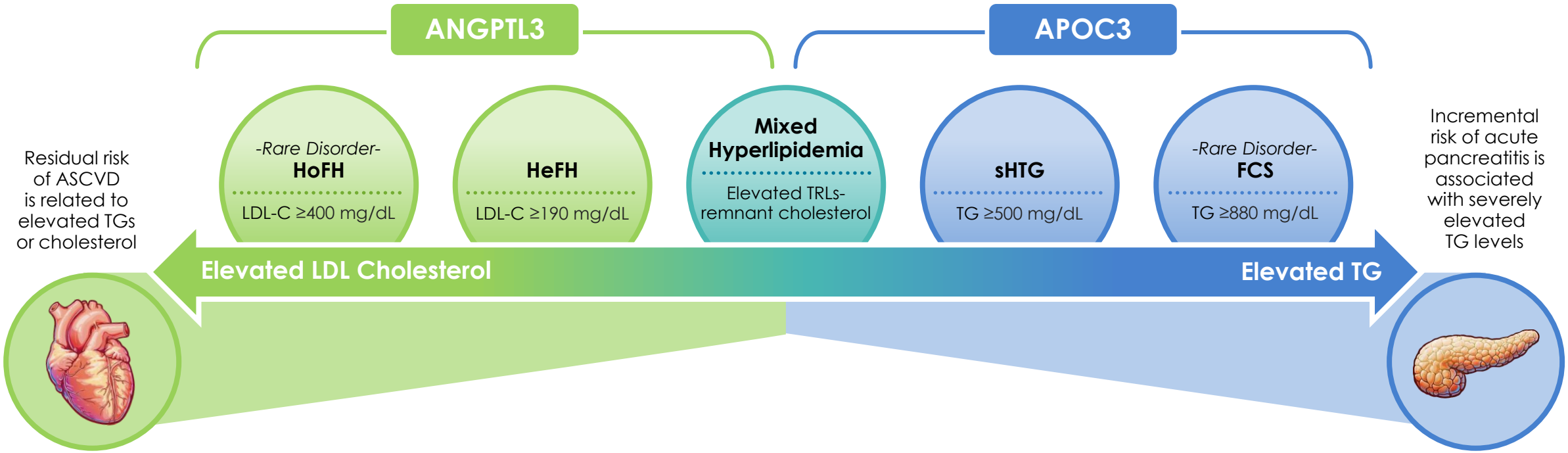
*Novel RNAi therapeutics can be designed to help inhibit **APOC3**.*

Chart not drawn to scale.
ASCVD, atherosclerotic cardiovascular disease; RNAi, ribonucleic acid interference; VLDL, very-low-density lipoprotein.

References: 1. Virani SS, et al. *J Am Coll Cardiol.* 2021;78(9):960-993. **2.** Mach F, et al. *Eur Heart J.* 2020;41(1):111-188. **3.** Simha V, et al. *BMJ.* 2020;371:m3109. **4.** Grundy SM, et al. *Circulation.* 2019;139(25):e1046-e1081. **5.** Hernandez P, et al. *Curr Atheroscler Rep.* 2021;23(11):72. **6.** Gaudet D, et al. *N Engl J Med.* 2014;371(23):2200-2206. **7.** Ginsberg HN, et al. *Eur Heart J.* 2021;42(47):4791-4806. **8.** Kypreos KE, et al. *Angiology.* 2019;70(3):197-209. **9.** Gangabadage CS, et al. *J Biol Chem.* 2008;283(25):17416-17427. **10.** Goldberg RB, et al. *Front Endocrinol (Lausanne).* 2020;11:593931. **11.** Larsson M, et al. *J Lipid Res.* 2017;58(9):1893-1902. **12.** Hegele RA. *Eur Heart J.* 2022;43(14):1413-1415. **13.** Borén J, et al. *Front Endocrinol (Lausanne).* 2020;11:474. **14.** Ward NC, et al. *BioDrugs.* 2022;36(2):121-135. **15.** Baratta F, et al. *Int J Mol Sci.* 2023;24(5):4268. **16.** Bharadiya VM, et al. *Curr Cardiovasc Risk Rep.* 2022;16:131-144. **17.** Björnson E, et al. *Eur Heart J.* 2023;44(39):4186-4195. **18.** Hussain A, et al. *Curr Atheroscler Rep.* 2020;22(7):25. **19.** Nordestgaard BG. *Circ Res.* 2016;118(4):547-563. **20.** Musunuru K, et al. *Circ Res.* 2016;118(4):579-585. **21.** Langsted A, et al. *J Intern Med.* 2020;288(1):116-127. **22.** Paquette M, et al. *Atherosclerosis.* 2019;283:137-142. **23.** Ballantyne CM, et al. *N Engl J Med.* 2024. doi:10.1056/NEJMoa2404143

Multiple Potential Disease Targets for Plozasiran

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.

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.

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Promising Plozasiran Results Across the Triglyceride Spectrum

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Plozasiran for Managing Persistent Chylomicronemia and Pancreatitis Risk

Gerald F. Watts, D.Sc., M.D., Ph.D., Robert S. Rosenson, M.D., Robert A. Hegele, M.D., Ira J. Goldberg, M.D., Antonio Gallo, M.D., Ph.D., Ann Mertens, M.D., Ph.D., Alexis Baass, M.D., Rong Zhou, Ph.D., Ma'an Muhsin, M.D., Jennifer Hellawell, M.D., Nicholas J. Leeper, M.D., and Daniel Gaudet, M.D., Ph.D., for the PALISADE Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Plozasiran, an RNA Interference Agent Targeting APOC3, for Mixed Hyperlipidemia

Christie M. Ballantyne, M.D., Szilard Vasas, M.D., Masoud Azizad, M.D., Peter Clifton, M.B., B.S., Ph.D., Robert S. Rosenson, M.D., Ting Chang, Ph.D., Stacey Melquist, Ph.D., Rong Zhou, Ph.D., Ma'an Mushin, M.D., Nicholas J. Leeper, M.D., Jennifer Hellawell, M.D., and Daniel Gaudet, M.D., Ph.D.

JAMA Cardiology

Research

JAMA Cardiology | Original Investigation

Plozasiran (ARO-APOC3) for Severe Hypertriglyceridemia
The SHASTA-2 Randomized Clinical Trial

Daniel Gaudet, MD, PhD; Denes Pall, MD, PhD; Gerald F. Watts, DSc, PhD, MD; Stephen J. Nicholls, MBBS, PhD; Robert S. Rosenson, MD; Karen Modesto, MD; Javier San Martin, MD; Jennifer Hellawell, MD; Christie M. Ballantyne, MD

NEJM Evidence

ORIGINAL ARTICLE

RNA Interference Therapy Targeting Apolipoprotein C-III in Hypertriglyceridemia

Daniel Gaudet, M.D., Ph.D.,[1] Peter Clifton, M.B.B.S., Ph.D.,[2] David Sullivan, M.B.B.S.,[3] John Baker, M.D.,[4] Christian Schwabe, M.D.,[5] Susan Thackwray, M.B., B.Ch.,[6] Russell Scott, M.B.Ch.B., Ph.D.,[7] James Hamilton, M.D.,[8] Bruce Given, M.D.,[8] Stacey Melquist, Ph.D.,[8] Rong Zhou, Ph.D.,[8] Ting Chang, Ph.D.,[8] Javier San Martin, M.D.,[8] Gerald F. Watts, D.Sc., Ph.D., D.M.,[9,10] Ira J. Goldberg, M.D.,[11] Joshua W. Knowles, M.D., Ph.D.,[12] Robert A. Hegele, M.D.,[13] and Christie M. Ballantyne, M.D.[14]

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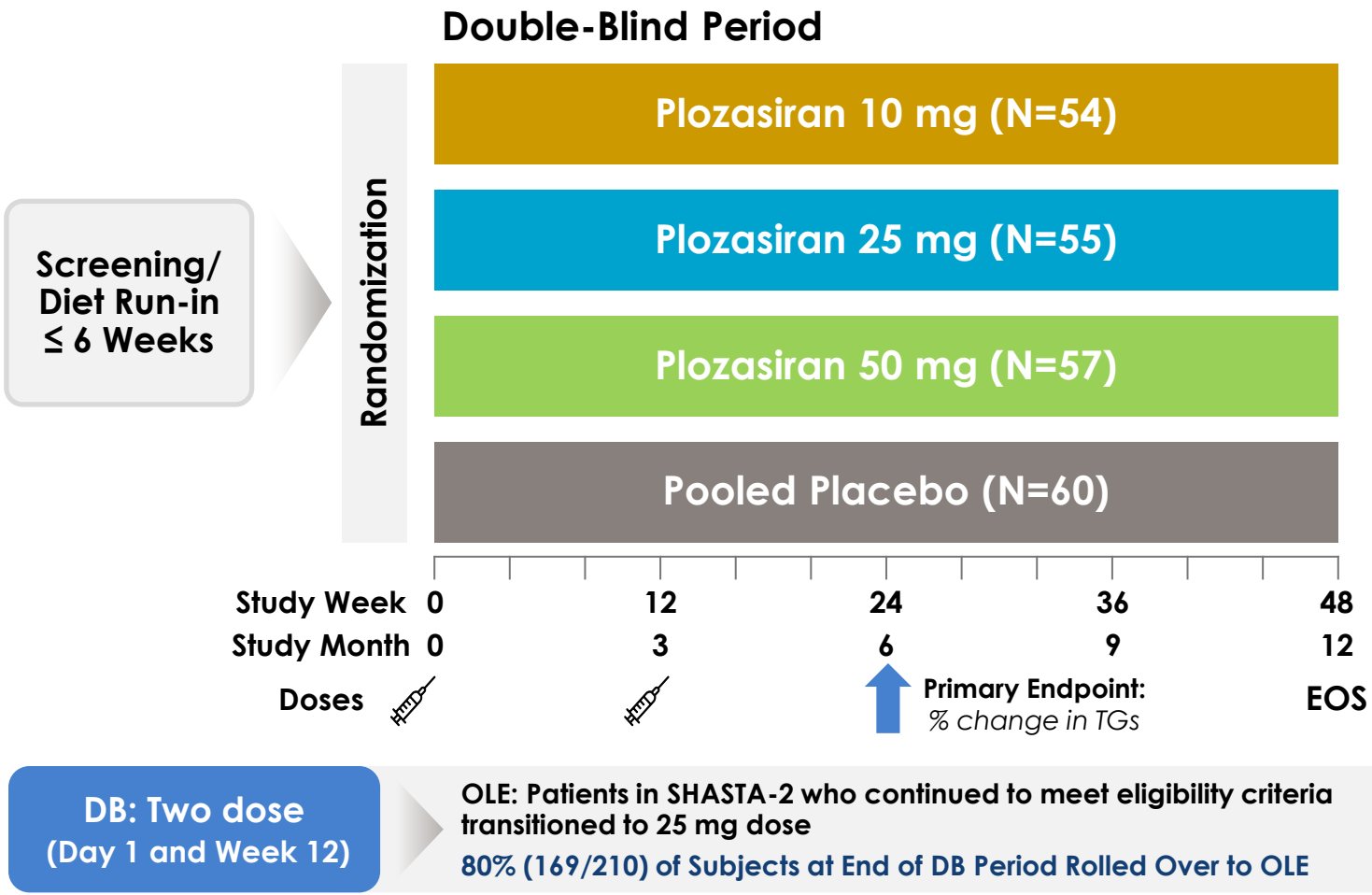
Robust Response Across the Hypertriglyceridemia Landscape

	Study	Indication	Key Results
SUMMIT PROGRAM	PALISADE	FCS	• ~80% reduction in triglycerides versus baseline • Most patients below acute pancreatitis risk thresholds • Similar response in patients with genetic FCS or clinical FCS • Statistically significant reduction in acute pancreatitis
	SHASTA-2	sHTG	• ~75% reduction in triglycerides versus baseline • 90% of patients achieved triglyceride levels less than 500 mg/dL • Improvements in multiple atherogenic lipid and lipoproteins
	MUIR	Mixed Hyperlipidemia	• ~58% reduction in triglycerides versus baseline • Triglyceride levels normalized (below 150 mg/dL) in most patients (79-92%) randomized to a treatment arm • Reductions in non-HDL-C of 24%, apoB of 19%, and remnant cholesterol of 49%

SHASTA-2 Design in Patients with Severe Hypertriglyceridemia



Study Population: sHTG history of TG ≥ 500 mg/dL and fasting TG of 500–4,000 mg/dL during screening period

Key Endpoints*: % change from baseline and over time in:

- **Primary endpoint:** TG
- **Key LP parameters:** APOC3, non-HDL-C, LDL-C, HDL-C, APOB, Remnant Cholesterol
- **Safety**

Data Analysis:

- Phase 2 study data evaluated at Week 24 and Week 48
- All patients were eligible to enroll in an Open Label Extension (OLE) at end of the study

*All samples taken after ≥ 10 hour fast.

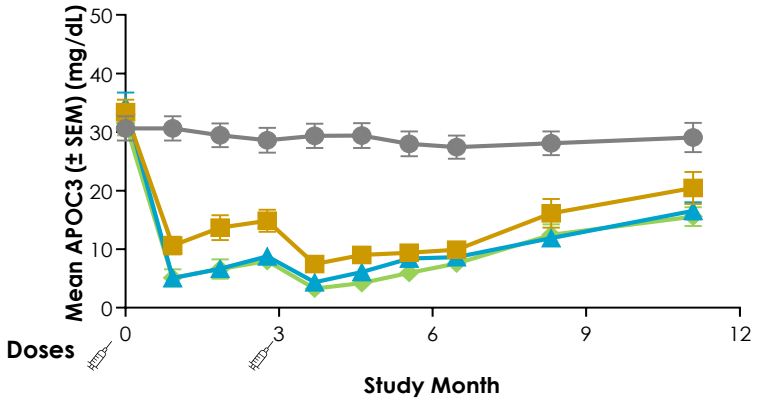
Gaudet D, et al. JAMA Cardiol. Published online April 7, 2024. doi:10.1001/jamacardio.2024.0959

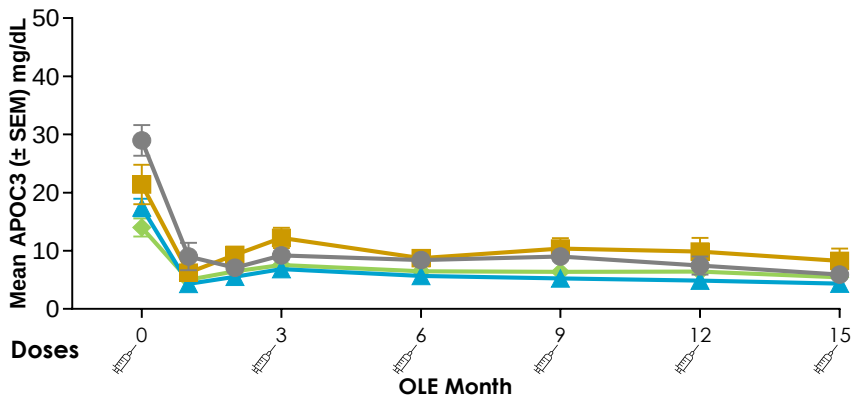
ApoB, apolipoprotein B; **APOC3**, apolipoprotein C3; **DB**: double blind; EOS, end of study; **HDL-C**, high density lipoprotein cholesterol; **LDL-C**, low density lipoprotein cholesterol; **LP**, lipoprotein; **OLE**, open label extension; **TG**, triglycerides; **TRL**, triglyceride-rich lipoprotein; **VLDL-C**, very low-density lipoprotein cholesterol; **W**, week.

Deep and Durable Reductions in APOC3 and Triglycerides

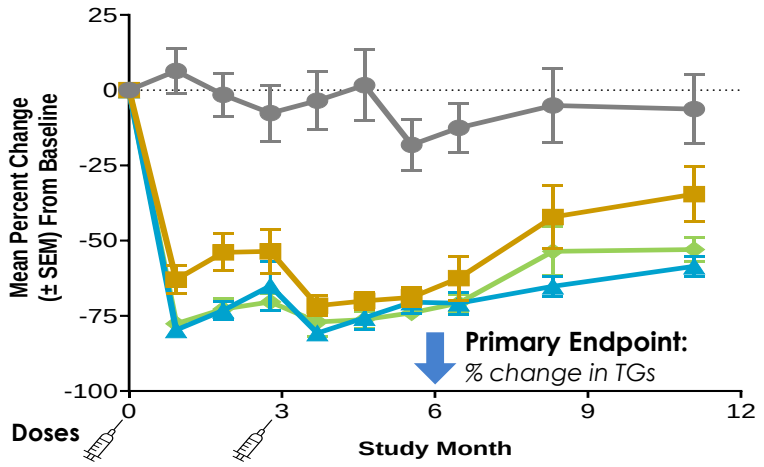
Randomized Period | **OLE**

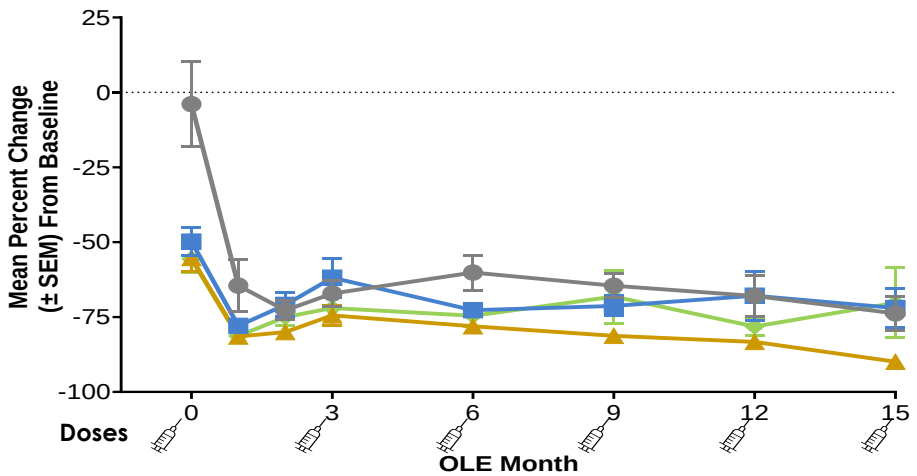
Mean APOC3





Mean % Change TG





Placebo | Plozasiran 10 mg | Plozasiran 25 mg | Plozasiran 50 mg

Gaudet D, et al. JAMA Cardiol. Published online April 7, 2024. doi:10.1001/jamacardio.2024.0959

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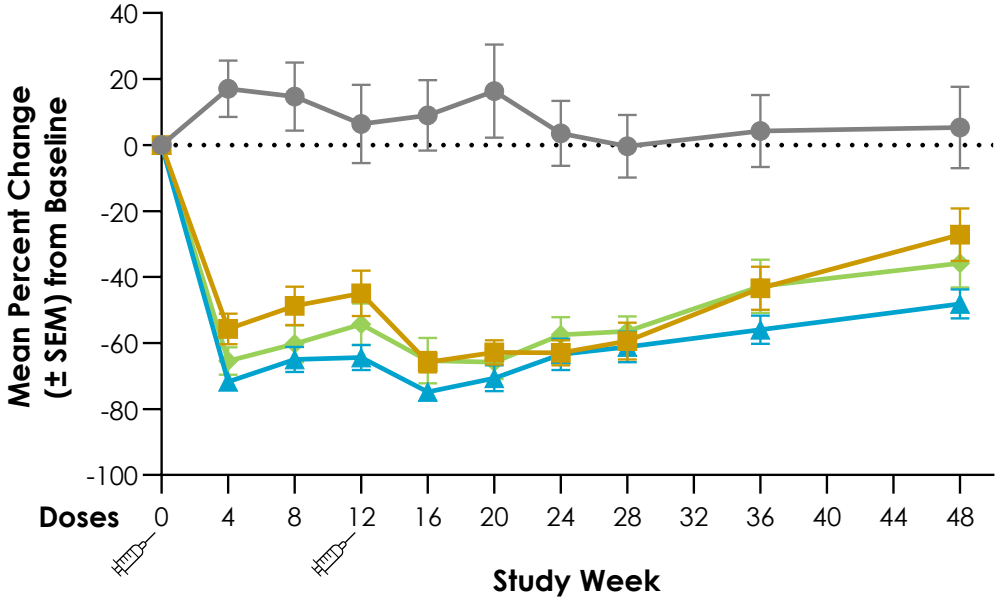
SHASTA-2

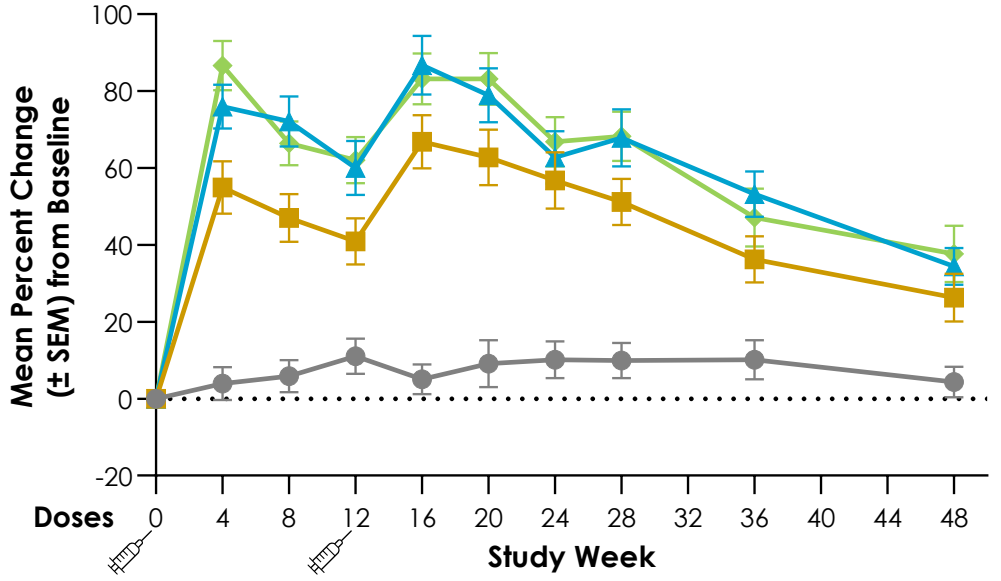
Decreased Remnant Cholesterol and Increased HDL-C

Remnant Cholesterol



LS Mean* % Change from Baseline at Week 24				
Week 24	2%	-60% p<0.0001	-62% p<0.0001	-57% p<0.0001

HDL-C



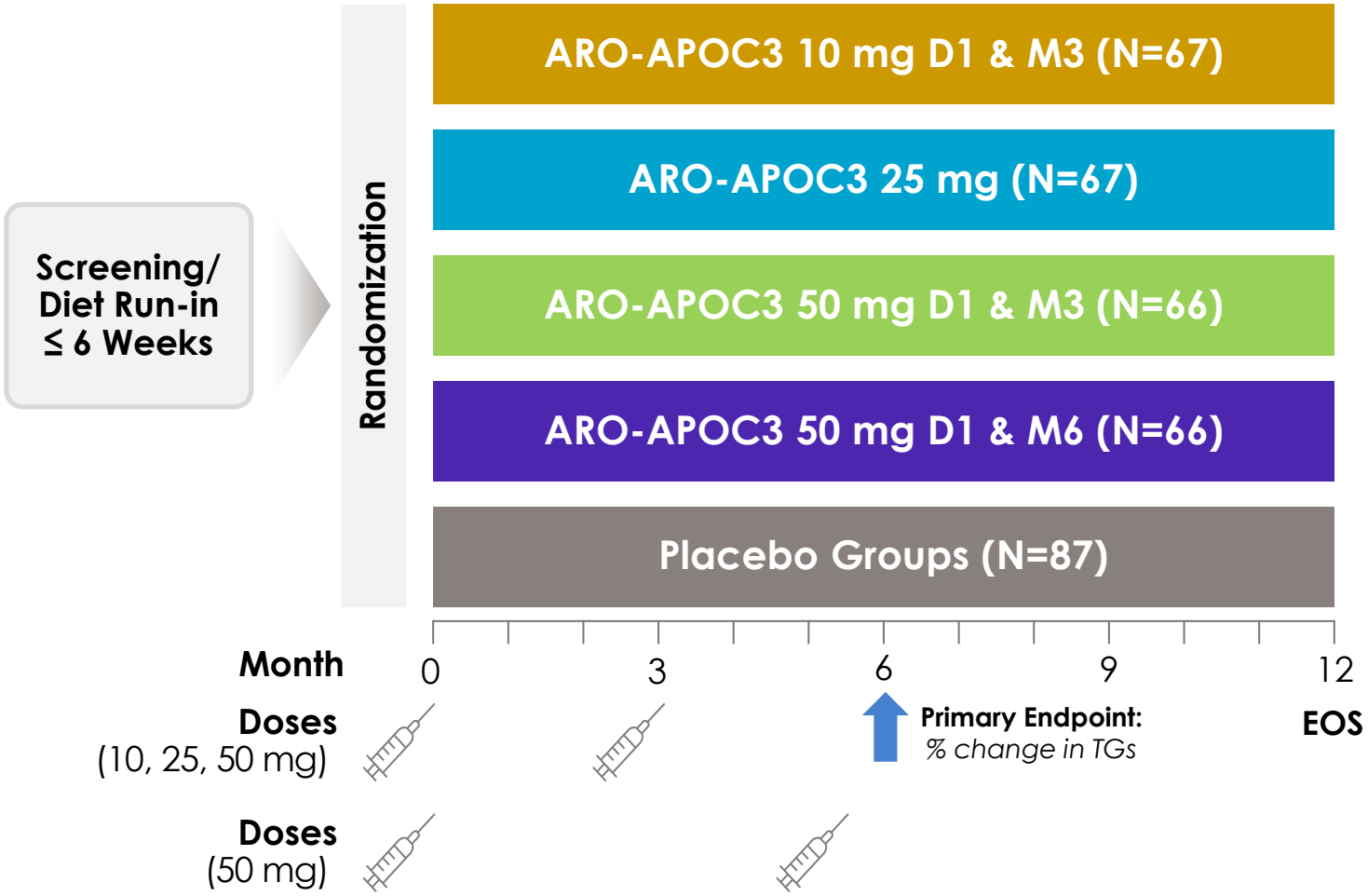
LS Mean* % Change from Baseline at Week 24				
Week 24	11%	54% p<0.0001	63% p<0.0001	68% p<0.0001

Placebo Plozasiran 10 mg Plozasiran 25 mg Plozasiran 50 mg

For all panels: *Analysis of Covariance (ANCOVA) with repeated measures was used for statistical modeling. Nadir at 16 weeks where Placebo corrected LSM of 77% difference was achieved, i.e. 135 mg/dL from 942 mg/dL mean baseline. Gaudet D, et al. JAMA Cardiol. Published online April 7, 2024. doi:10.1001/jamacardio.2024.0959

HDL-C, high density lipoprotein cholesterol; **LS**, least squares; **SEM**, standard error of the mean.

MUIR Design in Patients with Mixed Hyperlipidemia



Study Population:

- Fasting TG 150–499 mg/dL and either
  - LDL-C ≥ 70 mg/dL or
  - Non-HDL-C ≥ 100 mg/dL
- Stable optimal statin therapy

Key Endpoints*:

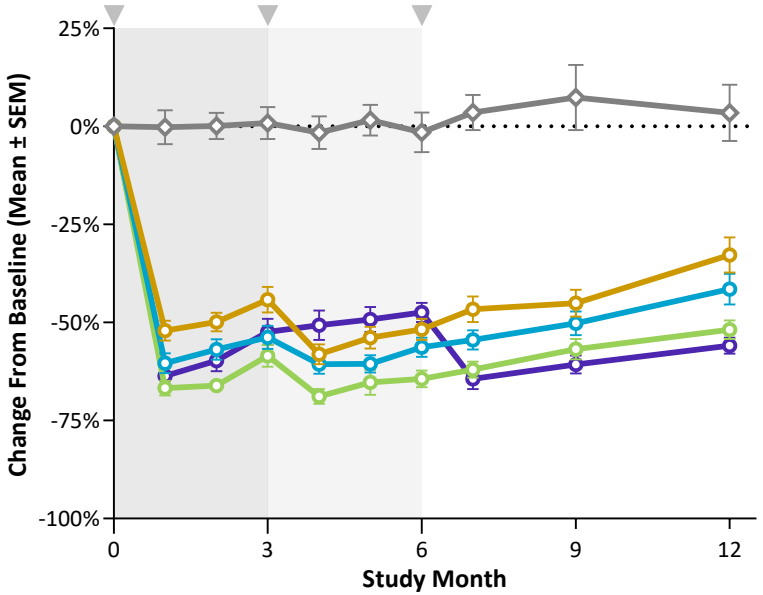
- % change from baseline in:
  - **TG** (Primary Endpoint)
  - APOC3
  - non-HDL-C, ApoB, LDL-C, HDL-C
  - Remnant Cholesterol

Ballantyne CM, et al. N Engl J Med. Published online May 28, 2024. doi:10.1056/NEJMoa2404143

Reductions in APOC3, TGs, and Remnant Cholesterol

Triglycerides

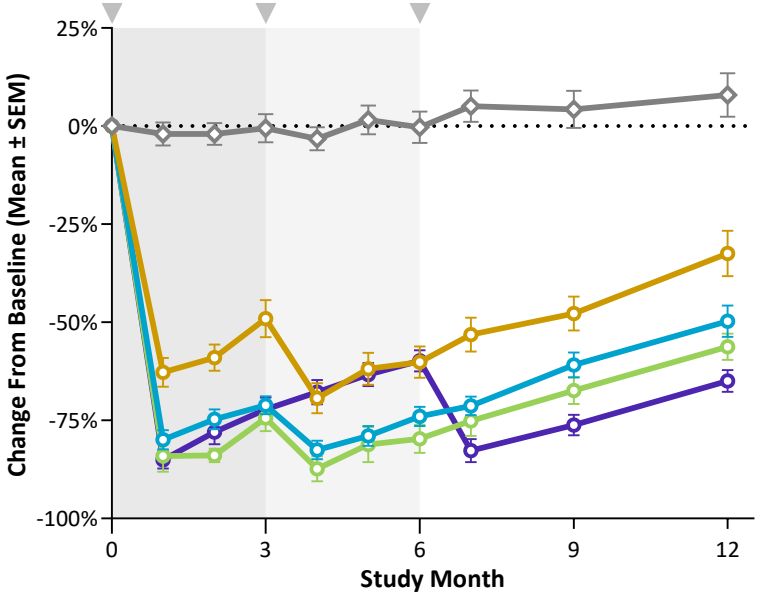
Primary Endpoint:
% change in TG at 24 weeks



Change from Baseline (LS Mean*[a])

24 Weeks	**-2%**	**-52%** p<0.0001	**-58%** p<0.0001	**-64%** p<0.0001	**-46%** p<0.0001

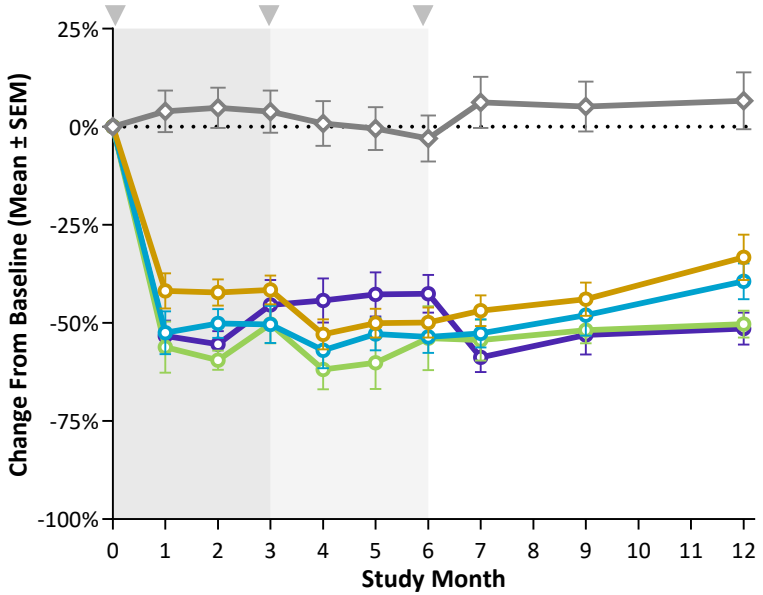
APOC3



Change from Baseline (LS Mean*)

24 Weeks	**-2%**	**-59%** p<0.0001	**-74%** p<0.0001	**-80%** p<0.0001	**-58%** p<0.0001

Remnant Cholesterol[b]



Change from Baseline (LS Mean*)

24 Weeks	**-5%**	**-48%** p<0.0001	**-54%** p<0.0001	**-53%** p<0.0001	**-42%** p<0.0001

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10 mg Q3M | 25 mg Q3M | 50 mg Q3M | 50 mg Q6M | Placebo

▼ Q3M/Q6M Dosing

[a] Three patients with BLOQ values at baseline were removed from the analysis; [b] based on calculation: remnant cholesterol = (total cholesterol) – (HDL-C) – (LDL-C, ultracentrifugation)
*Analysis of Covariance (ANCOVA) with repeated measures modeling was used for statistical modeling; Ballantyne CM, et al. N Engl J Med. Published online May 28, 2024. doi:10.1056/NEJMoa2404143

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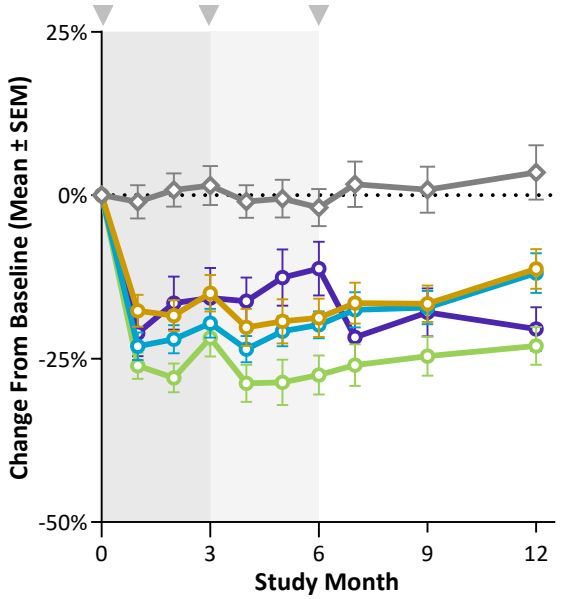
MUIR

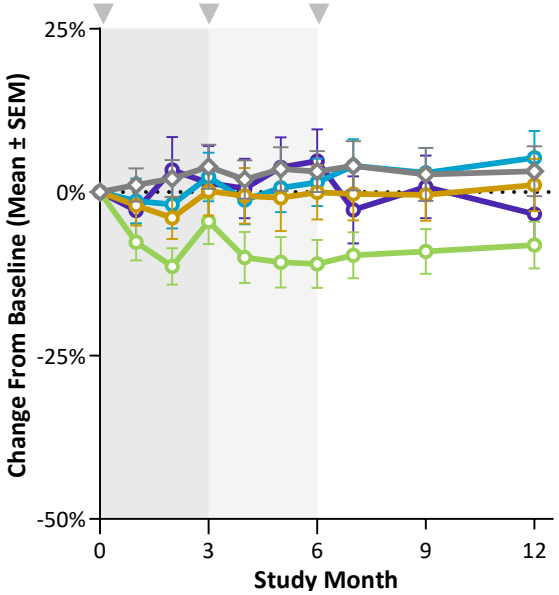
Positive Impact on Atherogenic Lipids/Lipoproteins

Non-HDL-C



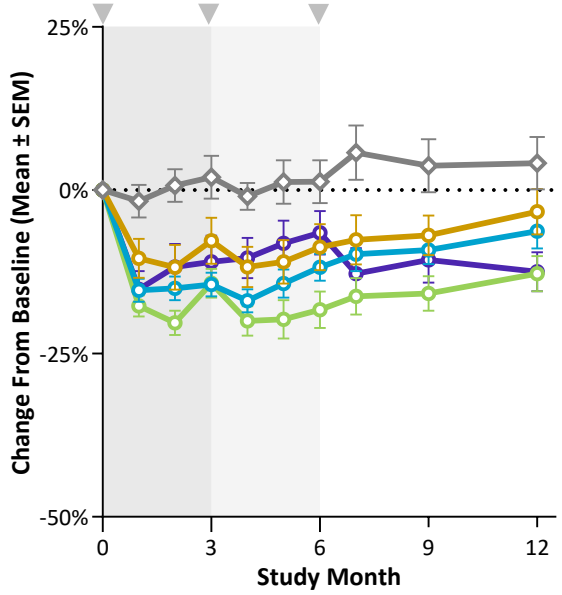
Change from Baseline (LS Mean)					
24 Weeks	-3%	-19%	-20%	-27%	-10%

LDL-C



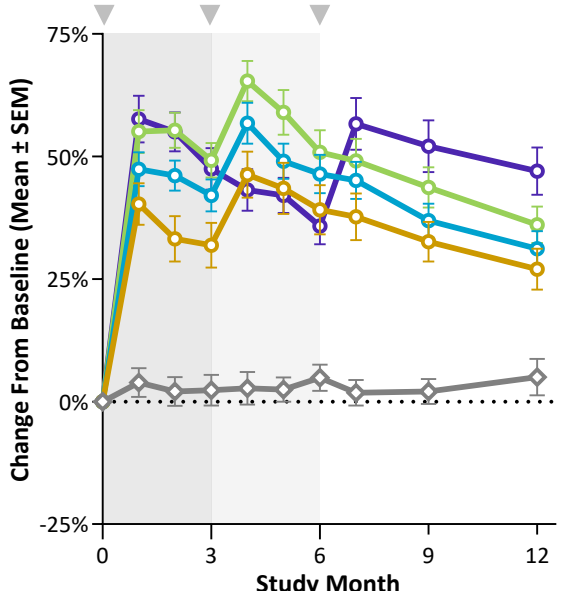
Change from Baseline (LS Mean)					
24 Weeks	3%	-1%	1%	-10%	6%

ApoB



Change from Baseline (LS Mean)					
24 Weeks	1%	-10%	-12%	-18%	-6%

HDL-C



Change from Baseline (LS Mean)					
24 Weeks	5%	38%	47%	51%	33%

Plozasiran

10 mg Q3M | 25 mg Q3M | 50 mg Q3M | 50 mg Q6M | Placebo

Q3M/Q6M Dosing

Ballantyne CM, et al. N Engl J Med. Published online May 28, 2024. doi:10.1056/NEJMoa2404143

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Comprehensive SUMMIT Clinical Program

SUMMIT PROGRAM

Familial Chylomicronemia Syndrome (FCS)	PALISADE	In adults with **FCS and TG ≥880 mg/dL (N=75)**, the primary endpoint was to evaluate change in TG levels at Month 10*	Study Completed	Phase 3
Severe Hypertriglyceridemia (SHTG)	SHASTA-2	In adults with **TG ≥500 mg/dL (N=226)**, the primary endpoint was to evaluate change in TG levels at Month 6[1]*	Study Completed	Phase 2
	SHASTA-3	In adults with **TG ≥500 mg/dL (N=405)**, the primary endpoint is to evaluate change in TG levels at Month 12*[†]	Currently Enrolling	Phase 3
	SHASTA-4	In adults with **TG ≥500 mg/dL (N=300)**, the primary endpoint is to evaluate change in TG levels at Month 12*	Currently Enrolling	Phase 3
	SHASTA-5	In adults with **TG >880 mg/dL and a history of >2 acute pancreatitis events (N=140)**, the primary endpoint will be to evaluate the time to first occurrence of positively adjudicated acute pancreatitis event*	Coming Soon	Phase 3
Mixed Hyperlipidemia	MUIR	In adults with **TG 150-499 mg/dL and non-HDL-C ≥100 mg/dL or LDL-C ≥70 mg/dL (N=353)**, the primary endpoint was to evaluate change in TG levels at Month 6[2]*	Study Completed	Phase 2
	MUIR-3	In adults with **TG 150-499 mg/dL (N=1328)**, the primary endpoint is to evaluate change in TG levels at Month 12	Currently Enrolling	Phase 3
	CAPITAN	In adults with e**levated levels of TRLs and residual risk of primary or secondary ASCVD events**, the primary endpoint will be to evaluate the time to first occurrence of any component of clinical composite endpoint of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and major adverse limb events	Coming Soon	Phase 3

*Open-label extension period or study is available for patients who participate in the clinical trial program. †A subset of patients enrolled in SHASTA-3 will undergo serial MRI-PDFF in a substudy to assess change in LFC.

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LFC, liver fat content; MI, myocardial infarction; MRI-PDFF, magnetic resonance imaging proton density fat fraction; TG, triglyceride; TRL, triglyceride-rich lipoprotein.

1. Gaudet D, et al. *JAMA Cardiol*. 2024:e240959. doi:10.1001/jamacardio.2024.0959 2. Ballantyne CM, et al. *N Engl J Med*. 2024. doi:10.1056/NEJMoa2404143

For more information or to refer a patient, please reach out to cardiomet@arrowheadpharma.com.
For additional information, please visit the Arrowhead Pharmaceuticals website. https://arrowheadpharma.com/science-and-innovation/clinical-trials/

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Plozasiran PALISADE Phase 3 Results – September 3, 2024

ESC 2024 Encore Presentation

Gerald F. Watts, DSc, MD, PhD
Winthrop Professor of Cardio-metabolic Medicine
University of Western Australia

arrowhead pharmaceuticals

PALISADE

A Randomised, Placebo-Controlled Phase 3 Study of Plozasiran in Patients with Familial Chylomicronemia Syndrome

Gerald F Watts: University of Western Australia

September 2, 2024

Financial 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.

Plozasiran is an investigational drug in late-stage development

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Persistent Chylomicronemia

- **Extremely high plasma triglycerides** (> 10 mmol/L, 880 mg/dL) in which the fat you eat and then absorbed as particles, called chylomicrons, cannot be cleared from the circulation[1].

- **Due to ultrarare bi-allelic recessive variants** (Familial Chylomicronemia Syndrome, FCS) **or more common genetic variants** (Multifactorial Chylomicronemia Syndrome) that **impair the lipolytic enzyme, lipoprotein lipase (LPL)**[1-4].
  - Adults with extreme chylomicronemia, a high-risk subset of which, can phenocopy classical FCS

- **Chylomicronemia causes multiple symptoms** (physical, cognitive, emotional), the most severe being **acute pancreatitis** and its life-threatening sequelae[5-8].
  - Directly related to Triglyceride levels > 5.5 mmol/L (>500 mg/dL)

- **Current therapeutic agents** (fibrates, n-3 fatty acids, statins, niacin) are **generally ineffective**

1. Brunzell JD, Bierman EL. Med Clin North Am. 1982;66(2):455–6 2. Pallazola VA, et al. *Eur J Prev Cardiol*. 2020;27(19):2276-8. 3. Warden BA, et al. *J Clin Lipidol*. 2020;14(2):201-6. 4. M Paquette et al. Journal of Clinical Endocrinology & Metabolism, Volume 106, Issue 9, September 2021, Pages e3473–e3482, 5. Gelrud A, et al. Expert Rev Cardiovasc Ther 2017;15(11):879-887. 6. Murphy MJ, et al. JAMA Intern Med. 2013;173(2):162–4. 7. Yuan G, Al-Shali KZ, Hegele RA. CMAJ. 2007;176(8):1113–20. 8. Nawaz H, et al. Am J Gastroenterol. 2015 Oct;110(10):1497-503. 9. Dron JS, Hegele RA. Front Endocrinol (Lausanne) 2020;11:455.10. Hansen SEJ et al. Clinical Gastroenterology and Hepatology 2021;19(8):1652-1660.e6

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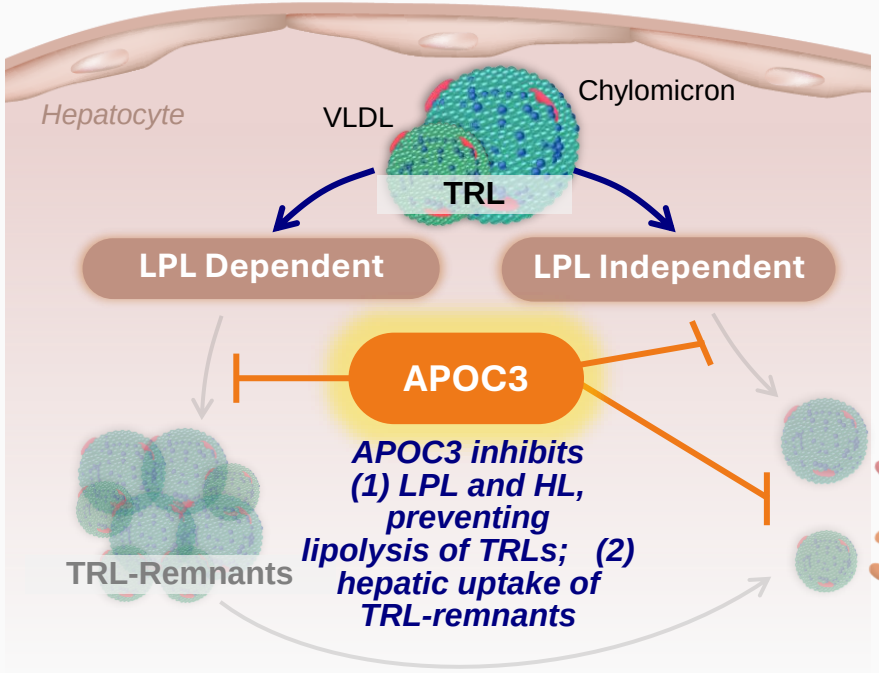
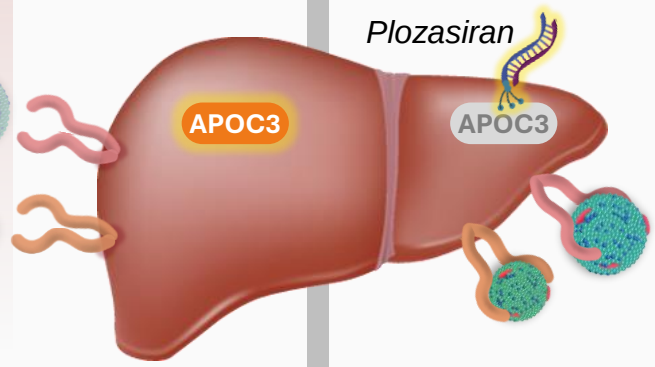
Plozasiran (ARO-APOC3) is an Investigational siRNA Therapeutic Targeting APOC3, a Key Regulator of TG and TRL Metabolism

CHYLOMICRONEMIA[1,2]

APOC3 inhibits lipolysis and hepatic clearance of TRLs, increasing TGs

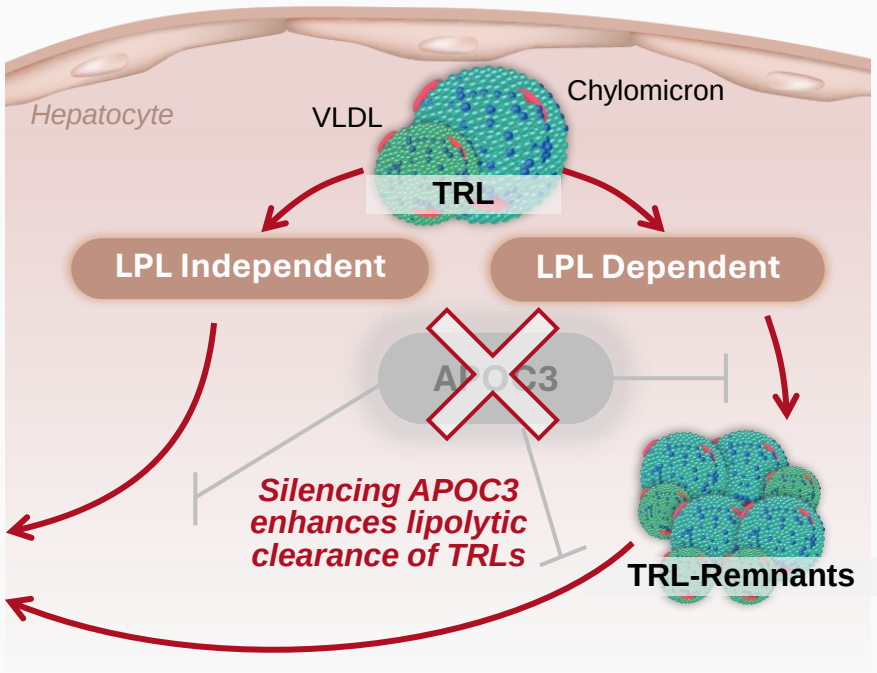


APOC3 inhibits LPL and delays clearance of TRL-remnants by preventing uptake by liver receptors, increasing plasma TGs



PLOZASIRAN[2]

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



Silencing APOC3 enhances TG lipolysis and TRL-remnant clearance by hepatic receptors, reducing plasma 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; **TG**=triglycerides; **TRL**=triglyceride rich lipoproteins; **VLDL**=very low-density lipoprotein.

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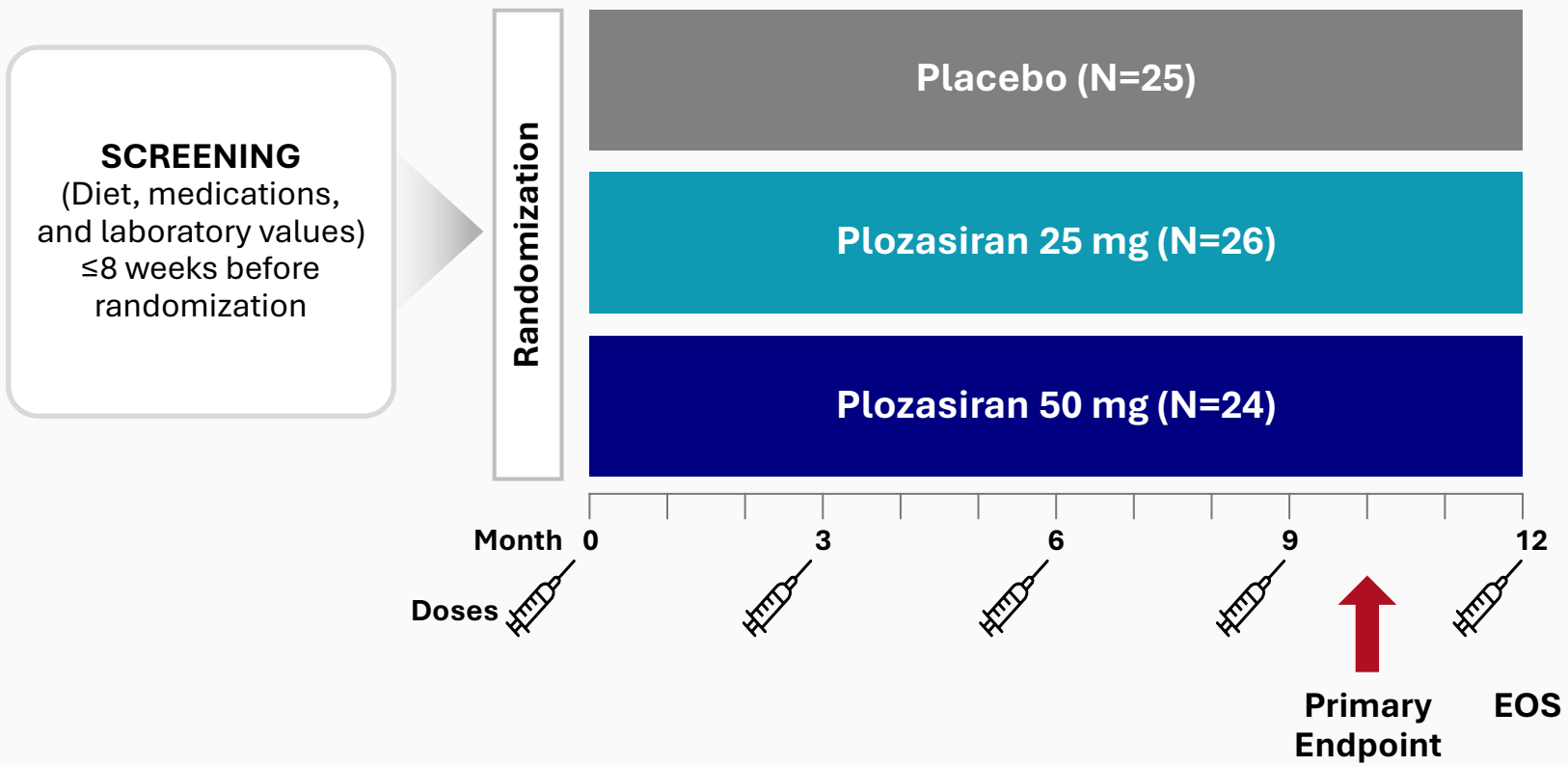
PALISADE: Randomized Placebo-Controlled Phase 3 Study of Plozasiran in Patients with FCS



Primary Endpoint:

- Placebo-adjusted median percent change in triglycerides at Month 10

Multiplicity-controlled key secondary endpoints:

1. Percent change from baseline at Months 10 and 12 (averaged) in fasting triglycerides
2. Percent change from baseline at Month 10 in fasting APOC3
3. Percent change from baseline at Month 12 in fasting APOC3
4. Incidence of positively adjudicated events of acute pancreatitis during the randomized period

APOC3=apolipoprotein C3; **FCS**=familial chylomicronemia syndrome; **EOS**=end of study.

PALISADE Enrolled Patients with FCS Defined Clinically or Genetically Confirmed

Criteria included history of multiple TG measurements above 11.3 mmol/L (1000 mg/dL), despite best standard of care; plus at least one of the following:

1. **Prior genetic testing diagnostic of FCS* OR**
2. **Recurrent episodes of acute pancreatitis§ OR**
3. **Recurrent hospitalizations for severe abdominal pain without other explainable cause OR**
4. **History of childhood pancreatitis OR**
5. **Family history of HTG-induced acute pancreatitis**

Genetic testing was done on all patients without prior testing for FCS variants

*Supportive genetic testing includes but is not limited to homozygous, compound heterozygous, or double heterozygote for loss-of-function or otherwise inactivating mutations in genes affecting lipoprotein lipase activity including LPL, APOC2, APOA5, GPIHBP1, GPD1, or LMF1; or evidence of low LPL activity (<20% of normal) based on source-verifiable documentation; § not caused by alcohol or cholelithiasis; HTG=hypertriglyceridemia

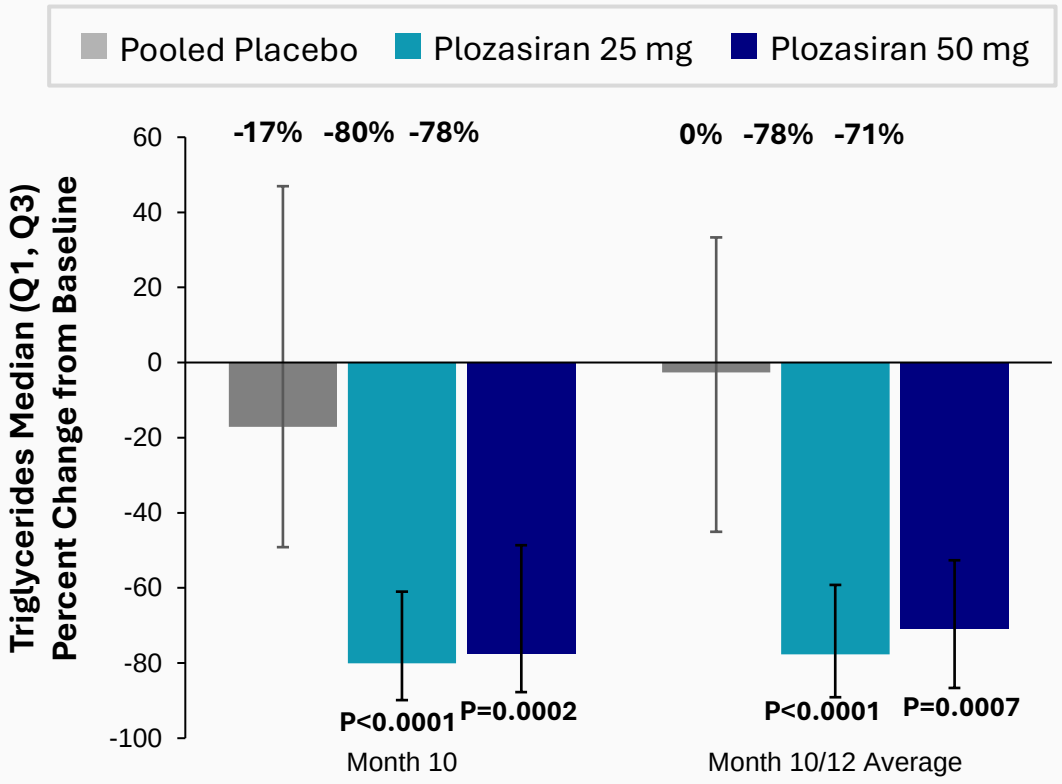
PALISADE Baseline Characteristics

Characteristic	Pooled Placebo (N=25)	Plozasiran 25 mg (N=26)	Plozasiran 50 mg (N=24)
Mean (SD) Age, years	47 (14)	48 (14)	43 (11)
Female, n (%)	11 (44)	14 (54)	13 (54)
Male, n (%)	14 (56)	12 (46)	11 (46)
White, n (%)	19 (76)	19 (73)	17 (71)
Mean (SD) BMI, kg/m^2	25 (4)	26 (4)	25 (5)
Median (Q1, Q3) APOC3, mg/dL	39 (29, 50)	39 (27, 44)	30 (18, 37)
Mean (SD) APOC3, mg/dL	40 (18)	39 (17)	33 (20)
Median (Q1, Q3) Triglyceride, mg/dL	2053 (1435, 2755)	2008 (1204, 3361)	1902 (1434, 2948)
Median (Q1, Q3) Triglyceride, mmol/L	23 (16, 31)	23 (14, 38)	22 (16, 33)
Mean (SD) Triglyceride, mg/dL	2272 (1141)	2350 (1375)	2492 (1523)
Mean (SD) Triglyceride, mmol/L	26 (13)	27 (16)	28 (17)
Receiving Statins n (%)	11 (44)	11 (42)	12 (50)
Fibrates, n (%)	16 (64)	19 (73)	15 (63)
Omega-3 fatty acids, n (%)	6 (24)	9 (35)	7 (29)
Diabetes or Pre-diabetes, n (%)	11 (44)	10 (39)	7 (29)
Genetic Confirmation of FCS, n (%)	14 (56)	14 (54)	16 (67)
Previous episode of pancreatitis, n (%)	22 (88)	23 (89)	22 (92)

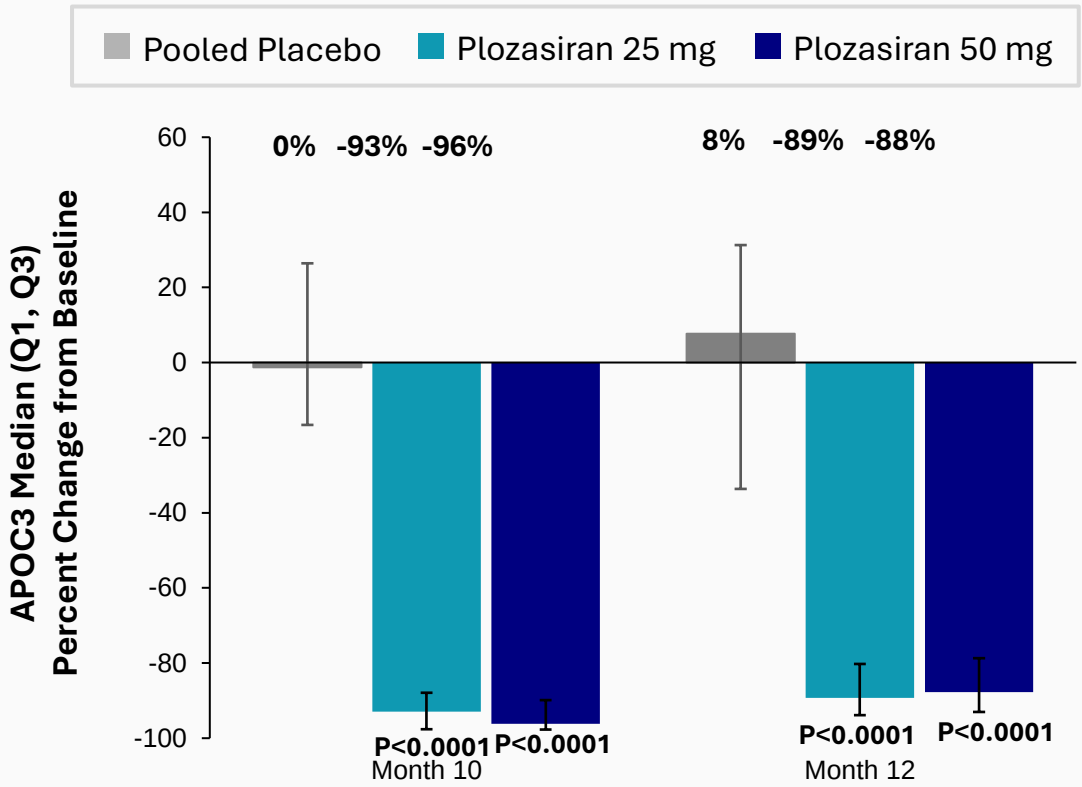
Data are reported as mean (±SD) unless otherwise noted. Note: Diabetic patients are defined as having HbA1c ≥6.5% or fasting glucose ≥126 mg/dL or with medical history of 'diabetes' or receiving diabetic medications at baseline. *% = 100 x n/N', N' is the number of diabetic or prediabetic patients at baseline.**APOC3**=apolipoprotein C3; **BMI**=body mass index; **FCS**=familial chylomicronemia syndrome; **N**=number; **Q**=quartile; **SD**=standard deviation; **W**=week.

Plozasiran Reduced Plasma Triglycerides and APOC3 Relative to Placebo in Persistent Chylomicronemia

Median Triglycerides†



Median APOC3

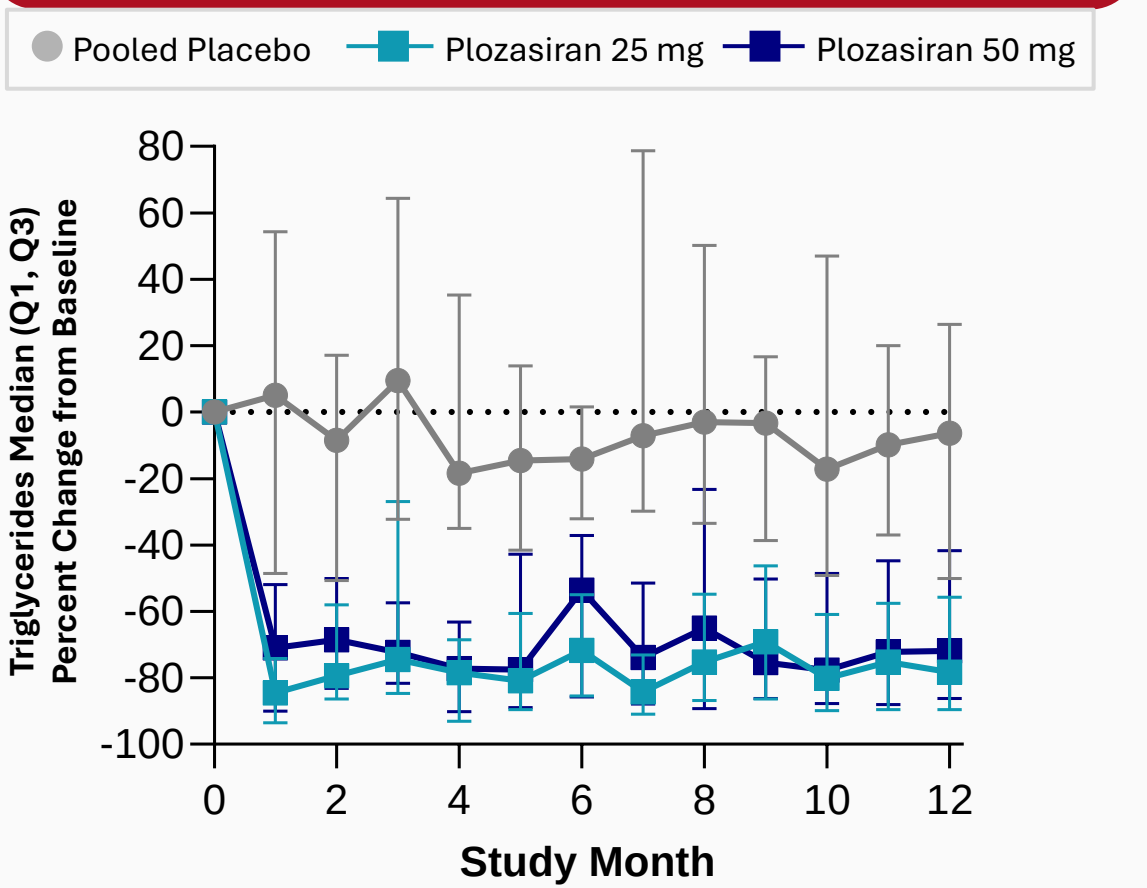


*P<0.001 vs placebo; †Primary and first key secondary endpoints

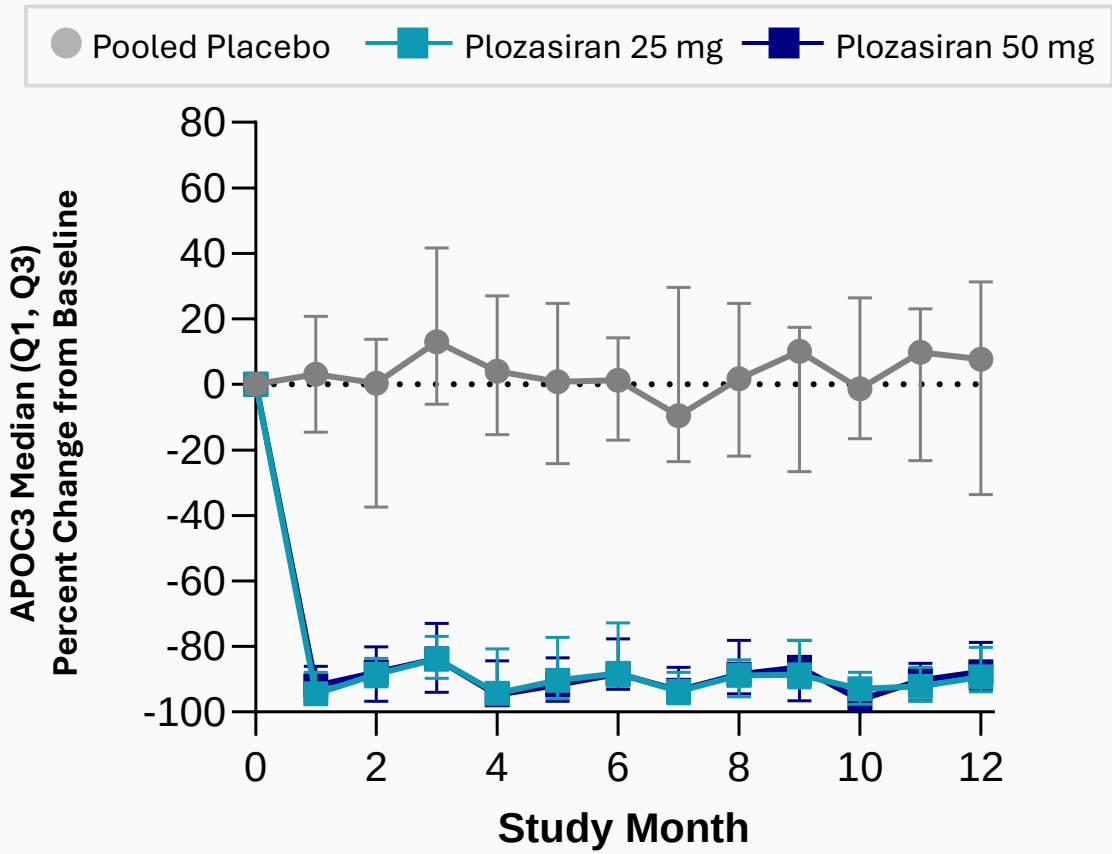
APOC3=apolipoprotein C3; **Q1**=1st quartile; **Q3**=3rd quartile.

Plozasiran Response at 1 Month Persisted to 12 Month Endpoint for Median Change in Triglycerides and APOC3

Median Triglycerides



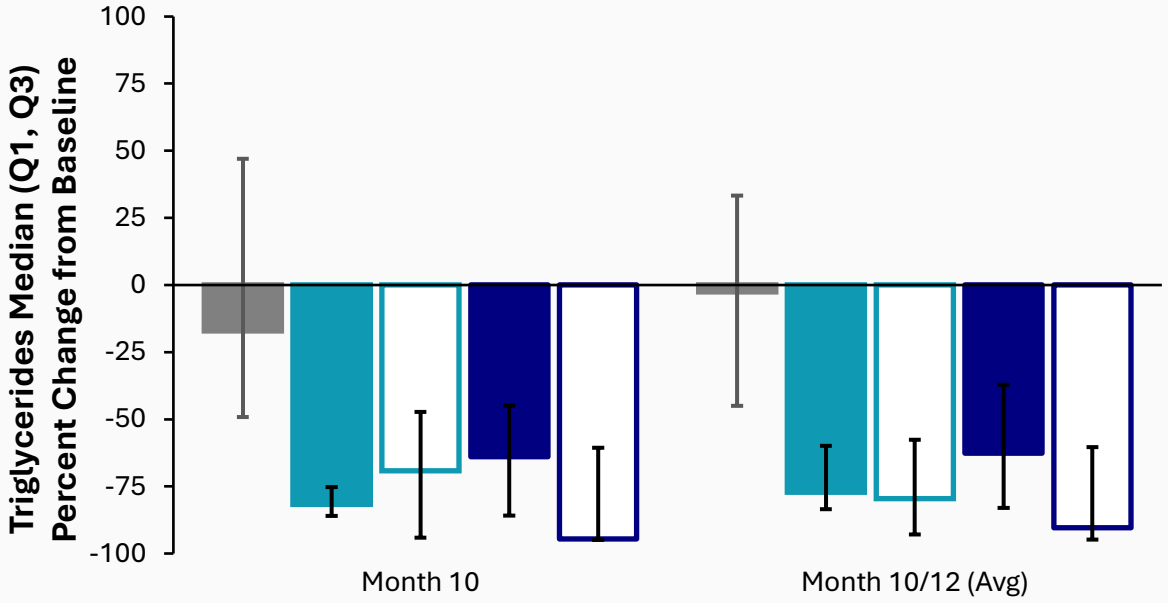
Median APOC3



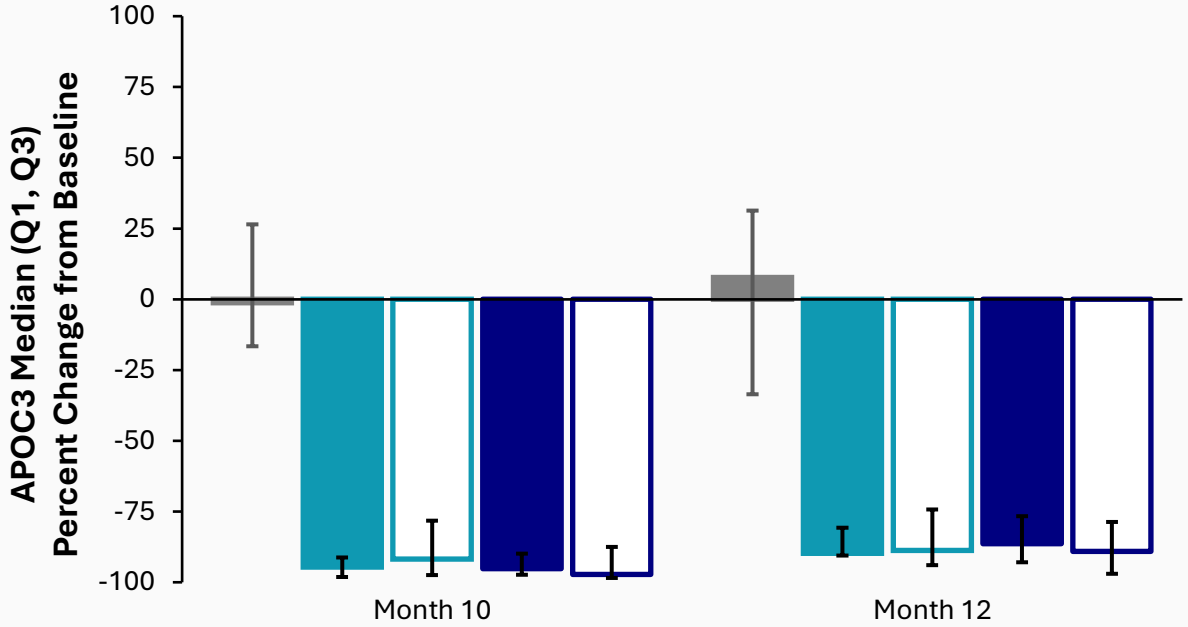
APOC3=apolipoprotein C3; **Q1**=1st quartile; **Q3**=3rd quartile.

Reductions in Triglyceride and APOC3 Levels According to Genetically Confirmed FCS

Triglycerides



APOC3



Pooled Placebo

With Genetic Confirmation of FCS
- Plozasiran 25 mg
- Plozasiran 50 mg

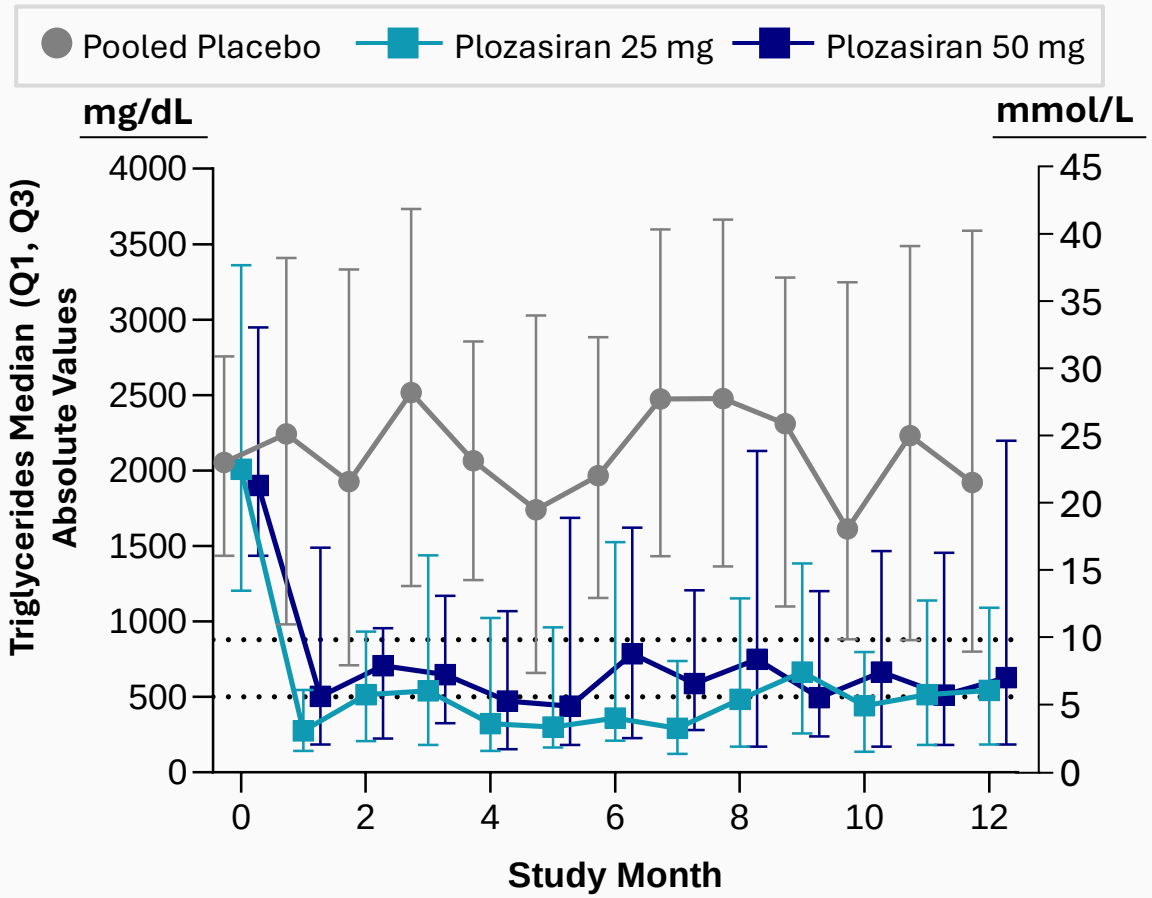
Without Genetic Confirmation of FCS
- Plozasiran 25 mg
- Plozasiran 50 mg

APOC3=apolipoprotein C3; **FCS**=familial chylomicronemia syndrome; **Q1**=1st quartile; **Q3**=3rd quartile.

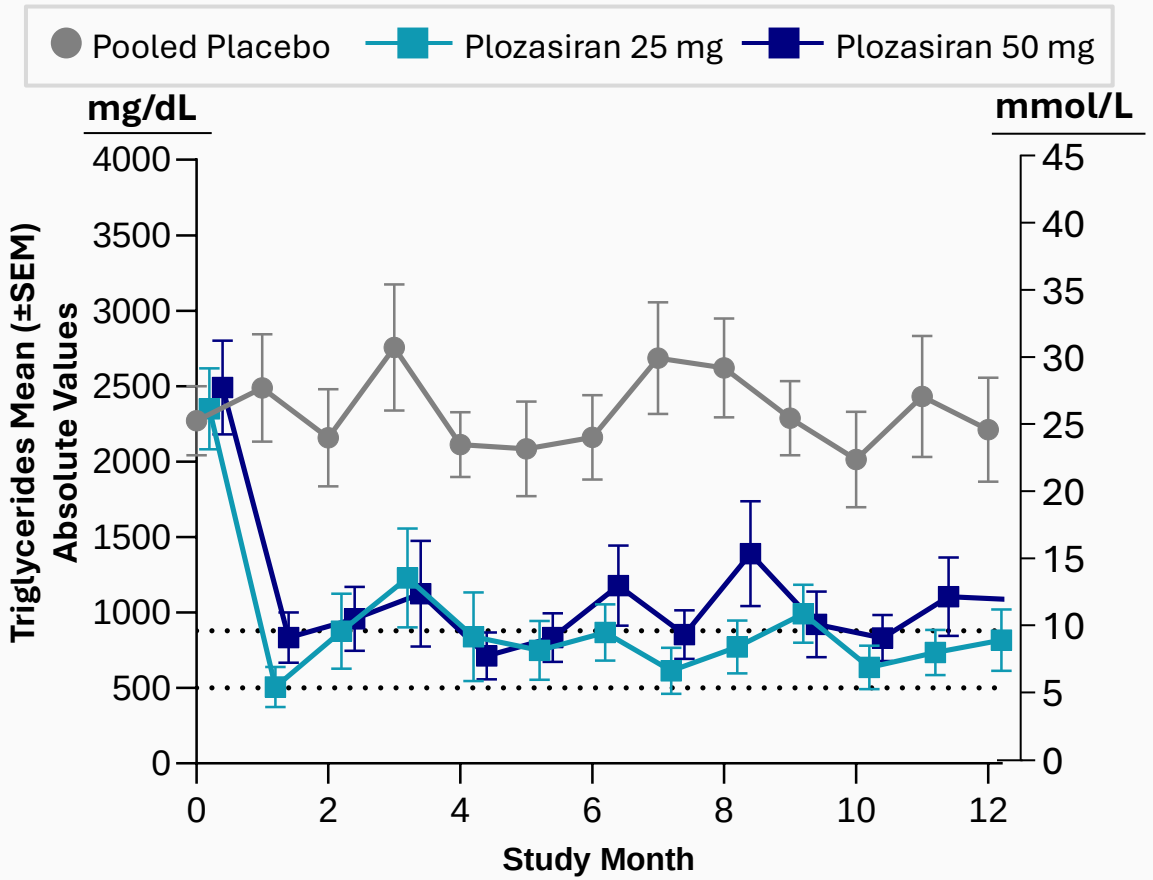
Plozasiran Reduced Plasma Triglyceride Levels to Below Thresholds for Risk of Acute Pancreatitis

PALISADE

Median Absolute Triglyceride Levels

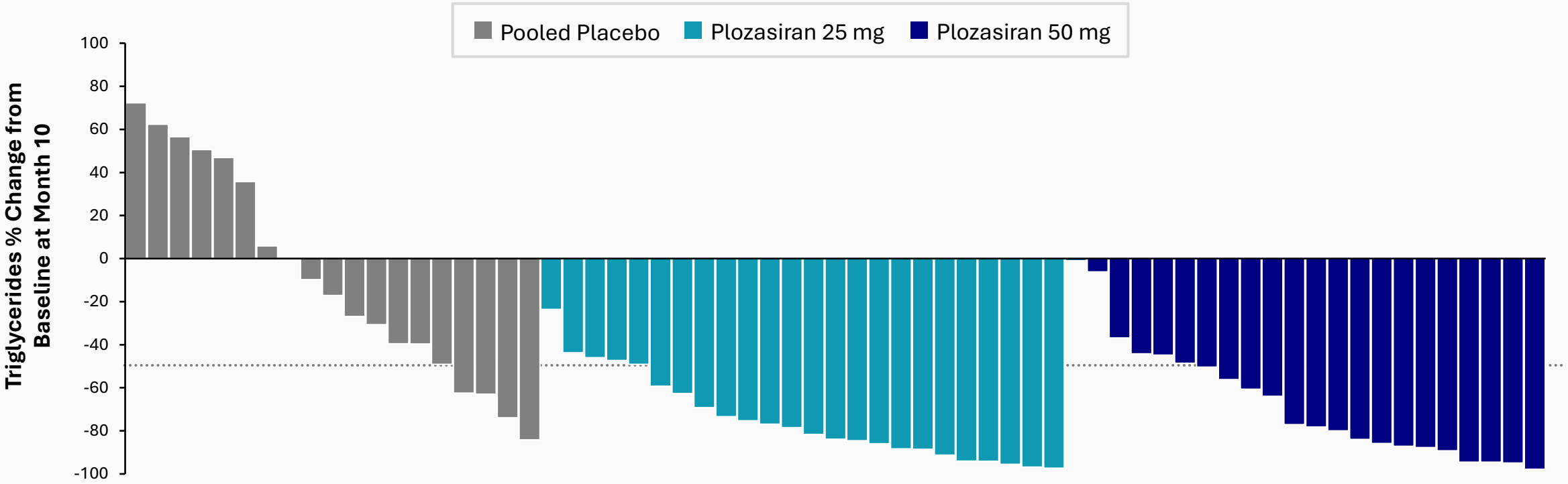


Mean Absolute Triglyceride Levels



Q1=1st quartile; **Q3**=3rd quartile; **SEM**=standard error of mean.

Reductions in Plasma Triglycerides and Percentage of Patients Attaining TGs Below Risk Thresholds for Pancreatitis

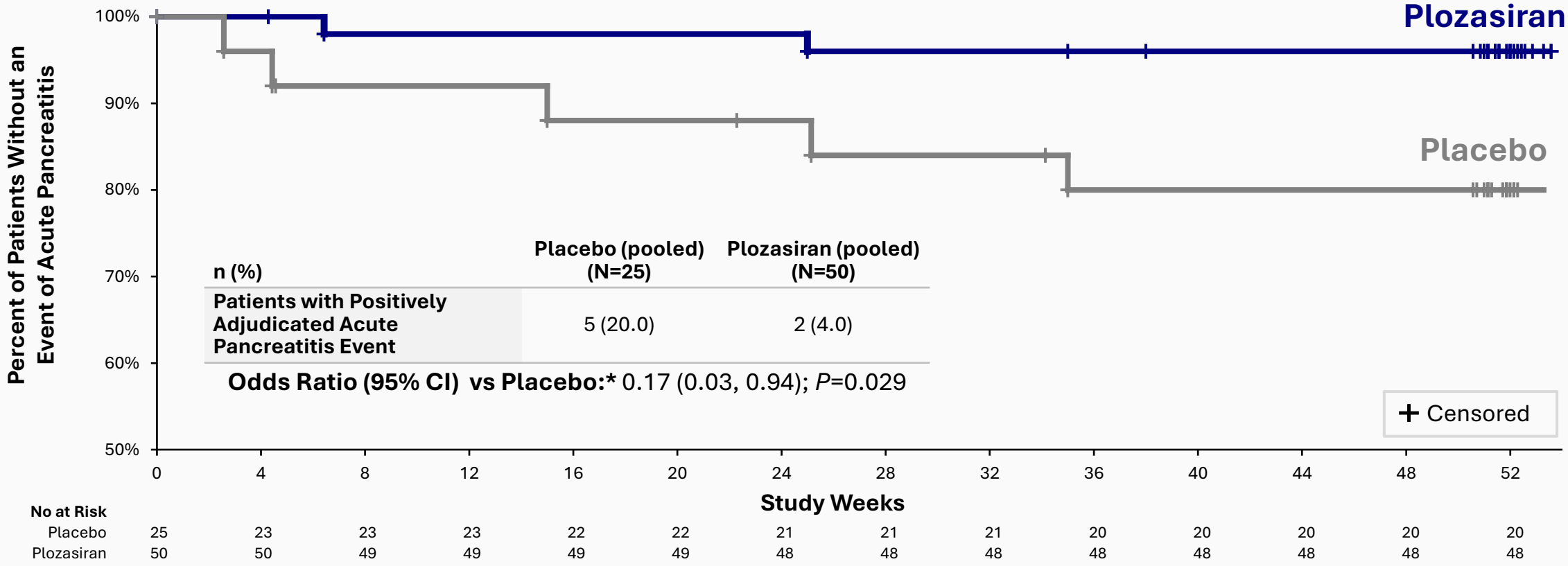


n (%)	Placebo (Pooled) (n=19)	Plozasiran 25 mg (n=24)	Plozasiran 50 mg (n=22)
All patients who reached triglycerides < 5.5 mmol/L (500 mg/dL) at month 10	1 (5%)	12 (50%)	10 (46%)
All patients who reached triglycerides < 10 mmol/L (880 mg/dL) at month 10	**4 (21%)**	**18 (75%)**	**12 (55%)**
All patients who reached triglycerides < 11 mmol/L (1000 mg/dL) at month 10	6 (32%)	20 (83%)	15 (68%)

Thresholds above 500 and 880 mg/dL increase risk of AP and CVD; Extremely high TG levels >1000 mg/dL can lead to "chylomicron syndrome," causing AP; **APOC3**=apolipoprotein C3.

Plozasiran Reduced the Incidence of Acute Pancreatitis

Time to First Pancreatitis Event



n (%)	Placebo (pooled) (N=25)	Plozasiran (pooled) (N=50)
Patients with Positively Adjudicated Acute Pancreatitis Event	5 (20.0)	2 (4.0)

Odds Ratio (95% CI) vs Placebo:* 0.17 (0.03, 0.94); *P*=0.029

No at Risk														
Placebo	25	23	23	23	22	22	21	21	21	20	20	20	20	20
Plozasiran	50	50	49	49	49	49	48	48	48	48	48	48	48	48

*Odds ratio, 95% CI, and P-value were based on CMH test stratified by baseline TG category.
7 incident cases occurred in 5 of 25 (20%) participants receiving placebo and 2 incident cases occurred in 2 of 50 (4%) participants in the plozasiran-treated group.**CI**=confidence interval; **CMH**=Cochran-Mantel-Haenszel; **TG**=triglyceride.

Summary of Adverse Events

	Pooled Placebo (N=25)	Plozasiran	
		25 mg (N=26)	50 mg (N=24)
Patients with Any TEAEs	20	23	20
Most Common TEAEs, N (%)			
Abdominal Pain	5 (20)	7 (27)	6 (25)
COVID-19 Infection*	0 (0)	5 (19)	7 (29)
Nasopharyngitis	3 (12)	5 (19)	2 (8)
Headache	2 (8)	3 (12)	5 (21)
Nausea	2 (8)	4 (15)	3 (13)
Back Pain	2 (8)	3 (12)	2 (8)
Upper respiratory tract infection	2 (8)	3 (12)	2 (8)
Diarrhea	2 (8)	1 (4)	4 (17)
Severe TEAEs	5 (20)	3 (12)	3 (13)
Serious TEAEs	7 (28)	5 (19)	2 (8)
Deaths	0 (0)	0 (0)	0 (0)
Premature Discontinuations	6 (24)	3 (12)	2 (8)
HbA1c, mean (SD)			
Baseline	6.1 (1.33)	5.7 (0.90)	5.59 (1.15)
Month 12	6.2 (1.17)	5.98 (1.00)	5.83 (1.56)
Platelet count, 10^9/liter, mean (SD)			
Baseline	217.9 (80.5)	204.4 (70.4)	192.9 (50.7)
Mean change from baseline at Month 10	25.9 (38.2)	28.7 (61.2)	-4.4 (48.2)
Mean change from baseline at Month 12	8.6 (47.5)	-4.3 (40.8)	-8.7 (50.8)

- A greater proportion of placebo-treated patients experienced SAEs
- Fewer premature discontinuations with plozasiran
- No reductions in platelet counts
- Hyperglycemia with plozasiran confined to patients with pre-diabetes and diabetes
- No deaths

*The observed difference in COVID-19 occurrence in this trial was not seen in the larger phase 2b trials in mixed hyperlipidemia and severe hypertriglyceridemia also conducted during the COVID-19 pandemic, and likely was a chance finding.
HbA1c=glycosylated hemoglobin; **SD**=standard deviation; **SAE**=serious adverse event; **TEAE**=treatment emergent adverse event.

Conclusions

PALISADE met all trial endpoints (alpha-controlled)

- Plozasiran (quarterly dosing) significantly reduced triglycerides in patients with persistent chylomicronemia (FCS or FCS-like syndrome*) at 10 months; over half of patients achieved TG treatment goals
- Reductions in TGs and APOC3 apparent at 1 month and sustained thereafter with comparable efficacy in genetically and clinically defined patients
- Plozasiran significantly reduced acute pancreatitis at 12 months
- Favorable safety and tolerability similar to placebo
- Plozasiran is a novel therapeutic candidate for reducing plasma TG levels and risk of acute pancreatitis in patients with persistent chylomicronemia

*High risk MCS (patients with prior AP events and exceptionally high TGs)

APOC3=apolipoprotein C3; **FCS**=familial chylomicronemia syndrome; **mRNA**=messenger RNA; **siRNA**=small interfering RNA.



The study sponsors would like to thank

the patients who participated and their families,

and all investigators and staff who completed the trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Plozasiran for Managing Persistent Chylomicronemia and Pancreatitis Risk

Gerald F. Watts, D.Sc., M.D., Ph.D., Robert S. Rosenson, M.D., Robert A. Hegele, M.D., Ira J. Goldberg, M.D., Antonio Gallo, M.D., Ph.D., Ann Mertens, M.D., Ph.D., Alexis Baass, M.D., Rong Zhou, Ph.D., Ma'an Muhsin, M.D., Jennifer Hellawell, M.D., Nicholas J. Leeper, M.D., and Daniel Gaudet, M.D., Ph.D., for the PALISADE Study Group*

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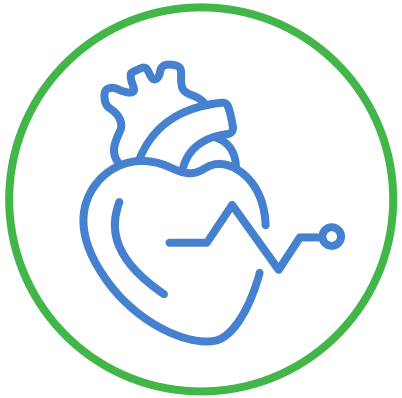
Plozasiran PALISADE Phase 3 Results – September 3, 2024



Commercial Readiness

Andy Davis
Senior Vice President, Head of Cardiometabolic Franchise

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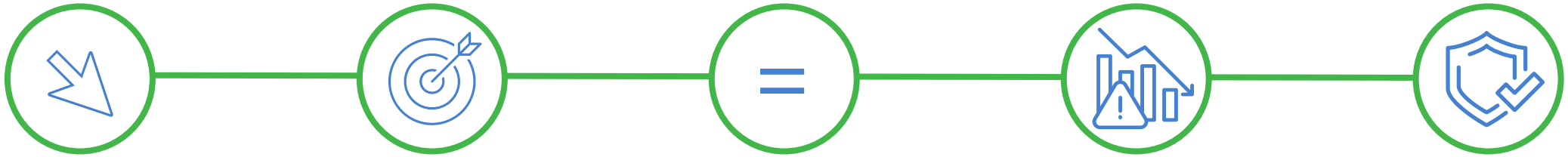
The Value Proposition of Plozasiran in FCS is Now Clear



TG Reduction

- **Deep:** reduction of 80% as early as month one[1]
- **Durable:** maintained throughout the treatment period

Goal Attainment

- Over 2/3 of plozasiran-treated patients reached levels **less than 880 mg/dL** and nearly 1/2 **less than 500 mg/dL**[2]

Consistent Effect

- Consistent TG reductions in patients with **genetically confirmed and clinically diagnosed FCS**

Risk Reduction

- **Statistically significant** reduction in risk of developing acute pancreatitis[3]

Attractive Profile

- **Favorable safety** and tolerability to date
- **Convenient dosing** every three-months

Delivering on what is important to patients, physicians, and payers

1. Compared to baseline
2. At month 10
3. In a pre-planned pooled analysis of active cohorts

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Our Commercialization Efforts Are On Track

	Key Launch Readiness Activities	
Medical	• Medical Education and Communication strategy developed with deployment of field medical underway	
Commercial Strategy	• Marketing and Market Access strategy developed and executing on key go-to-market activities	
Patient Services	• Patient hub provider selected and service offerings in development	
Regulatory	• Product development on track and regulatory interactions planned in the near future	
Commercial Field Force	• Field force go-to-market model decided and hiring plans established	
Launch	• Patient, provider, and payer Day 1 readiness	

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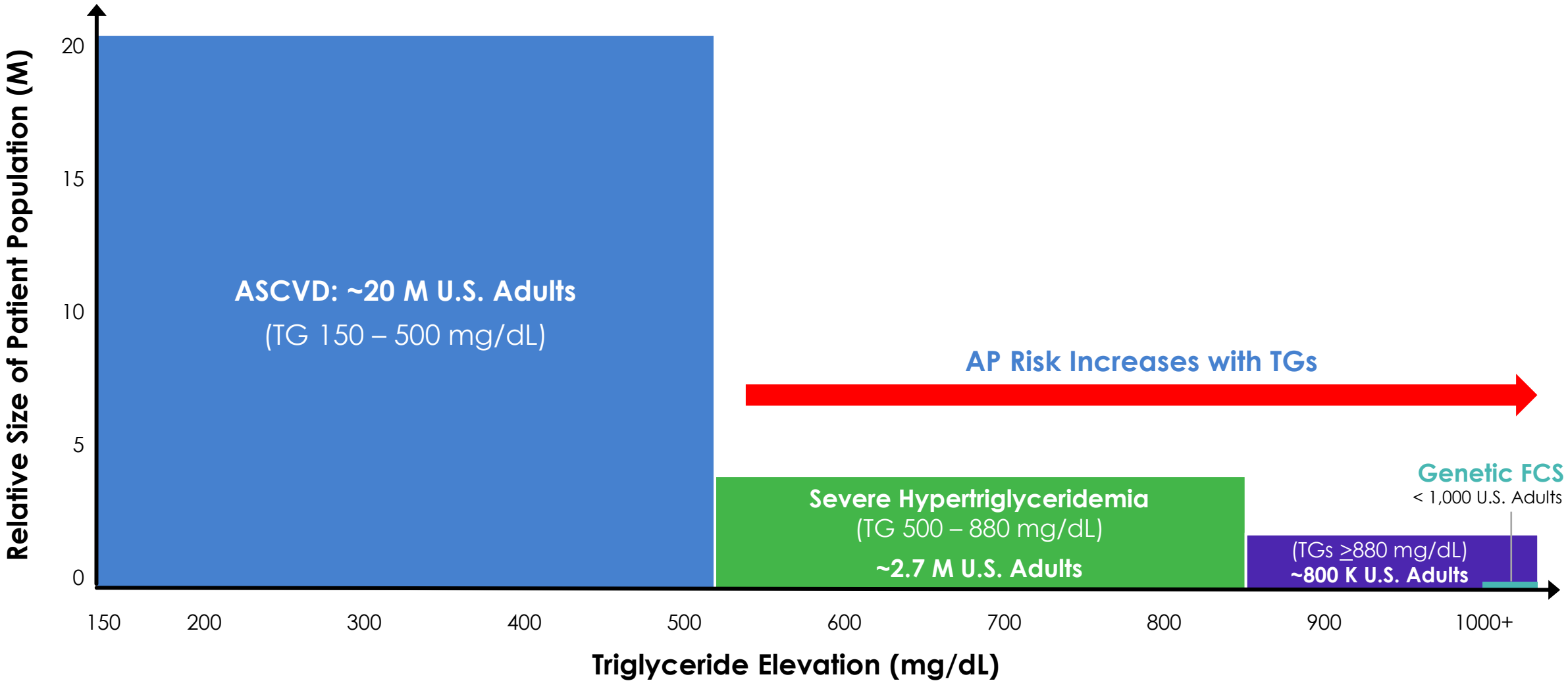
Plozasiran Addresses Multiple Triglyceride Segments



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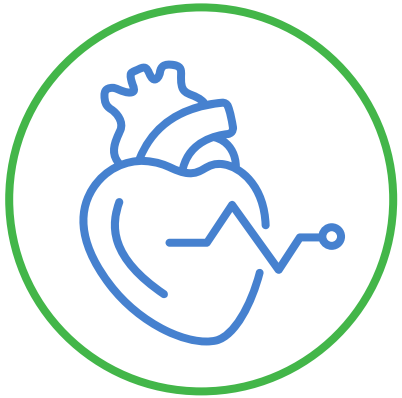
Plozasiran PALISADE Phase 3 Results – September 3, 2024



Concluding Remarks

Chris Anzalone, Ph.D.
President and CEO

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Arrowhead is Excited to Bring Plozasiran to FCS Patients

FCS patients deserve a powerful, reliable, and convenient therapy: plozasiran could provide that solution

Dramatic triglyceride lowering

- TGs reduced by 80% from baseline

TGs reduced to levels with lower risk of acute pancreatitis. At 25mg plozasiran:

- 83% of patients got below 1000 mg/dl
- 75% of patients got below 880 mg/dl
- 50% of patients got below 500 mg/dl

Reduction in acute pancreatitis

- Reduced risk of pancreatitis by 83%

Near complete suppression of APOC3

Convenient administration

- 4 SC doses per year

Favorable safety profile

We believe this will be attractive to patients, physicians, and payers

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This is an Important Step for Arrowhead…But Just the First

Plozasiran could be a pipeline in a drug

We hope to be serving FCS patients in 2025

NDA planned by EOY 2024

We are studying plozasiran in sHTG patients in multiple Phase 3s

Goal is to be fully-enrolled in 2025 and complete in 2026

We plan on studying plozasiran for ASCVD in broad population of patients

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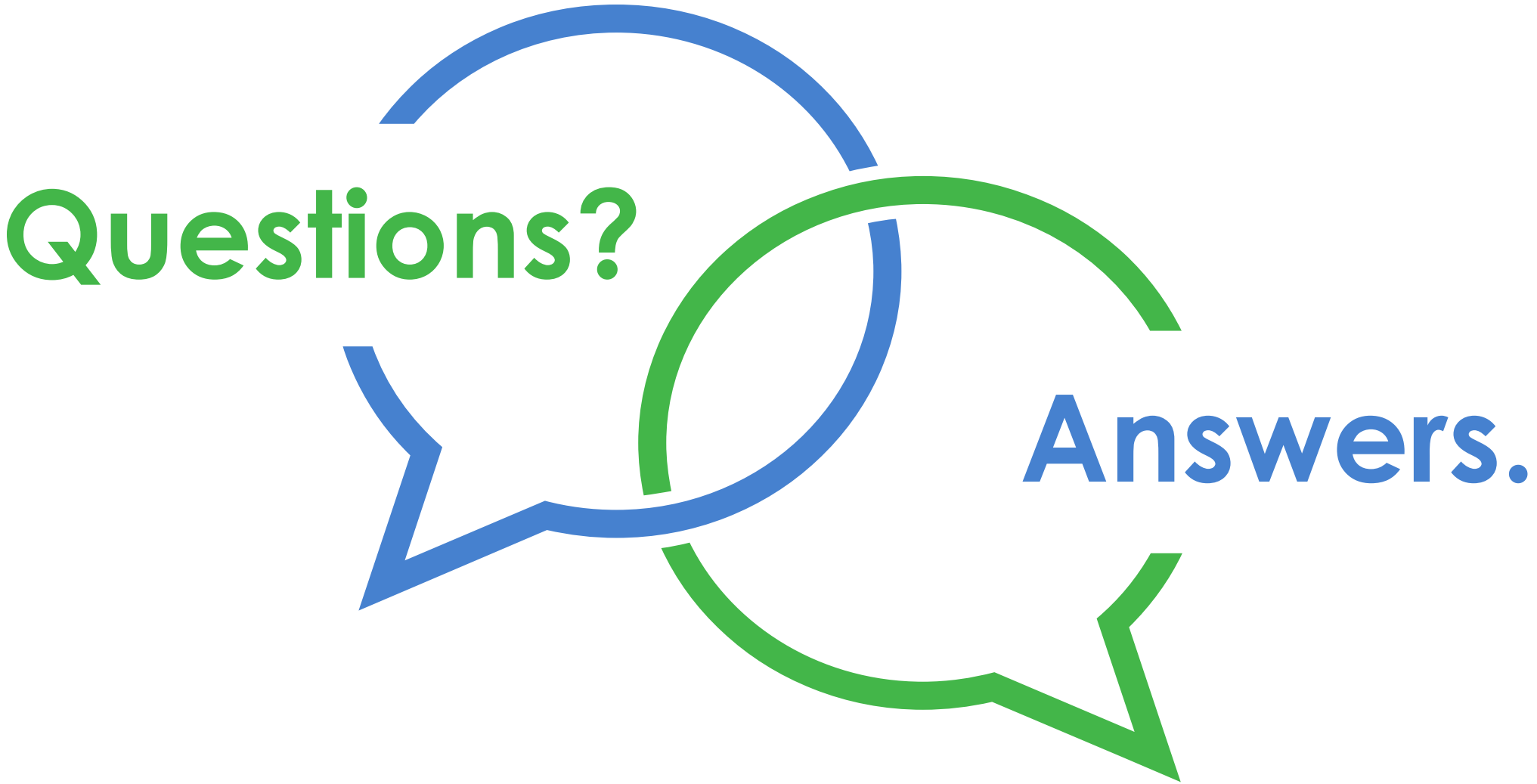

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