2024 Summer Series of R&D Webinars Part II – Cardiometabolic Programs

June 25, 2024

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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.

Cardiometabolic Webinar – June 25, 2024

Introductions and Cardiometabolic Update

Vince Anzalone, CFA
Vice President, Finance and IR

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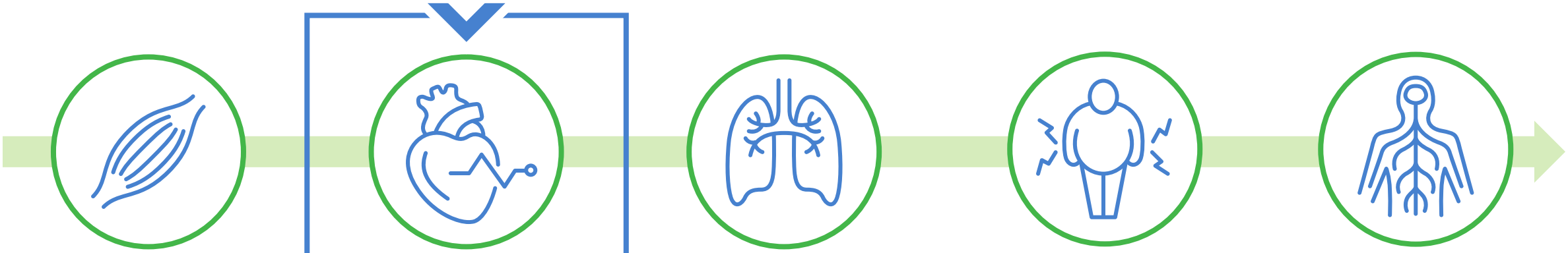
2024 Summer Series of R&D Webinars



Muscle

ARO-DM1 and ARO-DUX4

May 23, 2024

Cardiometabolic

Plozasiran and Zodasiran

June 25, 2024

Pulmonary

ARO-RAGE, ARO-MUC5AC, ARO-MMP7

July 16, 2024

Obesity/ Metabolic

ARO-INHBE and New Adipose Target

August 15, 2024

Central Nervous System

Platform and Pipeline Updates

Sept. 25, 2024

2024 Summer Series Goals

- Provide focused time to cover underappreciated parts of our pipeline
- Detail advances in the TRiM™ platform
- Hear directly from the Arrowhead team that worked on the programs
- Get external physician perspective on each disease area

Cardiometabolic Webinar Agenda

Time	Topic	Presenter
11:00-11:10	Introductions and Cardiometabolic Update	Vince Anzalone, CFA
11:10-11:20	Arrowhead's Cardiometabolic Focus	Bruce Given, MD
11:20-11:35	The Unmet Need in Triglycerides	Christie Ballantyne, MD, FACP, FACC
11:35-11:50	Addressing the Triglyceride Spectrum of Diseases	Jennifer Hellawell, MD
11:50-12:00	Meeting the Triglyceride Challenge Beyond FCS	Bruce Given, MD
12:00-12:05	Arrowhead's Future in Cardiometabolic Disease	Bruce Given, MD
12:05-12:15	Our Take on the Triglyceride Market	Vince Anzalone, CFA
12:15-12:30	Q&A	Panel

Cardiometabolic Opinion Leader

Christie Ballantyne, MD, FACP, FACC

Chief, Section of Cardiovascular Research

Director, Center for Cardiometabolic Disease Prevention

Professor of Medicine, Molecular and Human Genetics, and Integrative Physiology

Christie M. Ballantyne, MD, is an internationally renowned expert on lipids, atherosclerosis and heart disease prevention. He is the Chief of Cardiovascular Research and the Director of Cardiometabolic Disease Prevention at Baylor College of Medicine. Dr. Ballantyne's research in the prevention of heart disease led him to become an established investigator for the American Heart Association. Since 1988, Dr. Ballantyne has received continuous funding from the National Institutes of Health to support his basic research of leukocyte-endothelial interactions, translational biomarkers and clinical trials. Clarivate Web of Science named Dr. Ballantyne as a "Highly Cited Researcher" from 2017 to 2022, being in the top 1% of the most-cited investigators. This distinction is based on his 800-plus journal publications in the areas of atherosclerosis, lipids and inflammation.

Who We Are

Arrowhead is a **RNAi therapeutics platform company** with a **broad pipeline** of **wholly owned and partnered** product candidates

- **14 clinical stage programs** (10 wholly-owned; 4 partnered)
- 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**

- **Targeted RNAi Molecule (TRiM™)** platform achieves **deep and durable gene silencing**
- **Fulfilling the promise** of bringing RNAi therapeutics to diseases **outside of the liver**

- **Non-dilutive capital** from Amgen, Takeda, GSK, and Royalty Pharma as milestones are achieved and royalties are earned
- Potential for **additional** product, platform, and structured finance **deals**

20 in '25: We Expect to Have 20 Individual Drugs in Clinical Trials or At Market in 2025

Arrowhead Clinical Pipeline

Therapeutic Area		Pre-clinical	Phase 1	Phase 2	Phase 3	Product Rights
Cardiometabolic	**Plozasiran (ARO-APOC3)** Hypertriglyceridemia					
	Zodasiran (ARO-ANG3) Dyslipidemia					
	Olpasiran CVD					AMGEN
	GSK4532990 NASH					gsk
	ARO-PNPLA3 NASH					
Pulmonary	**ARO-RAGE** Inflammatory					
	ARO-MUC5AC Muco-Obstructive					
	ARO-MMP7 IPF					
Liver	**Fazirsiran** Alpha-1 Liver Disease					Takeda
	Daplusiran/Tomligisiran HBV					gsk
Muscular	**ARO-DUX4** FSHD					
	ARO-DM1 DM1					
Other	**ARO-C3** Complement Mediated Disease					
	ARO-CFB Complement Mediated Disease					

Tissue Targets: Liver Lung Muscle

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Increasing Focus on Plozasiran in Cardiometabolic Pipeline

Focus is Critical Now

- Capital allocation decisions are more consequential in late clinical and commercial stages
- Our strategy is to commercialize select high value programs
- Need to ensure lead commercial stage programs are fully funded
- Partner other high value opportunities that we elect not to or are unable to invest in ourselves

Decision Point for Cardiometabolic

- Process we went through
- Where we landed
- What we learned
- What about zodasiran?

You Will Hear More Today About How We Are So Excited About the Plozasiran Opportunity and What We're Doing to Be Ready to Launch in 2025 and Build in the Years Beyond

Cardiometabolic Webinar – June 25, 2024

Arrowhead's Cardiometabolic Focus

Bruce D. Given, M.D.
Chief Medical Scientist

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Why Cardiometabolic ?

- Despite the many impressive advances in CV therapeutics, atherosclerotic cardiovascular disease (ASCVD) remains the number one cause of mortality in western societies
- We now understand that cardiovascular disease and metabolic syndromes are closely linked
  - Many patients with Mixed Hyperlipidemia (aka mixed dyslipidemia) and Severe Hypertriglyceridemia are obese and/or diabetic
  - Patients with obesity or diabetes are at high risk for ASCVD and often die from CV events
- Thus, the obesity and diabetes epidemics are also driving the number one killer in western societies – ASCVD
- Arrowhead was an early entrant into cardiology with siRNAs
- Now we are entering the obesity/metabolic space to continue these efforts
  - A separate webinar will be held on August 15, 2024, so this part of our portfolio will not be discussed today

Arrowhead's Cardiometabolic Focus

- Olpasiran – Arrowhead's first TRiM™ drug
- The draw of genetically proven targets continues
  - We saw opportunities in gain of function diseases (e.g. Z-AAT, PNPLA3 I148M)
  - But also in loss of function (e.g., APOC3, ANGPTL3, HSD17ß13)
    - The genetic case for Apolipoprotein C3 (APOC3)
    - and Angiopoetin Like 3 (ANGPTL3)

Human Genetic Validation of Hypertriglyceridemia Targets

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Loss-of-Function Mutations in *APOC3* and Risk of Ischemic Vascular Disease

Anders Berg Jørgensen, M.D., Ph.D., Ruth Frikke-Schmidt, M.D., D.M.Sc., Borge G. Nordestgaard, M.D., D.M.Sc., and Anne Tybjærg-Hansen, M.D., D.M.Sc.

ORIGINAL ARTICLE

Loss-of-Function Mutations in *APOC3*, Triglycerides, and Coronary Disease

The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute*

BRIEF REPORT

Exome Sequencing, *ANGPTL3* Mutations, and Familial Combined Hypolipidemia

Kiran Musunuru, M.D., Ph.D., M.P.H., James P. Pirruccello, B.S., Ron Do, M.S., Gina M. Peloso, M.S., Candace Guiducci, B.S., Carrie Sougnez, BS., Kiran V. Garimella, M.S., Sheila Fisher, M.L.A., Justin Abreu, M.S., Andrew J. Barry, B.S., Tim Fennell, B.S., Eric Banks, Ph.D., Lauren Ambrogio, B.S., Kristian Cibulskis, B.S., Andrew Kernytsky, Ph.D., Elena Gonzalez, B.S., Nicholas Rudzicz, M.S., James C. Engert, Ph.D., Mark A. DePristo, Ph.D., Mark J. Daly, Ph.D., Jonathan C. Cohen, Ph.D., Helen H. Hobbs, M.D., David Altshuler, M.D., Ph.D., Gustav Schonfeld, M.D., Stacey B. Gabriel, Ph.D., Pin Yue, Ph.D., and Sekar Kathiresan, M.D.

ORIGINAL ARTICLE

Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease

F.E. Dewey, V. Gusarova, R.L. Dunbar, C. O'Dushlaine, C. Schurmann, O. Gottesman, S. McCarthy, C.V. Van Hout, S. Bruse, H.M. Dansky, J.B. Leader, M.F. Murray, M.D. Ritchie, H.L. Kirchner, L. Habegger, A. Lopez, J. Penn, A. Zhao, W. Shao, N. Stahl, A.J. Murphy, S. Hamon, A. Bouzelmat, R. Zhang, B. Shumel, R. Pordy, D. Gipe, G.A. Herman, W.H.H. Sheu, I-T. Lee, K.-W. Liang, X. Guo, J.I. Rotter, Y.-D.I. Chen,* W.E. Kraus, S.H. Shah, S. Damrauer, A. Small, D.J. Rader, A.B. Wulff, B.G. Nordestgaard, A. Tybjærg-Hansen, A.M. van den Hoek, H.M.G. Princen, D.H. Ledbetter, D.J. Carey,* J.D. Overton, J.G. Reid, W.J. Sasiela, P. Banerjee, A.R. Shuldiner, I.B. Borecki, T.M. Teslovich, G.D. Yancopoulos, S.J. Mellis, J. Gromada, and A. Baras

APOC3, ANGPTL3 Genetic Validation and Clinical Data

Lipid Parameters in Heterozygotes and Homozygotes for APOC3 and ANGPTL3 LOF Mutations Versus Non-carriers

Metric (serum level)[c]	*APOC3* deficient heterozygote[1]	*APOC3* deficient homozygote[2]	*ANGPTL3* deficient heterozygote[3]	*ANGPTL3* deficient homozygote[3]
ApoC-III	-46%	-88.9%	NA	NA
ANGPTL3	NA	NA	-40% to -87%	undetectable
Triglycerides	-39%	-59.6%	-21.1%	-71.2%
LDL-C	-16%	Similar to non-carrier	-8.6%	-67.2%
HDL-C	+22%	+26.9%	-16.8%	-39.0%
CAD risk	-40%	Not reported	-41%[4]	NA
Adverse Phenotype/AEs	None described	None described	None described	None described

1. Triglyceride working group, *NEJM* 2014
2. Saleheen et al., *Nature* 2016
3. Minicocci et al., *J of Lipid Research* 2013
4. Dewey et al, *NEJM* 2017

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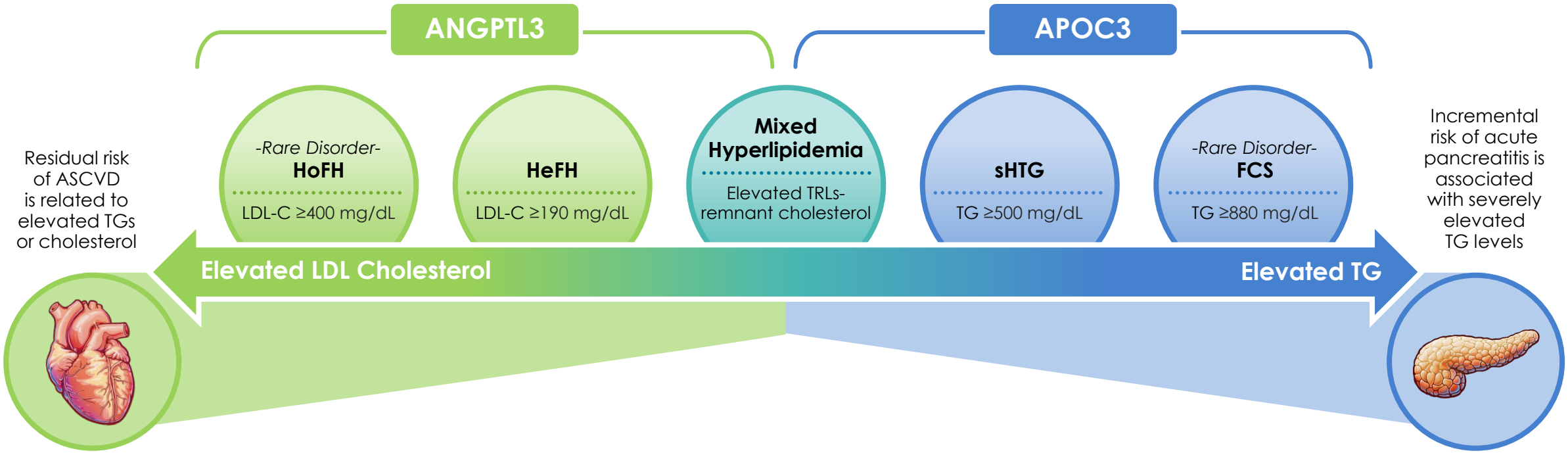
Arrowhead's Cardiometabolic Focus

- Olpasiran – Arrowhead's first TRIM drug
- The draw of genetically proven targets
  - There are opportunities in gain of function diseases (e.g., AAT, PNPLA3)
  - But also in loss of function examples……
    - The genetic case for Apolipoprotein C3 (APOC3)
    - The genetic case for Angiopoetin like-3 (ANGPTL3)
- The case for *AND NOT OR*
  - Different lipoprotein/lipid effects translate to different clinical opportunities

Hyperlipidemia and the CV Treatment Landscape

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.

Cardiometabolic Webinar – June 25, 2024

Triglycerides – a Poorly Treated, Large Cardiovascular Frontier with Major Unmet Needs

Christie Ballantyne, MD

Chief, Section of Cardiovascular Research

Director, Center for Cardiometabolic Disease Prevention

Professor of Medicine, Molecular and Human Genetics, and Integrative Physiology

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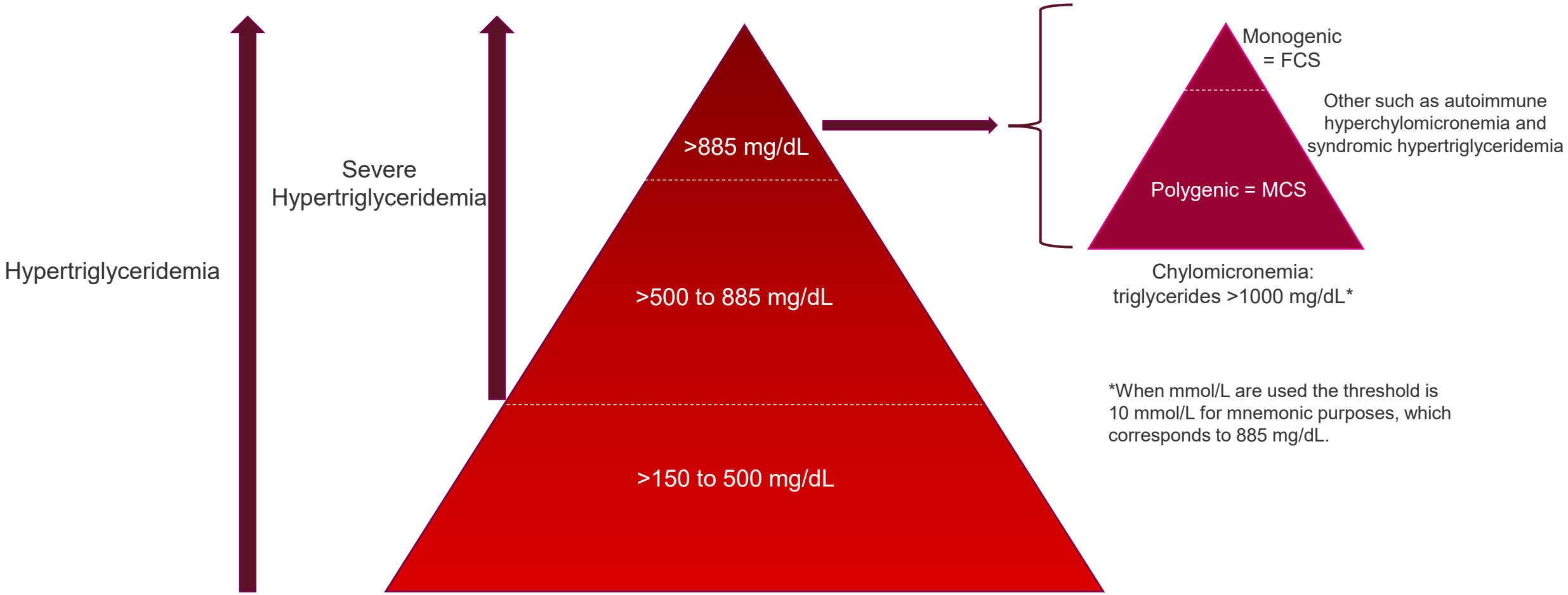
Christie M. Ballantyne, MD

Center for Cardiometabolic Disease Prevention

Baylor College of Medicine
Houston, Texas

Baylor College of Medicine

The Spectrum of sHTG



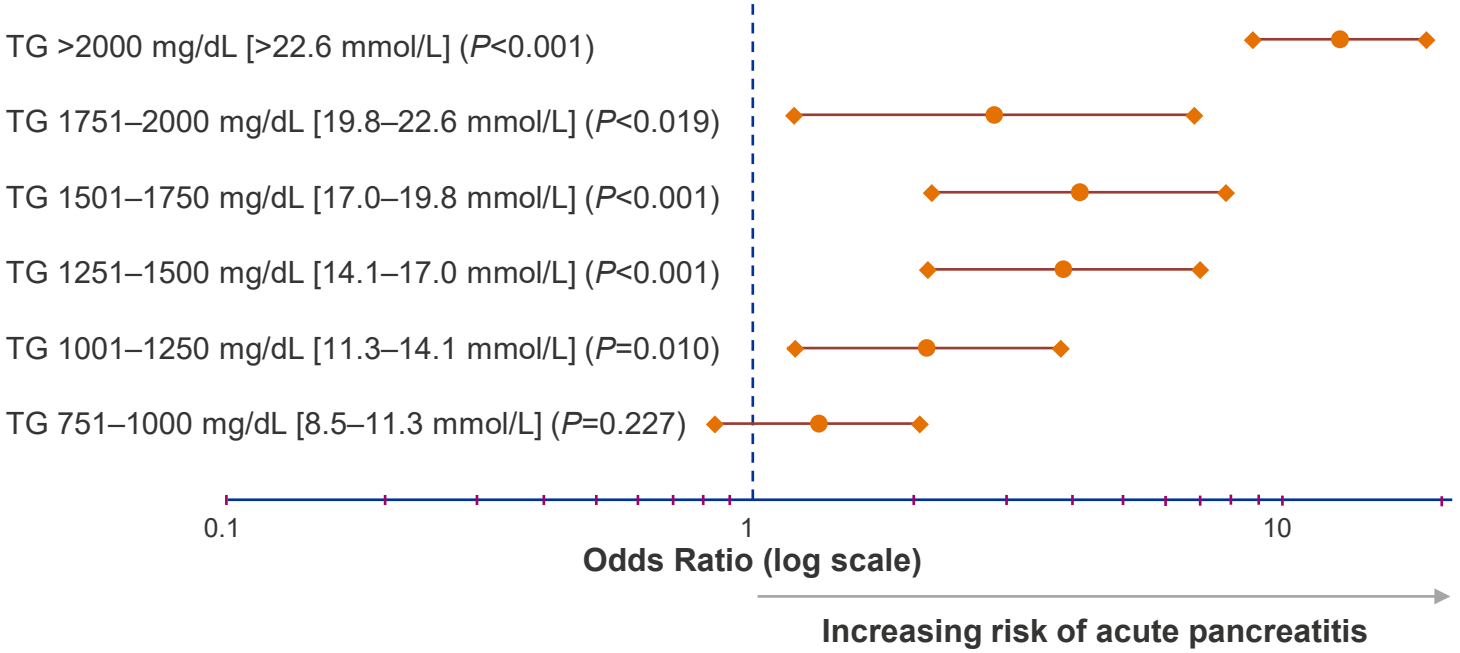
*When mmol/L are used the threshold is 10 mmol/L for mnemonic purposes, which corresponds to 885 mg/dL.

sHTG, severe hypertriglyceridemia; FCS, familial chylomicronemia syndrome; MCS, multifactorial chylomicronemia syndrome.
Figure adapted from Gallo A, et al. *Curr Atheroscler Rep.* 2020;22:63. Ginsberg HN, et al. *Eur Heart J.* 2021;42:4791-4806. Grundy SM, et al. *Circulation.* 2019;139:e1082-e1143.

sHTG is associated with a pronounced risk of acute pancreatitis in a real-world population

- Higher TG ranges were typically associated with a higher risk of acute pancreatitis than with lower TG ranges
- A significantly increased risk for acute pancreatitis in patients with TG levels >2000 mg/dL (22.6 mmol/L) OR 12.8; 95% CI 8.8–18.6; *P*<0.0001

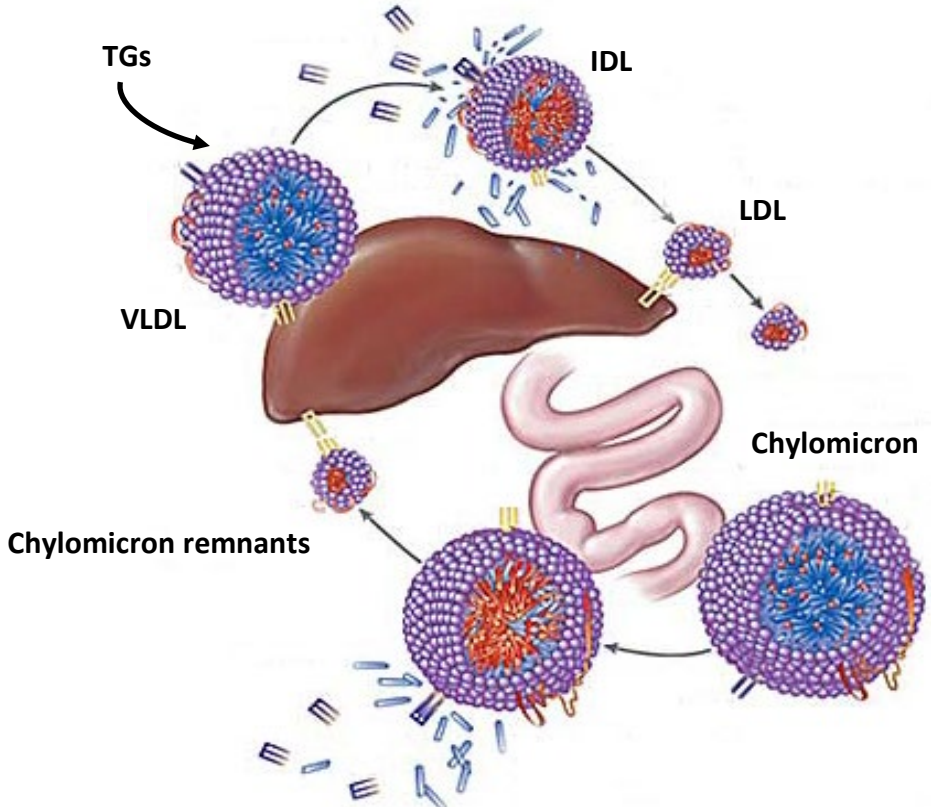
Risk of Acute Pancreatitis by Increasing TG Level: Retrospective Cohort Study Based on US Insurance Claims Data (N=53,627)



A multivariable logistic regression model was created in a sample combining patients from Cohorts A, B, and C, and using as the main predictors a set of 6 indicator variables based on TG ranges on index date.
CI, confidence interval; OR, odds ratio; sHTG, severe hypertriglyceridemia; TG, triglyceride.
Toth PP, *et al*. *Atherosclerosis* 2014;237:790-797.

Overview of Severe Hypertriglyceridemia (sHTG)

Pathophysiology of sHTG



Characterized by fasting TG levels ≥500 mg/dL[1]

- Normal TG levels ≤150 mg/dL
- Impaired clearance or overproduction of TG-rich VLDL and chylomicrons

Prevalence of 3.4 M patients in the US[1,2]

- Most present with comorbid conditions such as diabetes, hypertension, and metabolic syndromes

Primary risks are developing acute pancreatitis[2,3] and CV disease[4]

- Risk of acute pancreatitis is known to increase with TG levels >1000 mg/dL
- Clinically relevant risk of CV complications in patients with TG levels of >150 mg/dL*

SoC is diet and lifestyle followed by pharmacotherapy[1,3]

- Generic fibrates followed by addition or switch to omega-3s are used in adjunct to diet and exercise
- Emphasis on low-fat diet or very low-fat diet in select patients

*Limited information on CV risk >500 mg/dL.

CV, cardiovascular; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; sHTG, severe hypertriglyceridemia; SoC, standard of care; TG, triglyceride; VLDL, very low-density lipoprotein.

1. Christian JB, et al. *Am J Cardiol*. 2011;107:891-897. 2. Toth PP, et al. *Atherosclerosis*. 2014;237:790-797. 3. Virani SS, et al. *J Am Coll Cardiol*. 2021;78:960-993. 4. Ginsberg HN, et al. *Eur Heart J*. 2021;42:4791-4806.

Genetic Factors Contribute to Elevated Levels of TG-Rich Lipoproteins

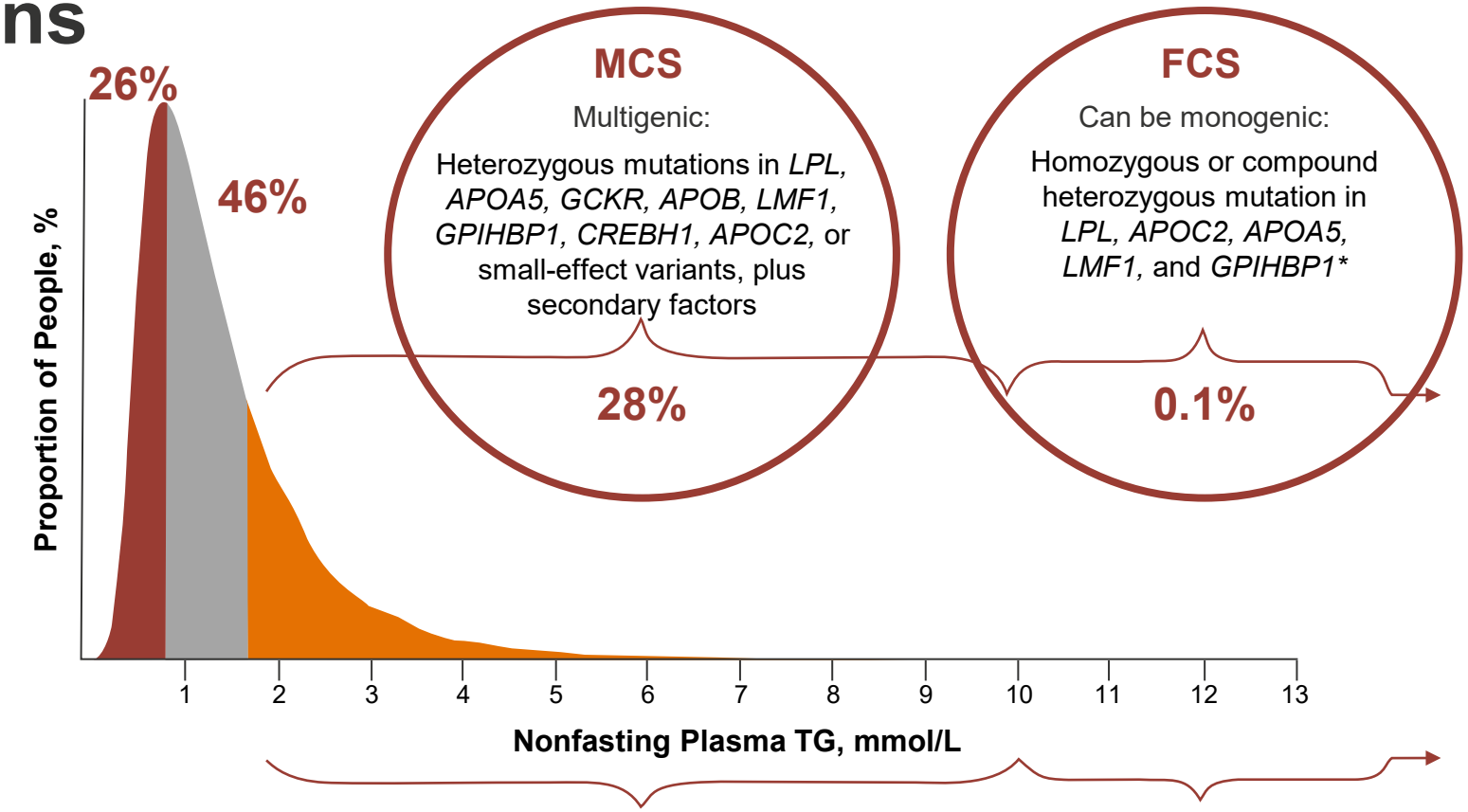


Figure adapted from: Hegele RA, et al. *Lancet Diabetes Endocrinol.* 2014;2:655-666.

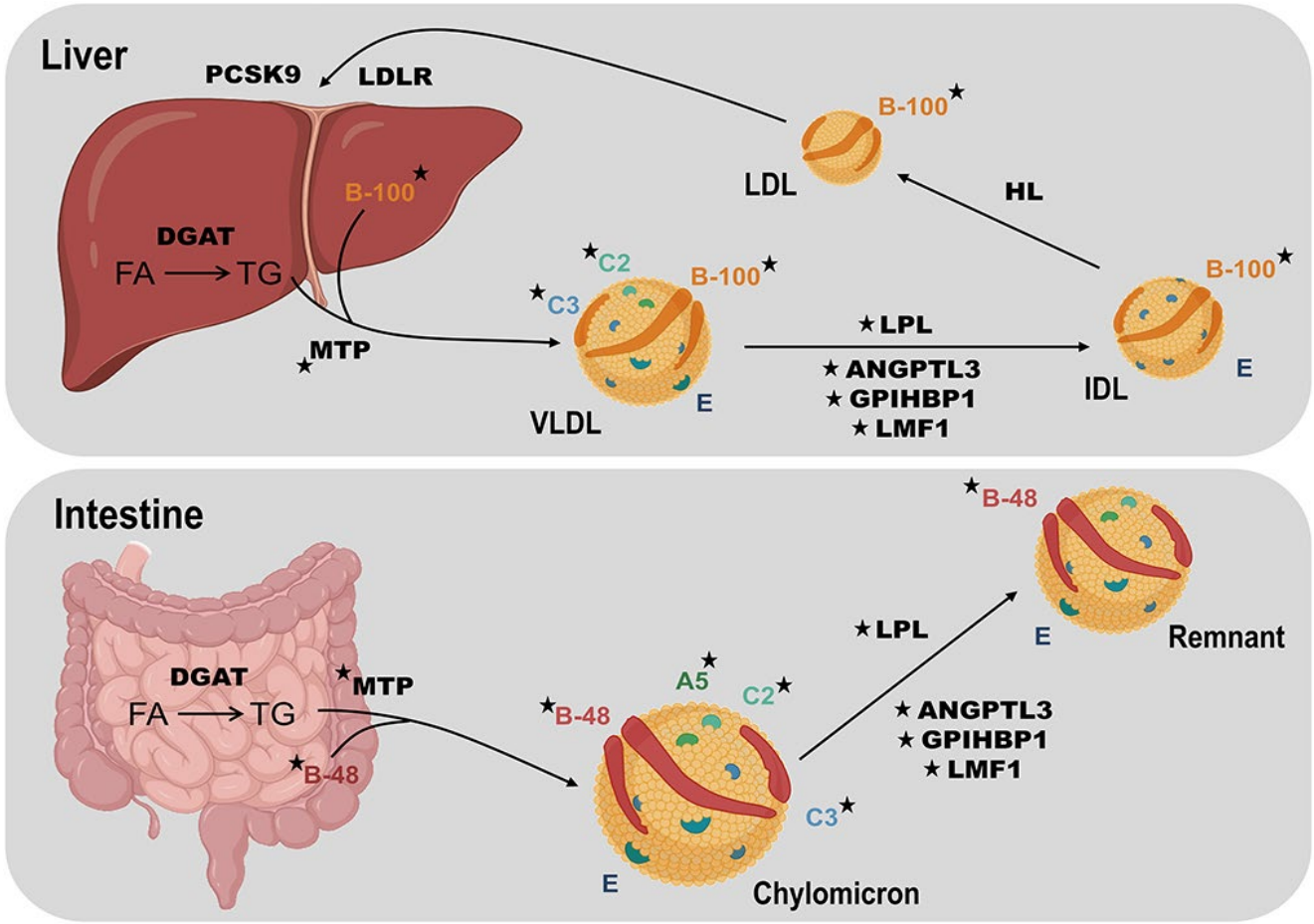
1. Moulin P, et al. *Atherosclerosis.* 2018;275:265-272.

Apo, apolipoprotein; CREBH1, cyclic adenosine monophosphate responsive element binding protein 1; CVD, cardiovascular disease; FCS, familial chylomicronemia syndrome; GCKR, glucokinase regulator; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein–binding protein 1; LMF1, lipase mutation factor 1; LPL, lipoprotein lipase; MCS, multifactorial chylomicronemia syndrome; TG, triglyceride.

*Additional genes are likely to be identified in future, since in more than one-third of patients with a phenotype similar to FCS, no deleterious mutations in these genes can be identified.[1]

Genetic Mutations in Chylomicronemia Syndromes

Form of Monogenic Chylomicronemia (FCS)	Gene Product Function
LPL deficiency[a] (LPL)[1]	Hydrolysis of TGs and peripheral uptake of FFA
ApoC-II deficiency (APOC2)[1]	Required cofactor of LPL
ApoA-V deficiency (APOA5)[1]	Enhancer of LPL activity
LMF1 deficiency (LMF1)[1]	Chaperone molecule required for proper LPL folding
GPIHBP1 deficiency (GPIHBP1)[1]	Stabilizes the binding of chylomicrons near LPL



[a]LPL deficiency represents 95% of monogenic mutations that cause FCS.
1. Adapted from Brahm AJ, Hegele RA. *Nat Rev Endocrinol*. 2015;11:352-362.
Figure adapted from Dron JS, Hegele RA. *Front Endocrinol (Lausanne)*. 2020;11:455.

ANGPTL3, angiopoietin-like protein 3; APO, apolipoprotein; DGAT, diglyceride acyltransferase; FA, fatty acid; FCS, familial chylomicronemia syndrome; FFA, free fatty acid; GPD1, glycerol-3-phosphate dehydrogenase 1); GPIHBP1, glycosylphosphatidylinositol-anchored high density lipoprotein–binding protein 1; HL, hepatic lipase; HTG, hypertriglyceridemia; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLR, LDL receptor; LMF1, lipase mutation factor 1; LPL, lipoprotein lipase; MTP, microsomal triglyceride transfer protein, PCSK9, proprotein convertase subtilisin/kexin type 9; TG, triglyceride, VLDL, very low-density lipoprotein.

Differentiating sHTG Subtypes[1-4]

	Familial Chylomicronemia Syndrome	Multifactorial Chylomicronemia
Population frequency	1–10:1,000,000	1:600 to 1:250
TG, mg/dL (mmol/L)	≥885 (≥10)	≥885 (≥10)
Primarily disturbed lipoprotein fractions	Elevations of chylomicrons	Elevations of chylomicrons and remnants Elevations of VLDL and IDL
Genetic basis	Monogenic	Polygenic
Relevant genetic determinants	Causative biallelic rare variants in canonical TG metabolism genes	Susceptibility may be conferred by heterozygous rare variants in genes canonically or peripherally involved in TG metabolism and/or the accumulation of common, small-effect TG-raising SNPs
Role of environmental (nongenetic) factors	May modulate severity but not expression of phenotype	Combination of genetic and environmental factors modulate expression and severity of phenotype
Time of presentation	Often presents in childhood with clinical manifestations of nausea, vomiting, failure to thrive, and abdominal pain	Presents in adulthood with clinical manifestations such as lipemia retinalis, hepatosplenomegaly, eruptive xanthomas, nausea, vomiting, and abdominal pain
Risk of ASCVD // Acute pancreatitis	Lower than MCS // 60%–88%	Moderate to high // 11%–37%

ASCVD, atherosclerotic cardiovascular disease; IDL, intermediate-density lipoprotein; MCS, multifactorial chylomicronemia syndrome; sHTG, severe hypertriglyceridemia; SNP, single-nucleotide polymorphism; TG, triglyceride; VLDL, very-low-density lipoprotein.

1. Gill PK, et al. *Curr Opin Cardiol.* 2021;36:264-271. 2. Chait A, Eckel RH. *Ann Intern Med.* 2019;170:626-634. 3. Paquette M, Bernard S. *Front Cardiovasc Med.* 2022;9:886266. 4. Baass A, et al. *J Intern Med.* 2020;287:340-348.

FCS vs MCS: Are we focusing on the most important clinical issue?

1. FCS and MCS are both rare, but the vast majority of individuals with pancreatitis due to chylomicronemia have MCS, not FCS
2. Most individuals with severe MCS and history of pancreatitis have a strong genetic (i.e. **familial**) basis: heterozygous for pathogenic variants in canonical TG related genes or other genetic disorders such as partial lipodystrophy + high polygenic risk score for TGs
3. The nomenclature is therefore misleading to individuals who are not experts, including healthcare administrators and payors

Consider new Terms: Sustained or persistent chylomiconemia syndrome

1. Patients with chylomiconemia that are resistant to efforts of lifestyle and currently approved medical therapies who remain at very high risk for pancreatitis, especially those with a past history of pancreatitis
2. Most of the individuals with MCS will respond to a combination of pharmacotherapy and lifestyle changes with improvement of TGs to consistently < 1000 mg/dl or 10 mmol/L
3. Although this clinical syndrome is more common than FCS, it is still rare on a population basis (<< 1 per 1,000)

Moderate HTG/high HTG are associated with a high risk of acute pancreatitis as well as myocardial infarction in the general population

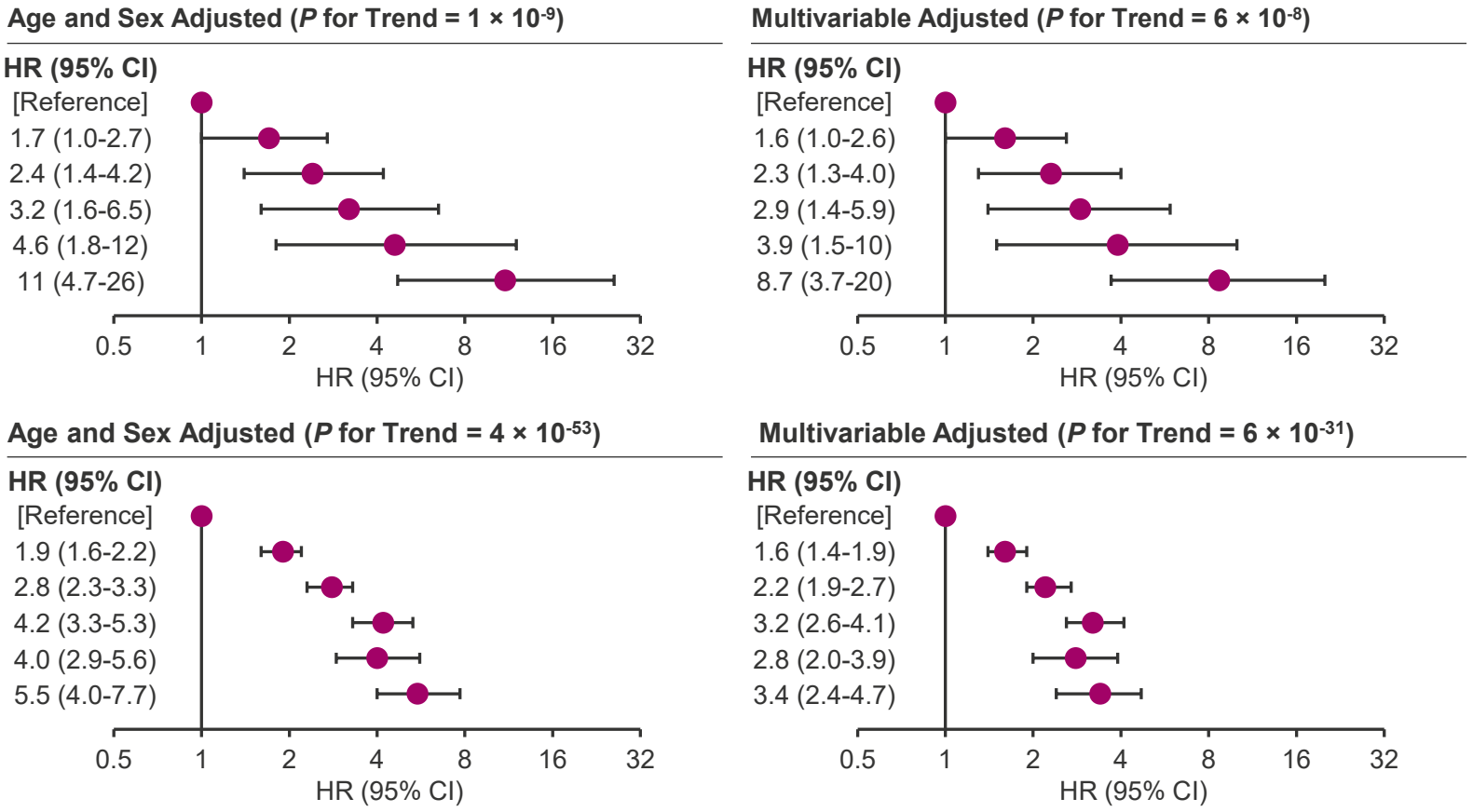
Risk of Event by Increasing TG Level: Prospective Cohort Study (N=116,550) (median follow-up 6.7 years)

A Acute pancreatitis

Triglycerides, mg/dL (nmol/L)	Individuals (Events)	Events per 10,000 Person-Years
<89 (<1.00)	31,044 (72)	2.7
89-176 (1.00-1.99)	54,215 (200)	4.3
177-265 (2.00-2.99)	19,427 (89)	5.5
266-353 (3.00-3.99)	6773 (35)	6.3
354-442 (4.00-4.99)	2485 (16)	7.5
≥443 (≥5.00)	2100 (22)	12

B Myocardial infarction

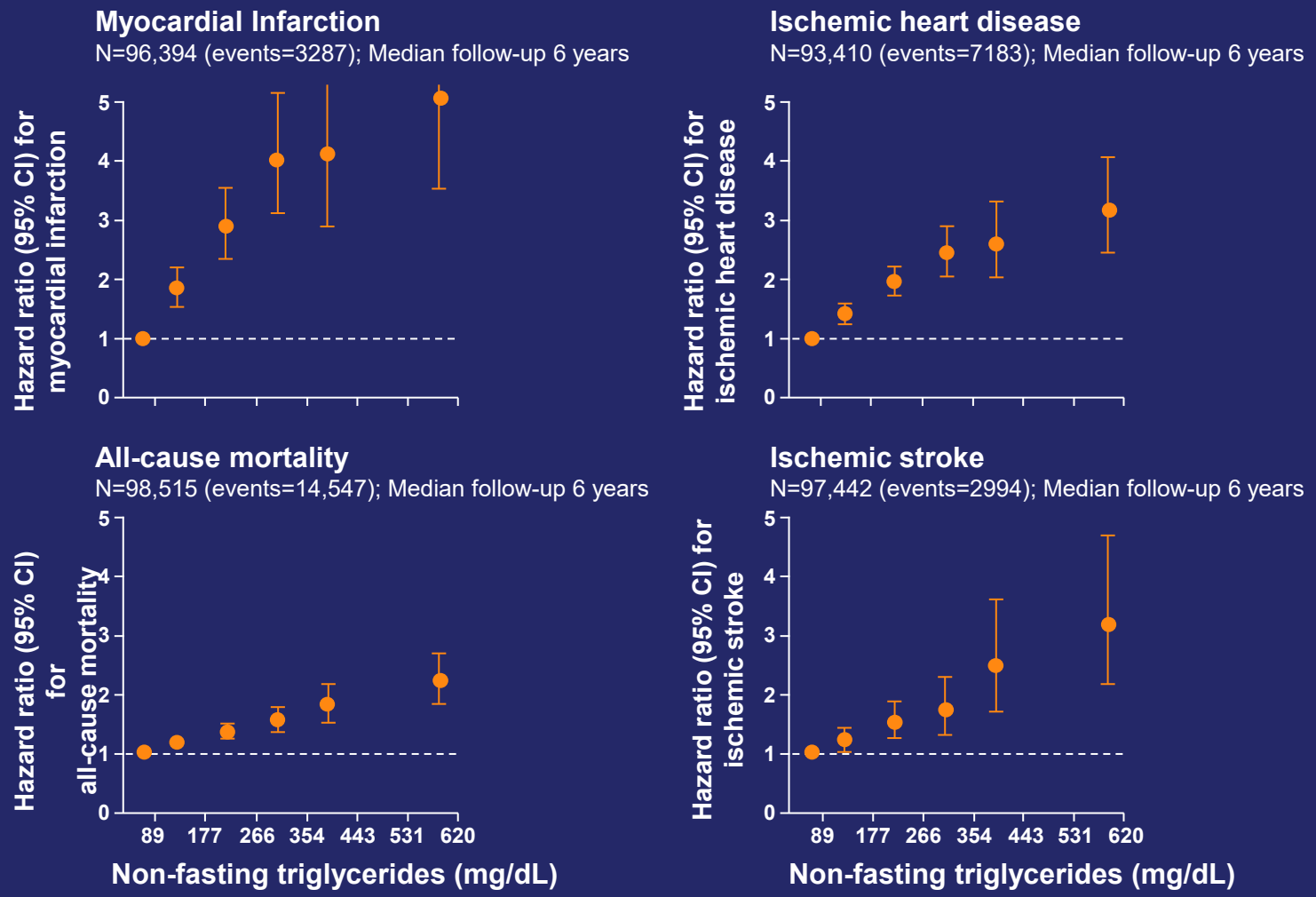
Triglycerides, mg/dL (nmol/L)	Individuals (Events)	Events per 10,000 Person-Years
<89 (<1.00)	30,689 (558)	22
89-176 (1.00-1.99)	53,295 (1850)	41
177-265 (2.00-2.99)	19,047 (875)	57
266-353 (3.00-3.99)	6629 (382)	72
354-442 (4.00-4.99)	2439 (139)	68
≥443 (≥5.00)	2049 (138)	78



CI, confidence interval; HR, hazard ratio; HTG, hypertriglyceridemia, TG, triglyceride.
Pedersen SB, et al. *JAMA Intern Med.* 2016;176:1834-1842.

Increasing TG Levels Associated with Increases CVD and All-cause Mortality

Copenhagen City Heart Study and Copenhagen General Population Study



Hazard ratios were estimated by Cox proportional hazard regression models, and were adjusted for age, sex, and trial group.
Nordestgaard BG et al. *Lancet.* 2014;384:626-35.

Genetically Altered LDL, TG, and Risk for CHD[1-3]

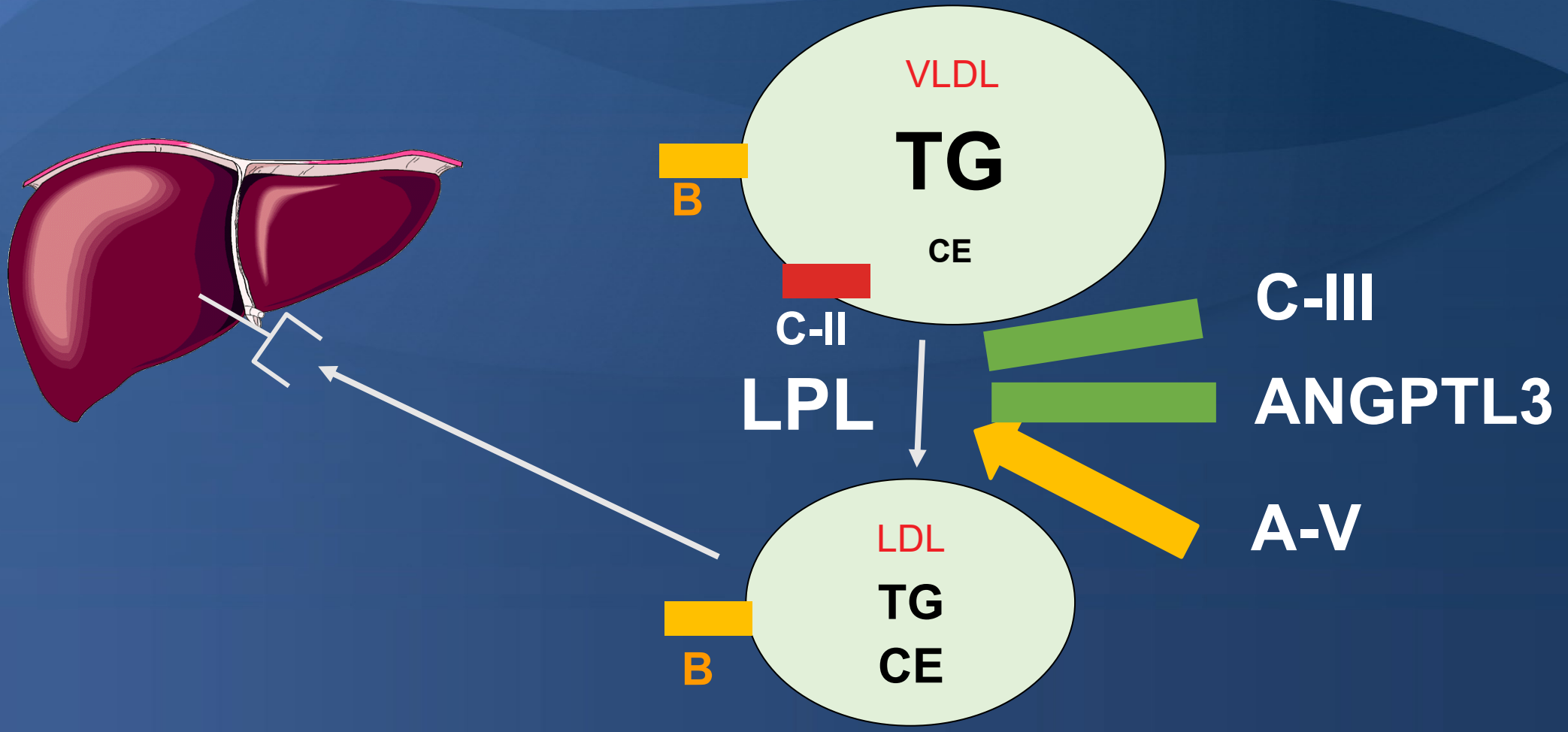
For every 1 SD change (~35 mg/dL) in genetically altered LDL, 50% increase in risk for CHD

For every 1 SD change (~90 mg/dL) in genetically altered TG, 50% increase in risk for CHD

Predictor	Effect size	P
$\beta_{LDL\text{-}C}$	0.39	1×10^{-22}
$\beta_{HDL\text{-}C}$	0.04	0.32
β_{TG}	0.40	2×10^{-10}

1. Do R et al. *Nat Genet*. 2013;45(11):1345-1352; 2. Ballantyne CM. Are triglycerides a cardiovascular risk factor? Presented at: 2014 National Lipid Association Fall Clinical Lipid Updates Session; August 22–24, 2014; Indianapolis, IN. https://www.lipid.org/node/1273. Accessed January 19, 2015; 3. Slide courtesy of Sekar Kathiresan, MD.

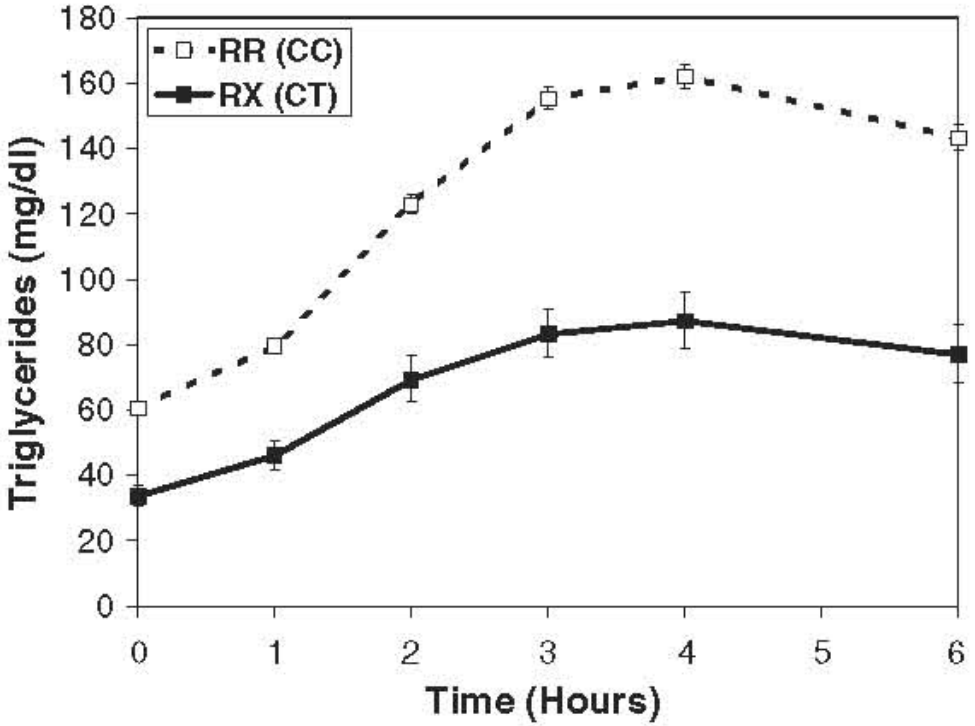
Gain of LPL Function, Gain of APOA5 Function, and Loss of APOC3 Function Reduces Risk for MI



ANGPTL3=angiopoietin-like 3; MI=myocardial infarction.

1. Rosenson RS et al. *J Am Coll Cardiol*. 2014;64(23):2525-2540; 2. Ballantyne CM. Are triglycerides a cardiovascular risk factor? Presented at: 2014 National Lipid Association Fall Clinical Lipid Updates Session; August 22–24, 2014; Indianapolis, IN. https://www.lipid.org/node/1273. Accessed January 19, 2015; 3. Slide courtesy of Sekar Kathiresan, MD.

TG levels before and during high-fat challenge by R19X *APOC3* genotype



Pollin TI et al. *Science*. 2008;322:1702-1705.

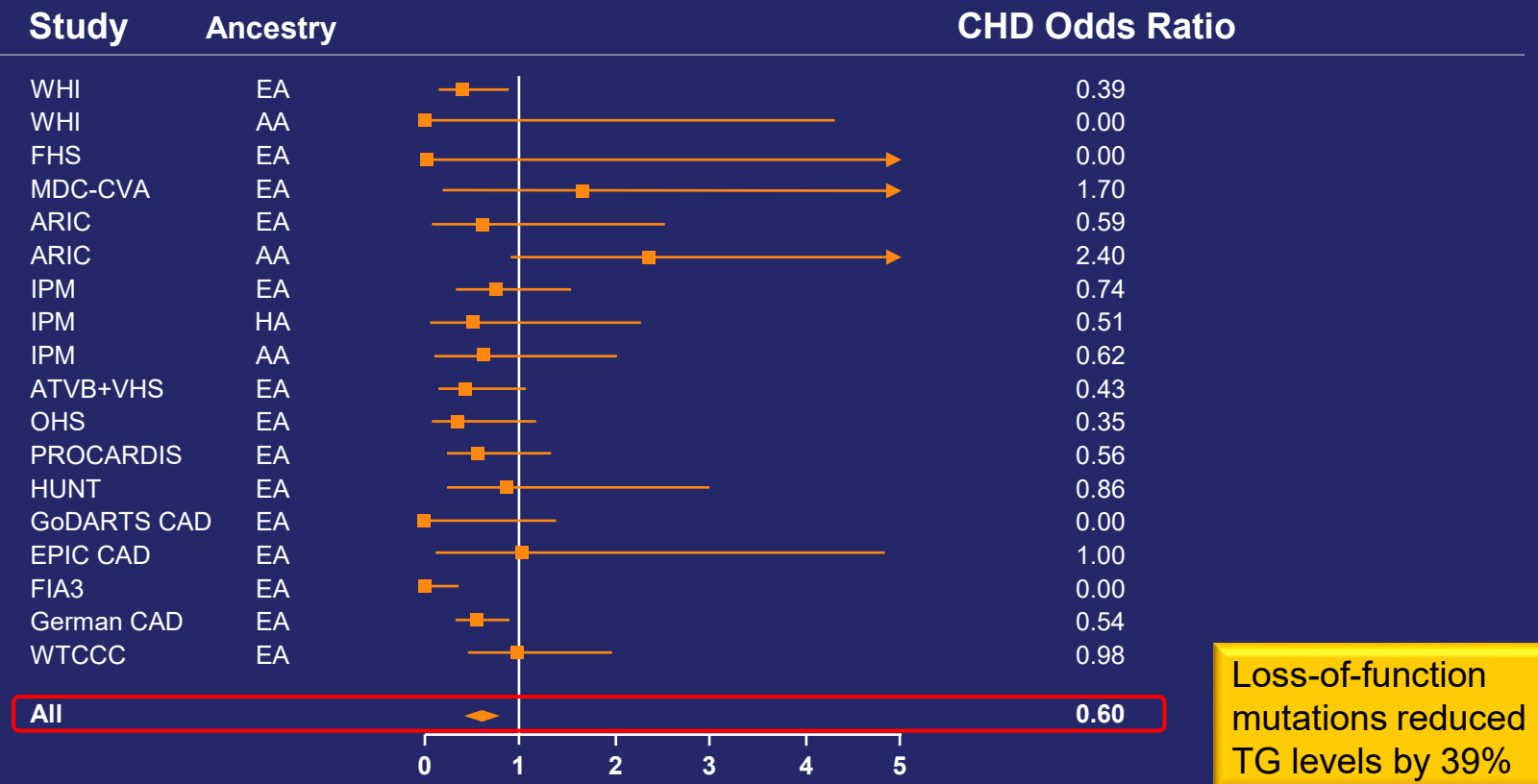
Loss of Function Mutation (R19X) in Apo CIII in the Amish

- Reduced Apo CIII levels in heterozygotes by 50%
- Decreased fasting and postprandial TGs
- Decreased non HDL-C, LDL-C, VLDL-C, IDL-C
- Increased HDL-C, HDL-2, HDL-3
- Reduced coronary calcium scores

Pollin TI et al. *Science*. 2008;322:1702-1705.

Apo C3 Loss-of-function Mutations Show Reduced CHD Risk

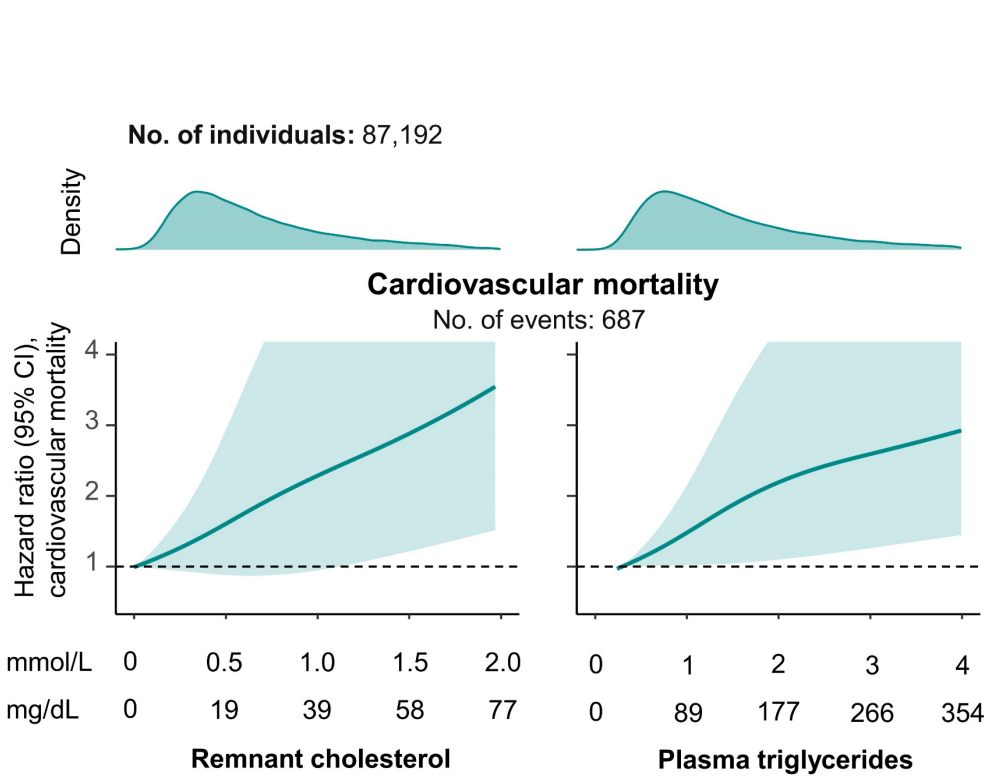
Odds ratio of CHD of subjects with any of 4 Apo C3 loss-of-function mutations among 110,970 participants (34,002 patients with CHD and 76,968 controls) in 14 studies

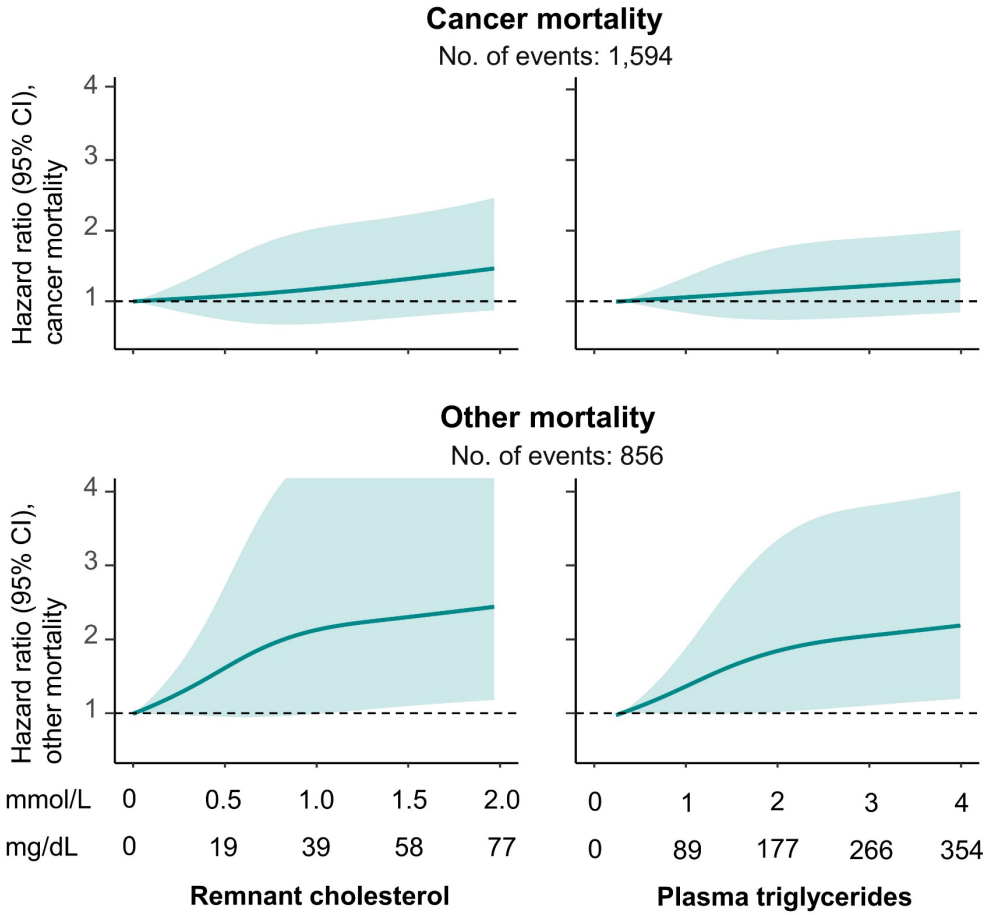


Loss-of-function mutations reduced TG levels by 39%

The TG and HDL Working Group of the Exome Sequencing Project, NHLBI. *New Eng J Med*. 2014;371:22-31.

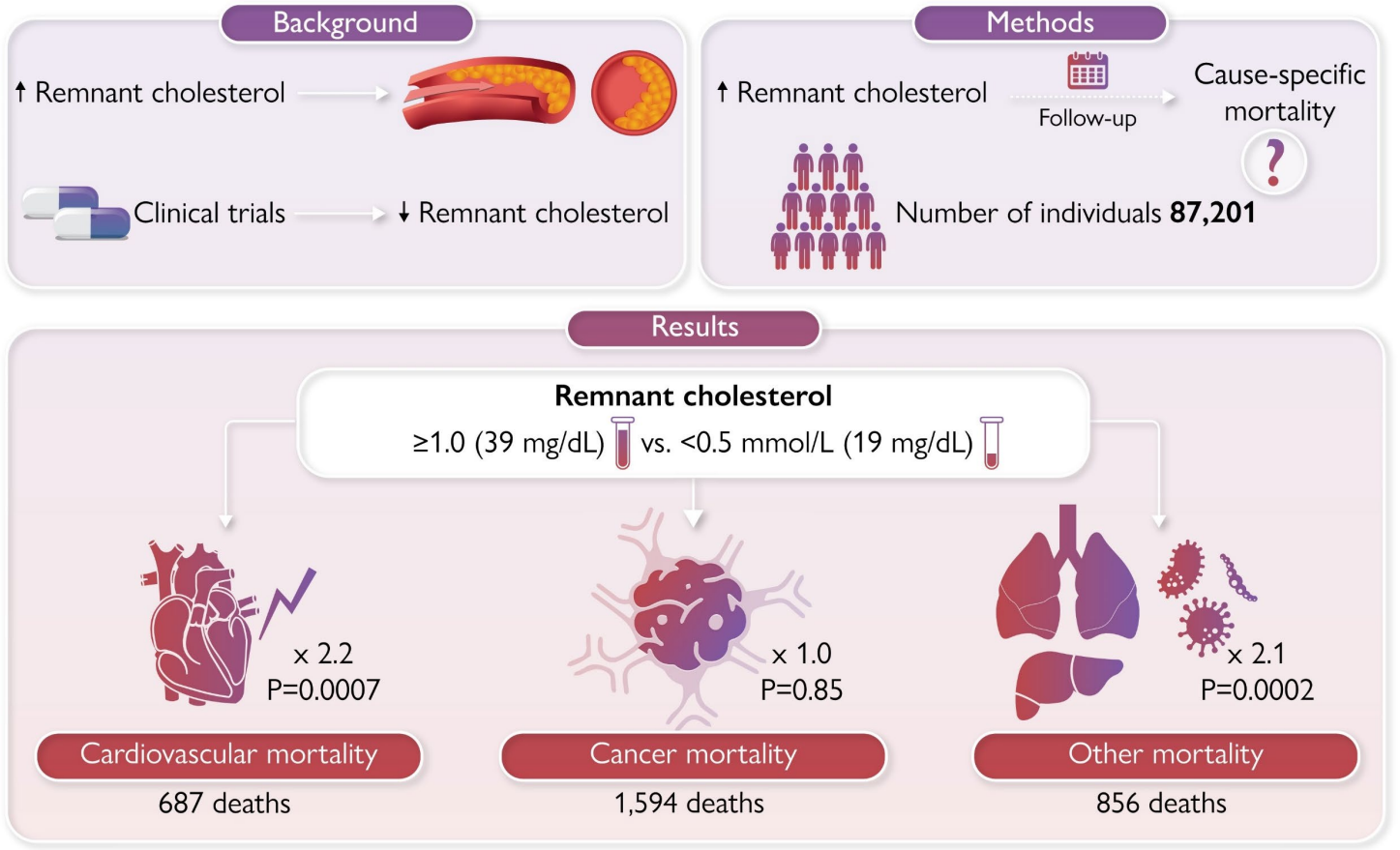
Cause-specific mortality as functions of remnant cholesterol and plasma triglycerides on continuous scales in the Copenhagen General Population Study





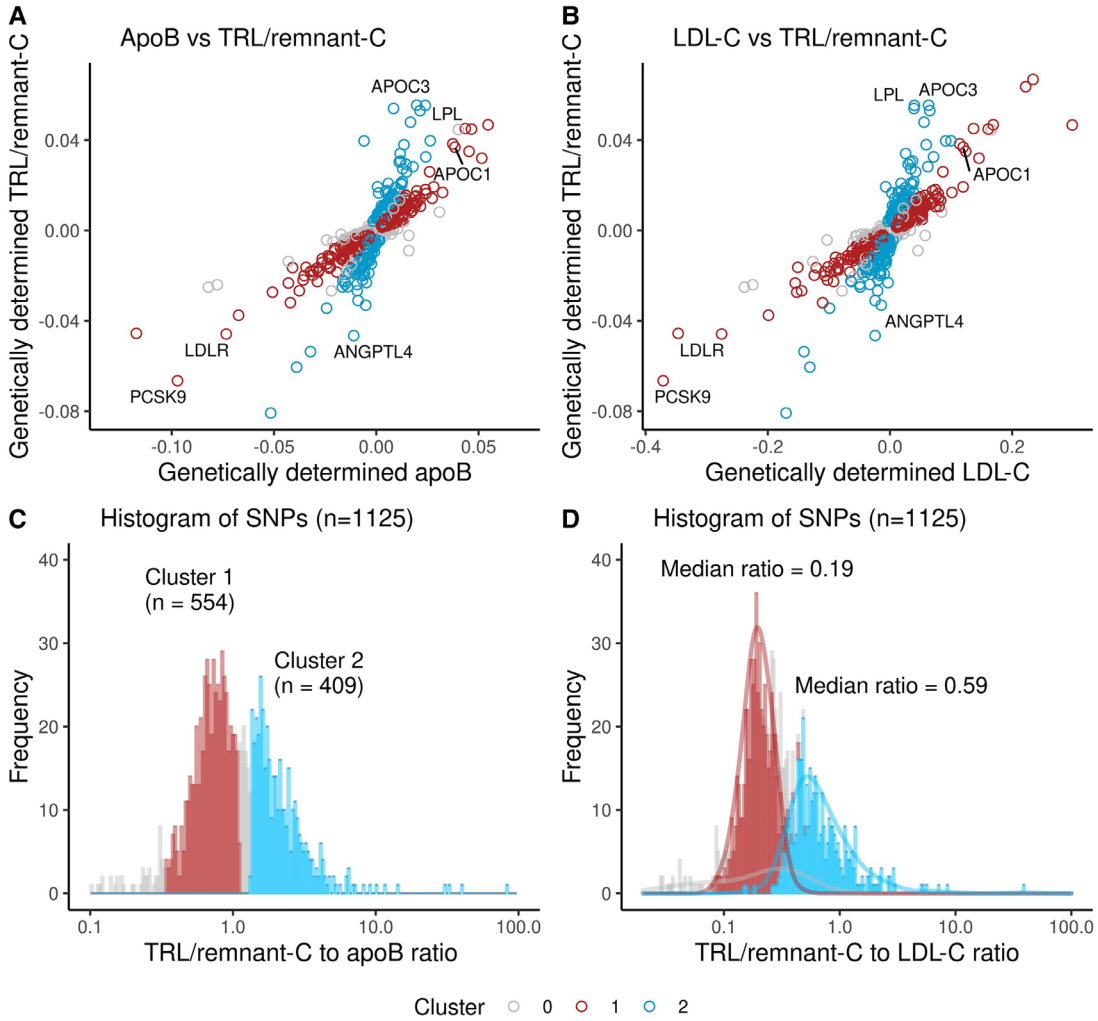
Wadström BN et al. *Eur Heart J* 2023;44:1432-1445.

Elevated remnant cholesterol, plasma triglycerides, and cardiovascular and noncardiovascular mortality



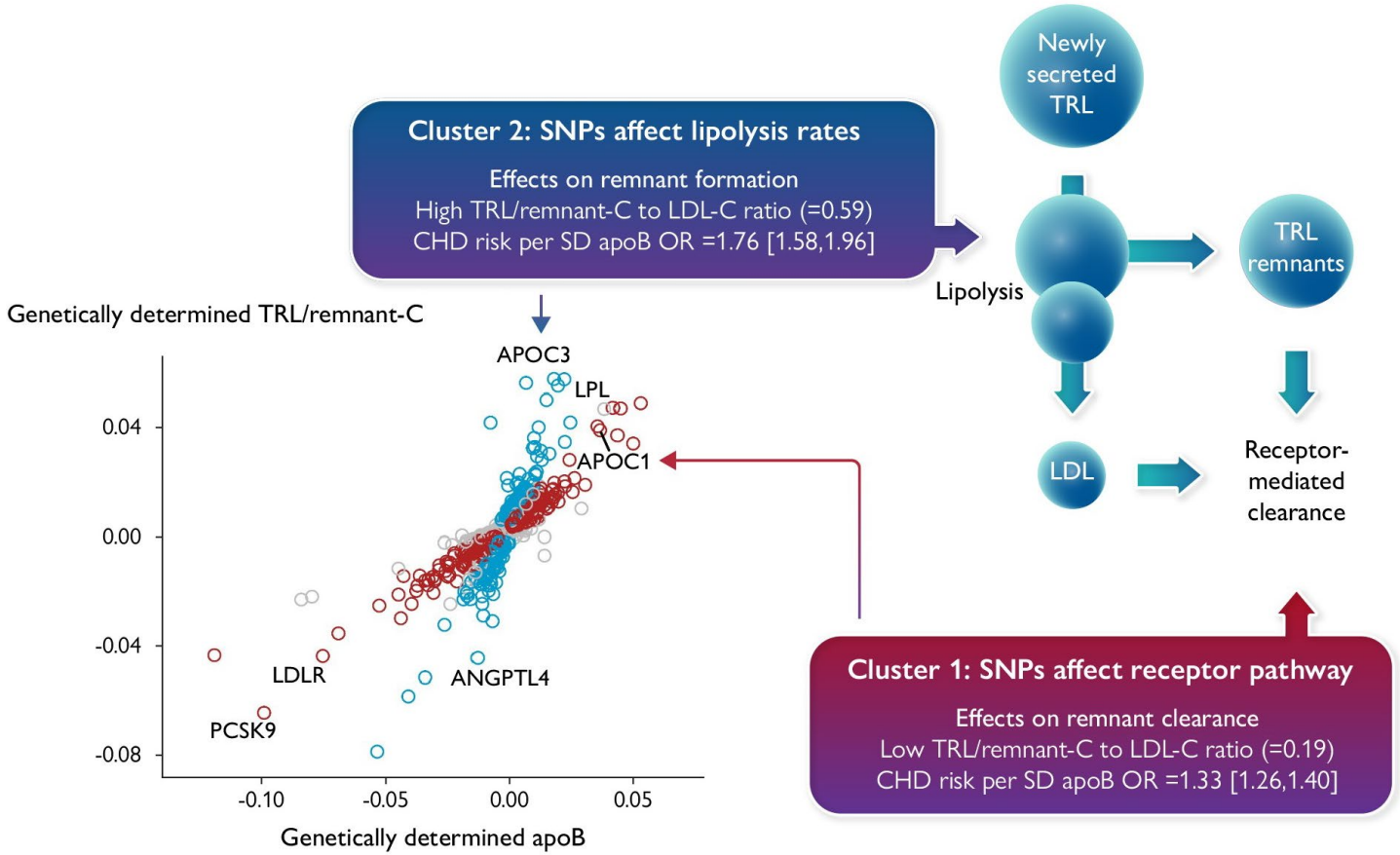
Wadström BN et al. *Eur Heart J* 2023;44:1432-1445.

Identification of genes influencing TRL/remnant cholesterol



Björnson E et al. *Eur Heart J* 2023;44:4186-4195.

Triglyceride-rich lipoprotein remnants, low-density lipoproteins, and risk of coronary heart disease: UK Biobank



Björnson E et al. *Eur Heart J* 2023;44:4186-4195.

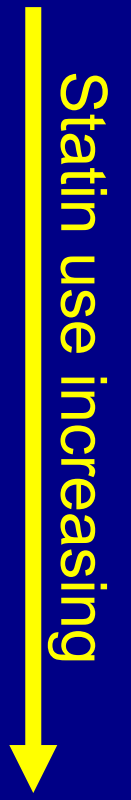
Familial Chylomicronemia Syndrome, Severe Hypertriglyceridemia with Pancreatitis: Areas of High Unmet Medical Need

- Familial Chylomicronemia Syndrome (FCS) caused by impaired lipoprotein lipase (LPL) leading to extremely high TG levels [>880 mg/dL (10 mmol/L)]
  - Prevalence of approximately 1 in 1 million[1] with increased prevalence in populations such as French Canadians (founder effect)[2]
  - Symptoms include chronic daily abdominal pain, acute and chronic pancreatitis, diabetes mellitus
  - **Refractory to standard TG lowering therapies**, standard of care is very low fat (<20 g) diet
- Severe High Triglycerides (sHTG) with pancreatitis
  - Polygenic disorder exacerbated by comorbidities, diet and lifestyle
  - Prevalence of TG > 500 mg/dL (> 5.65 mmol/L) 1.7%[3,4]
  - 4% increased risk of acute pancreatitis for every 100 mg/dL (1.1 mmol/L) TG increase [5]
- For both conditions adherence to current therapies including strict diet/lifestyle changes is challenging

[1] Brahm and Hegele, Nat Rev Endocrinol. (2015) 11:352-362
[2] Gagné C *et al.,* CMAJ (1989) 140: 405-411.
[3] Ford *et al.,* Arch Intern Med. (2009) 169:572-578.
[3] Christian JB *et al.*, Am J Cardiol. (2011) 107:891-897.
[4] Murphy MJ *et al.*, JAMA Intern Med. (2013) 173:162-164.

Outcomes Trials of Fibrates

Trial	Year reported	Fibrate	CHD risk reduction (primary end point)
ACCORD-Lipid	2010	Fenofibrate	8% (p = 0.32)
FIELD	2005	Fenofibrate	11% (p = 0.16)
BIP	2000	Bezafibarte	7.3% (p = 0.26)
VA-HIT	1999	Gemfibrozil	22% (p < 0.006)
HHS	1987	Gemfibrozil	34% (p < 0.02)
WHO	1978	Clofibrate	20% (p < 0.05)
CDP	1975	Clofibrate	7% (NS)



Elam M et al. *Clin Lipidol* 2011;6: 9–20.

Comparison of fibrate trials and corresponding Copenhagen General Population Study (CGPS) mimicking trials

Doi T et al. *J Intern Med* 2024;295:707-710.

Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT): Study Design

MEN AND WOMEN WITH TYPE 2 DIABETES

10,000 PARTICIPANTS
24 Countries

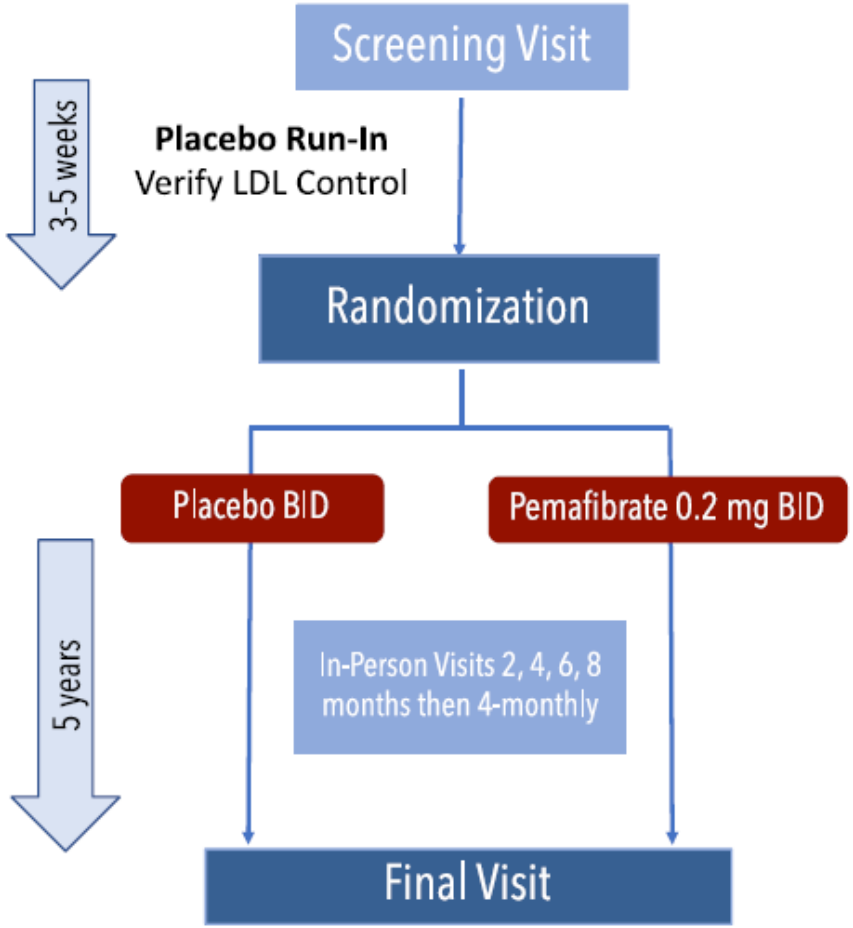
TG 200-499 mg/dl (2.26-5.64 mM) and HDL ≤ 40 mg/dl (1.03 mM)
Moderate-High Intensity Statin Therapy or LDL-C Control
(≤70 mg/dl other therapy or ≤100 mg/dl if statin intolerant)
1/3 Primary Prevention, 2/3 Secondary Prevention

ENDPOINTS

Event Driven: 1092 Primary Endpoints, 200 in ♀

PRIMARY ENDPOINT (MACE+):
Myocardial infarction, ischemic stroke, or unstable angina requiring unplanned revascularization, cardiovascular death.

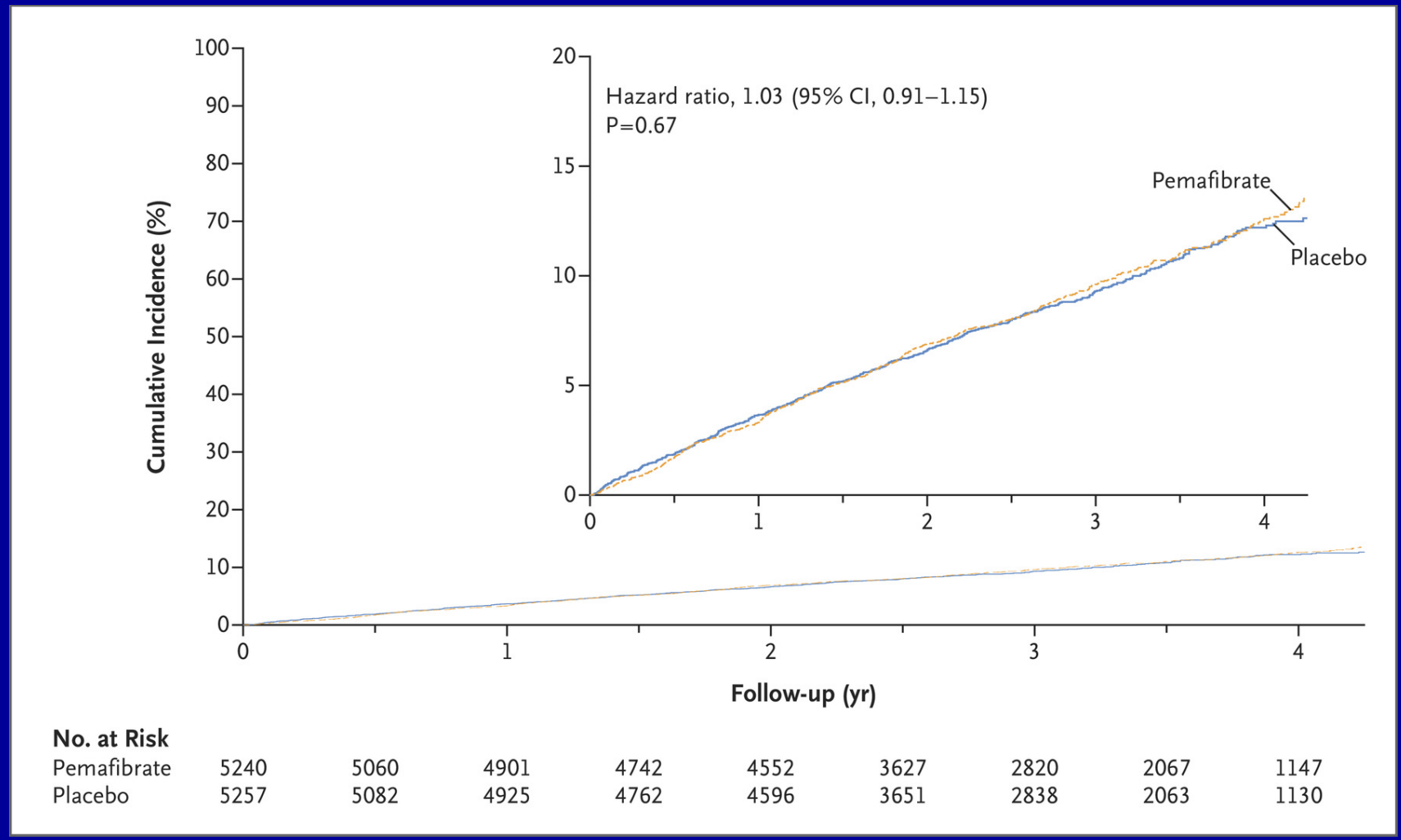
Secondary/Tertiary Endpoints: all-cause mortality, any coronary revascularization, heart failure, total stroke, retinopathy, nephropathy, glycemic control, PAD, biomarkers, QOL



Pradhan AD et al. Am Heart J 2018;206:80-93..

PROMINENT: Primary Endpoint—Cumulative Incidence of Cardiovascular Events

composite of nonfatal MI, ischemic stroke, coronary revascularization, or death from cardiovascular causes



Das Pradhan A et al. *N Engl J Med* 2022;387:1923-1934.

Why was there no benefit? Effects of Pemafibrate on Fasting Lipid Levels at 4 Months

Variable	Pemafibrate (N = 5240)	Placebo (N = 5257)	Treatment Effect†
	Median Value (IQR)		Mean % Change (95% CI)
Triglyceride level, measured			
Baseline — mg/dl	273 (227 to 342)	269 (226 to 338)	
4 Mo — mg/dl	189 (143 to 253)	254 (193 to 341)	
Median change from baseline — %	−31.1 (−48.9 to −9.6)	−6.9 (−28.4 to 20.2)	−26.2 (−28.4 to −24.10)
Remnant cholesterol level, calculated§			
Baseline — mg/dl	47 (38 to 60)	47 (37 to 59)	
4 Mo — mg/dl	32 (24 to 42)	39 (29 to 52)	
Median change from baseline — %	−31.3 (−49.1 to −8.2)	−15.6 (−36.8 to 10.8)	−18.2 (−20.3 to −16.1)
LDL cholesterol level, measured			
Baseline — mg/dl	79 (60 to 104)	78 (59 to 102)	
4 Mo — mg/dl	91 (71 to 115)	80 (62 to 105)	
Median change from baseline — %	14.0 (−6.3 to 41.4)	2.9 (−13.5 to 24.6)	12.3 (10.7 to 14.0)
Non-HDL cholesterol level, calculated§			
Baseline — mg/dl	128 (106 to 159)	128 (104 to 157)	
4 Mo — mg/dl	125 (102 to 153)	122 (100 to 154)	
Median change from baseline — %	−2.4 (−18.0 to 15.0)	−2.5 (−16.3 to 13.0)	−0.2 (−1.3 to 1.0)
Apolipoprotein B level, measured			
Baseline — mg/dl	90 (75 to 108)	89 (74 to 107)	
4 Mo — mg/dl	93 (77 to 111)	87 (73 to 105)	
Median change from baseline — %	3.2 (−12.0 to 19.7)	−1.6 (−13.4 to 11.8)	4.8 (3.8 to 5.8)

Das Pradhan A et al. *N Engl J Med* 2022;387:1923-1934.

Conclusions

1. Targeting apo CIII mRNA has been shown to lead to robust reduction in TG in patients with severe HTG (both FCS and MCS) with greater reductions in TGs than any available therapies and reductions in pancreatitis
2. Previous trials of fibrates added to statin failed to show reductions in CV events and also showed modest reductions in remnant cholesterol, and the most recent trials with pemafibrate failed to show any reductions in non-HDL-C and showed increases in apo B and LDL-C
3. In contrast to this, the phase 2 studies with plozasiran have shown greater reductions in TG and remnant cholesterol with significant reductions in both non-HDL-C and apo B
4. Genetic studies have shown that individuals with loss-of-function mutations in *APOC3* have reduced CV events

Cardiometabolic Webinar – June 25, 2024

Arrowhead's Emerging Opportunity with Plozasiran

Jennifer Hellawell, MD
Executive Director
Cardiometabolic Lead Physician

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Mature Data Across the Hypertriglyceridemia Landscape

Program	Study	Indication	Study Title	Status
SUMMIT PROGRAM	PALISADE	FCS	A Phase 3 Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Familial Chylomicronemia Syndrome	Complete
	SHASTA-2	sHTG	A Double-Blind, Placebo-Controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Severe Hypertriglyceridemia	Complete
	MUIR	Mixed Hyperlipidemia	A Double-Blind, Placebo-controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Mixed Hyperlipidemia	Complete

Cardiometabolic Webinar – June 25, 2024

Plozasiran Appears Best-in-Class in Familial Chylomicronemia Syndrome (FCS)

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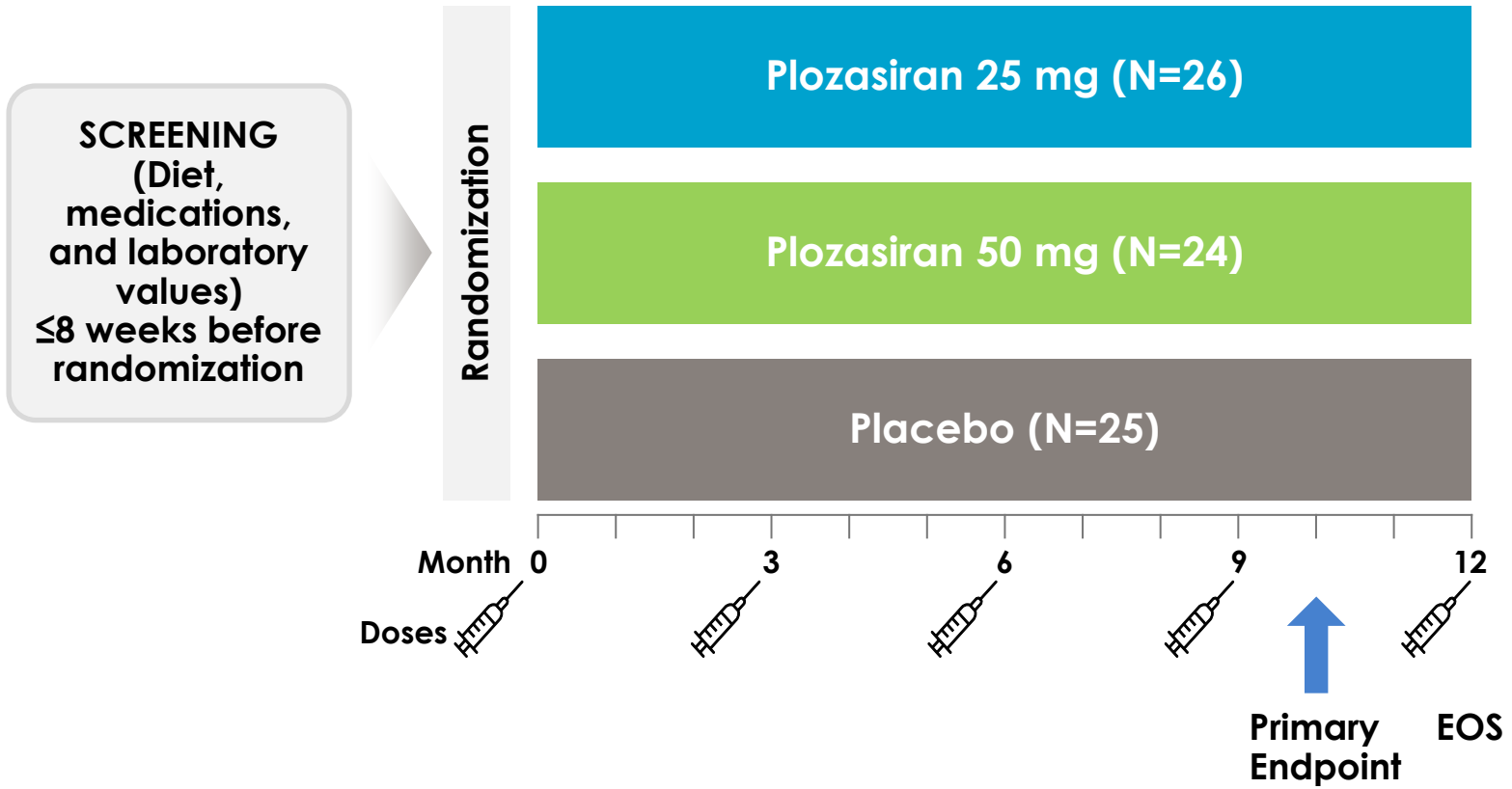
PALISADE: A Randomized Double-Blind Study of Plozasiran in FCS



Primary Endpoint:

- Placebo adjusted median change in triglycerides at Month 10

Multiplicity-controlled key secondary endpoints:

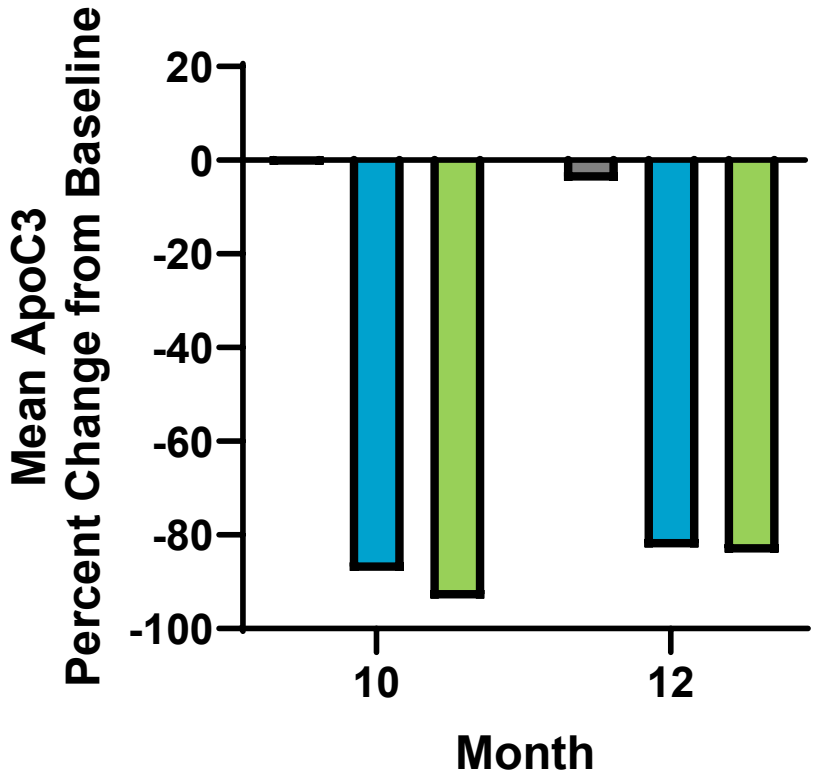
- Percent change from baseline at Months 10 and 12 (averaged) in fasting triglycerides
- Percent change from baseline at Month 10 in fasting APOC3
- Percent change from baseline at Month 12 in fasting APOC3
- Incidence of positively adjudicated events of acute pancreatitis during the randomized period

PALISADE Baseline Characteristics

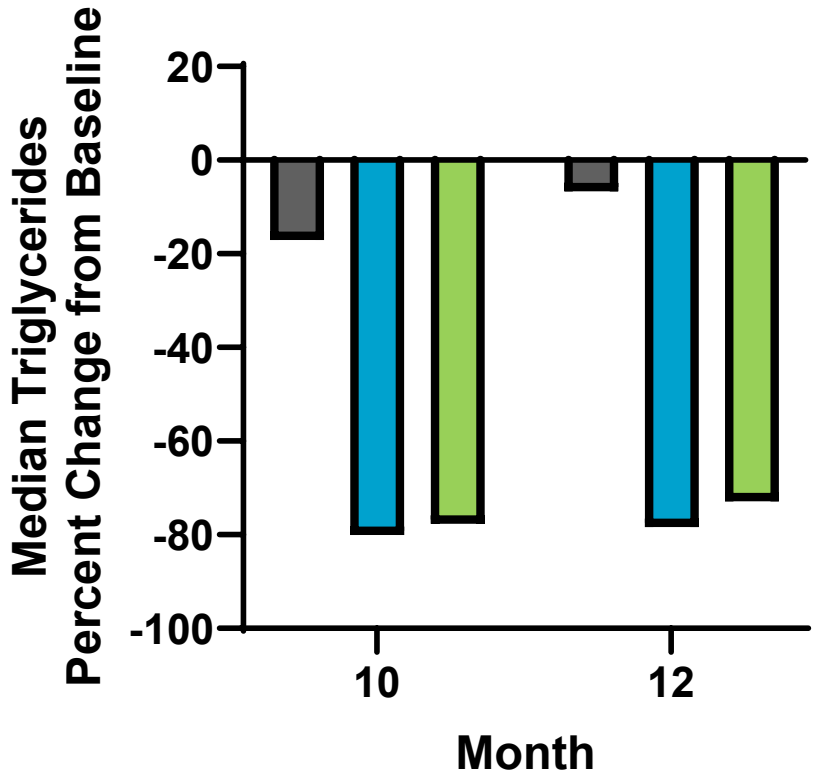
Baseline Characteristics	Enrolled (N=75)
Mean (SD) Age, Years	46.04 (13.27)
Men, n (%)	37 (49.3%)
Median (Q1, Q3) TG, mg/dL	2043.9 (1435.1, 2755.2)
Genetically or Clinically Confirmed FCS, n (%)	75 (100%)
Genetically Confirmed FCS	41 (55%)
History of Pancreatitis, n (%)	67 (89%)

Plozasiran Reduces APOC3 and Triglycerides in FCS: Positive PALISADE Topline Data

APOC3



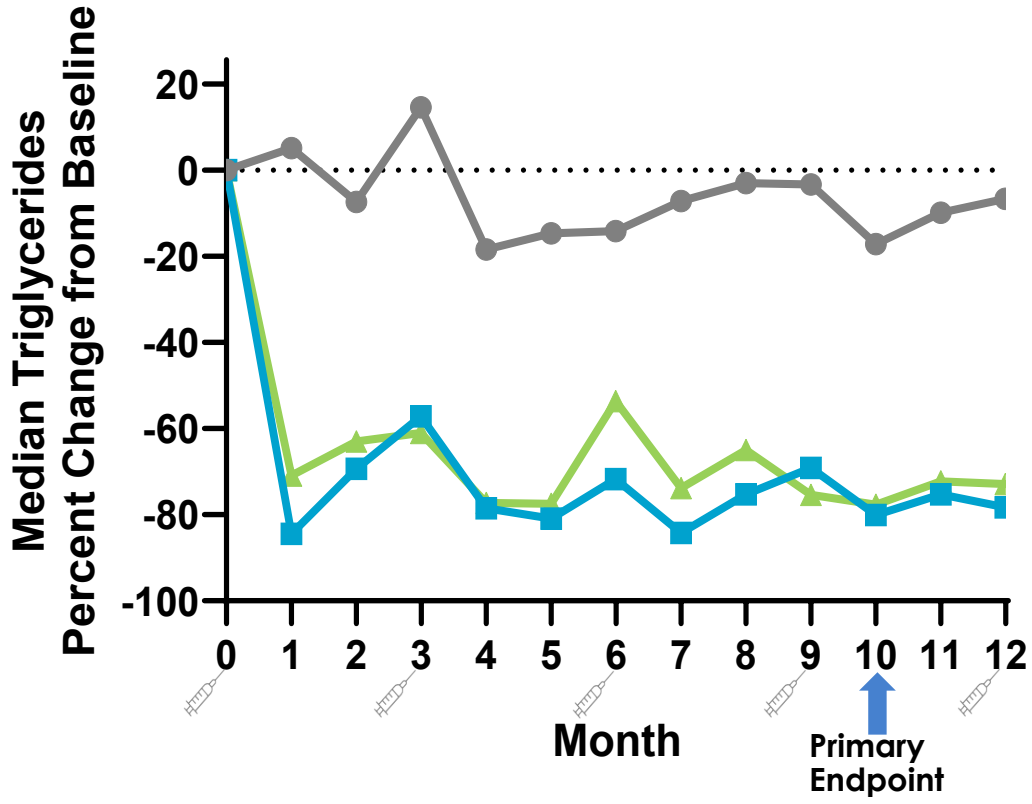
Triglycerides (Primary Endpoint)



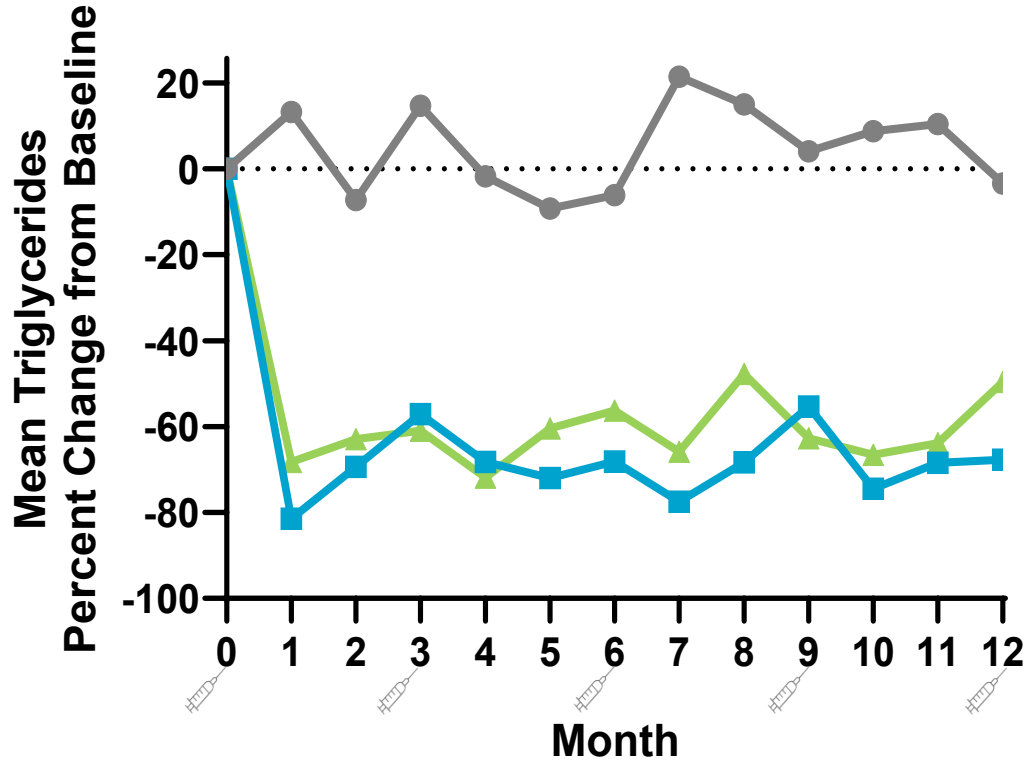
Placebo Plozasiran 25 mg Plozasiran 50 mg

Plozasiran Reduces Triglycerides in FCS Patients

Median Triglycerides



Mean Triglycerides



Placebo Plozasiran 25 mg Plozasiran 50 mg

PALISADE Summary of Adverse Events

	Pooled Placebo (N=25)	Plozasiran 25 mg (N=26)	Plozasiran 50 mg (N=24)
Subjects with Any TEAEs	20	23	20
Most Common TEAEs (N%)			
• Abdominal Pain	5 (20.0)	7 (26.9)	6 (25.0)
• COVID-19	0 (0.0)	5 (19.2)	7 (29.2)
• Nasopharyngitis	3 (12.0)	5 (19.2)	2 (8.3)
• Headache	2 (8.0)	3 (11.5)	5 (20.8)
• Nausea	2 (8.0)	4 (15.4)	3 (12.5)
• Upper respiratory tract infection	2 (8.0)	3 (11.5)	2 (8.3)
• Diarrhea	2 (8.0)	1 (3.8)	4 (16.7)
Severe TEAEs	5 (20.0)	2 (7.7)	3 (12.5)
Serious TEAEs	7 (28.0)	5 (19.2)	2 (8.3)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
Premature Discontinuations (Randomized Period)	6 (24.0)	3 (11.5)	2 (8.3)

TEAEs, treatment emergent adverse events

Cardiometabolic Webinar – June 25, 2024

Plozasiran Proves Itself in Severe Hypertriglyceridemia – SHASTA-2

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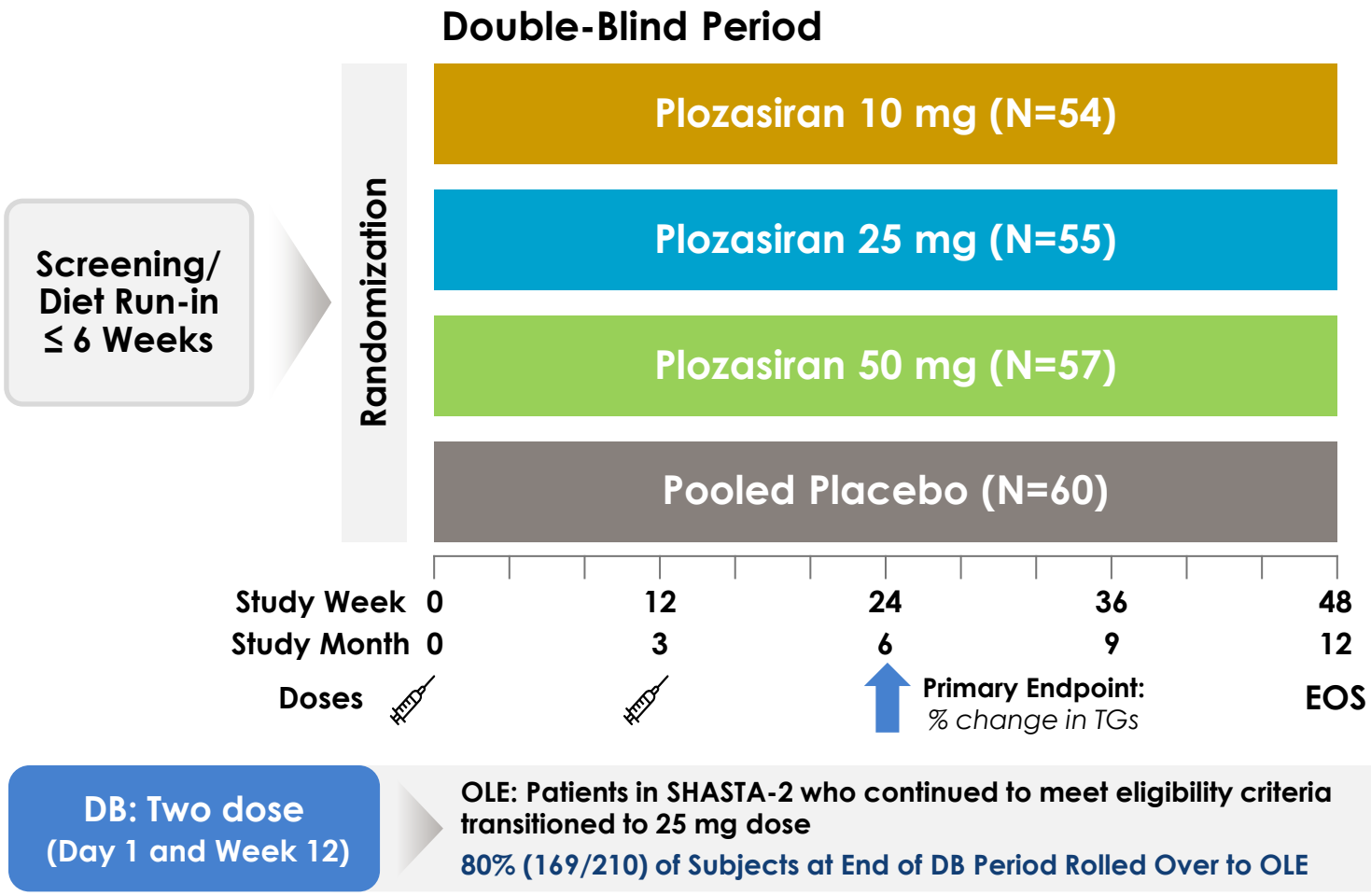
Plozasiran for the Treatment of sHTG: SHASTA-2 Study Design



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.

SHASTA-2: Baseline Characteristics

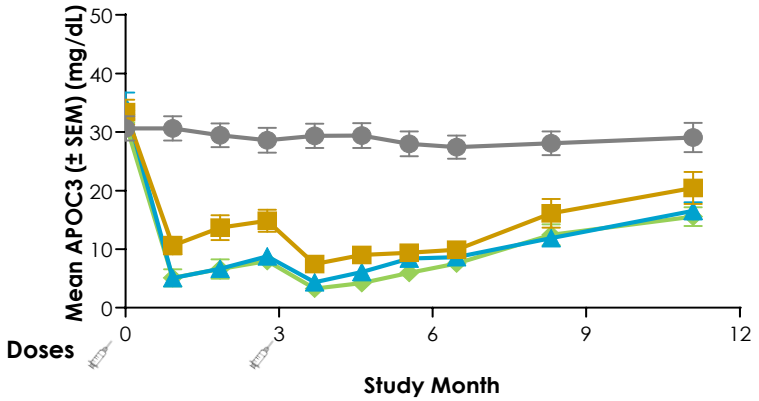
	Pooled Placebo (N=60)	Plozasiran 10 mg (N=54)	Plozasiran 25 mg (N=55)	Plozasiran 50 mg (N=57)
Mean (SD) age, years	56 (11)	53 (10)	56 (11)	54 (11)
Female, n (%)	14 (23)	8 (15)	12 (22)	16 (28)
White, n (%)	55 (92)	47 (87)	48 (87)	53 (93)
Mean (SD) BMI, kg/m^2	31 (4)	33 (5)	32 (5)	32 (5)
Mean (SD) APOC3[a], mg/dL	31 (16)	33 (15)	34 (17)	32 (16)
Median (Q1, Q3) triglyceride, mg/dL	679 (540, 929)	696 (559, 1088)	598 (517, 982)	663 (531, 1028)
Mean (SD) triglyceride, mg/dL	851 (507)	890 (577)	942 (756)	908 (653)
Mean (SD) non-HDL-C, mg/dL	185 (79)	209 (74)	206 (91)	196 (88)
Mean (SD) ApoB, mg/dL	95 (29)	103 (44)	103 (32)	110 (55)
Mean (SD) remnant cholesterol[b], mg/dL	115 (82)	134 (88)	132 (98)	124 (92)
Mean (SD) LDL-C, UC, mg/dL	69 (39)	75 (44)	74 (40)	72 (42)
Mean (SD) HDL-C, mg/dL	30 (12)	28 (9)	30 (11)	31 (13)

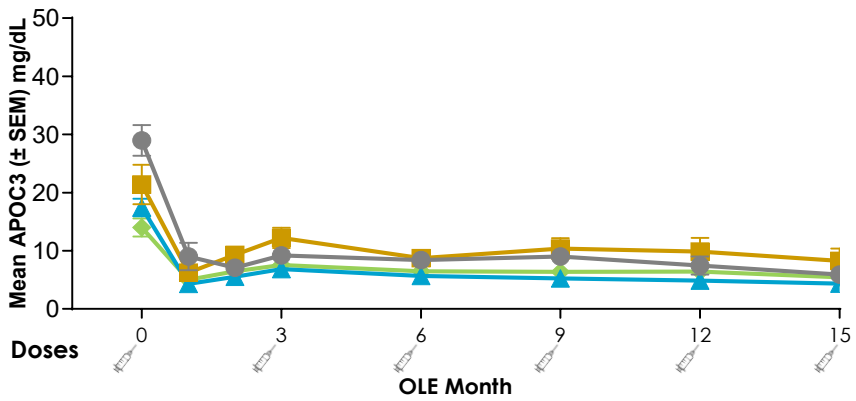
[a] Analysis that removed n=2 participants with baseline values below limits of quantitation (BLOQ) (ad hoc); [b] Based on calculation: Total cholesterol – HDL-C – LDL-C (UC).
Gaudet D, et al. JAMA Cardiol. Published online April 7, 2024. doi:10.1001/jamacardio.2024.0959
Data are shown for the full analysis set of 226, i.e., all randomized patients who received at least 1 dose of investigational product. **ApoB**, apolipoprotein B; **APOC3**, apolipoprotein C3; **BMI**, body mass index; **HDL-C**, high density lipoprotein cholesterol; **LDL-C**, low density lipoprotein cholesterol; **UC**, ultracentrifugation.

Plozasiran Lowers APOC3 and Triglycerides in sHTG Patients: SHASTA-2 Final Data

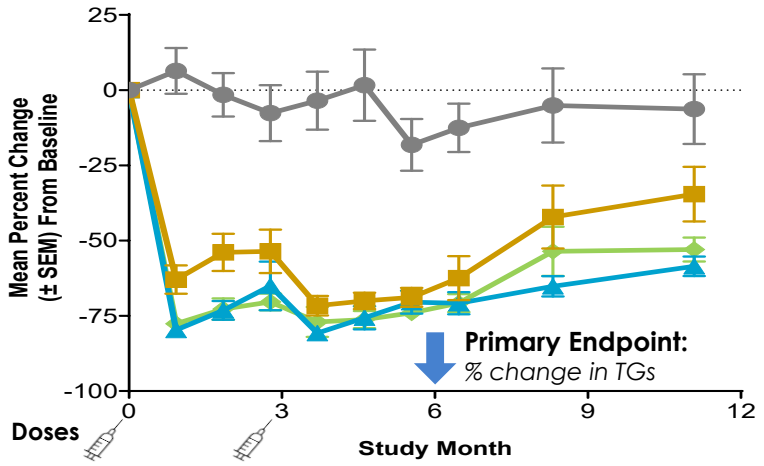
Randomized Period | **OLE**

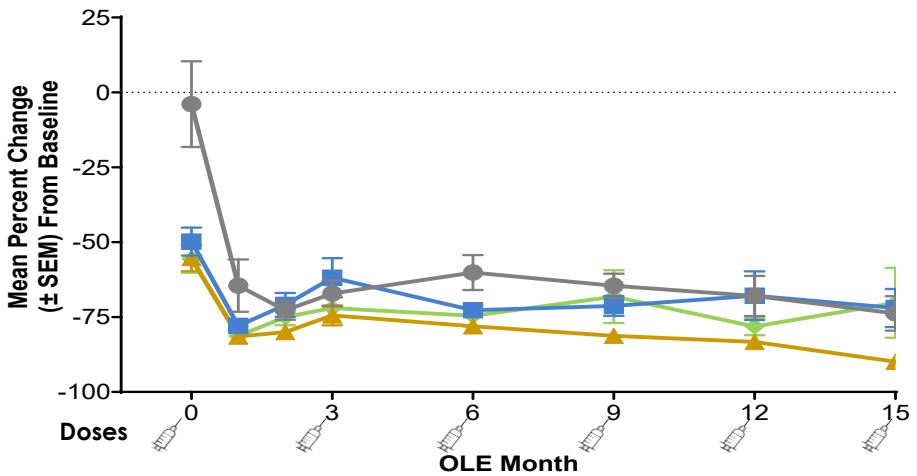
Mean APOC3





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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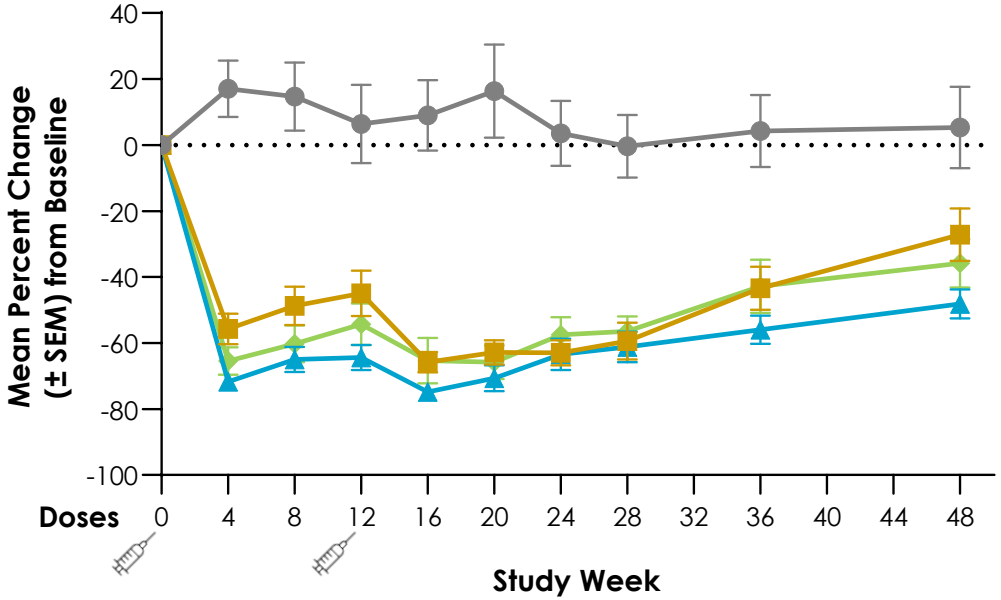
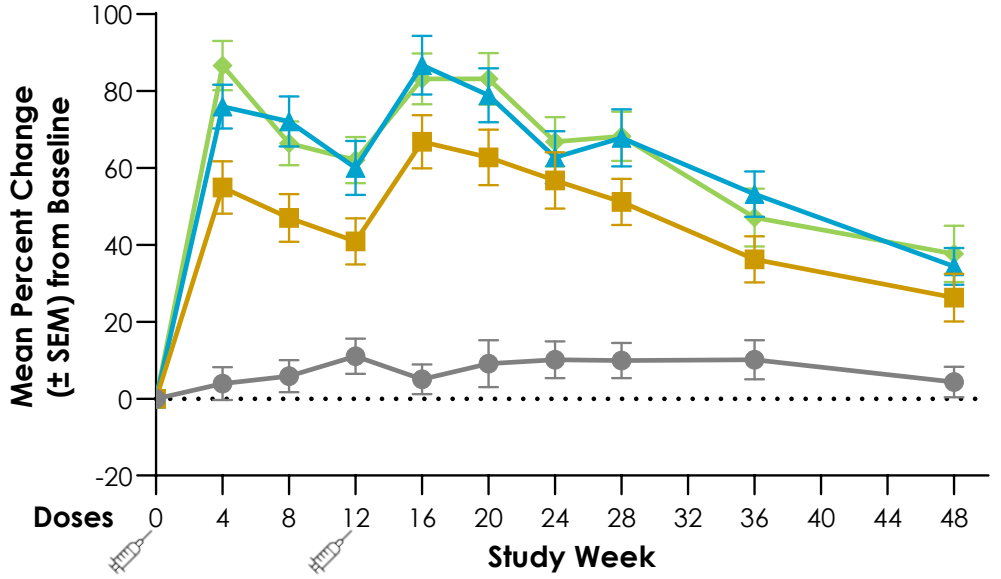
Plozasiran Decreased Remnant Cholesterol and Increased HDL-C

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.

SHASTA-2: Summary of Adverse Events

	Pooled Placebo (N=61)	Plozasiran 10 mg (N=54)	Plozasiran 25 mg (N=55)	Plozasiran 50 mg (N=56)
TEAEs	43 (70.5)	43 (79.6)	36 (65.5)	49 (87.5)
TEAEs occurring in ≥ 5 subjects				
• COVID-19	10 (16.4)	10 (18.5)	8 (14.5)	8 (14.3)
• Upper respiratory tract infection	4 (6.6)	5 (9.3)	4 (7.3)	7 (12.5)
• Headache	3 (4.9)	8 (14.8)	5 (9.1)	2 (3.6)
• Type 2 diabetes mellitus	3 (4.9)	1 (1.9)	4 (7.3)	6 (10.7)
• Urinary tract infection	5 (8.2)	4 (7.4)	1 (1.8)	2 (3.6)
• Arthralgia	4 (6.6)	2 (3.7)	1 (1.8)	4 (7.1)
Severe TEAEs	5 (8.2)	2 (3.7)	1 (1.8)	3 (5.4)
Serious TEAEs	10 (16.4)	4 (7.4)	2 (3.6)	7 (12.5)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Premature Discontinuations	4 (6.6)	5 (9.3)	3 (5.5)	4 (7.1)

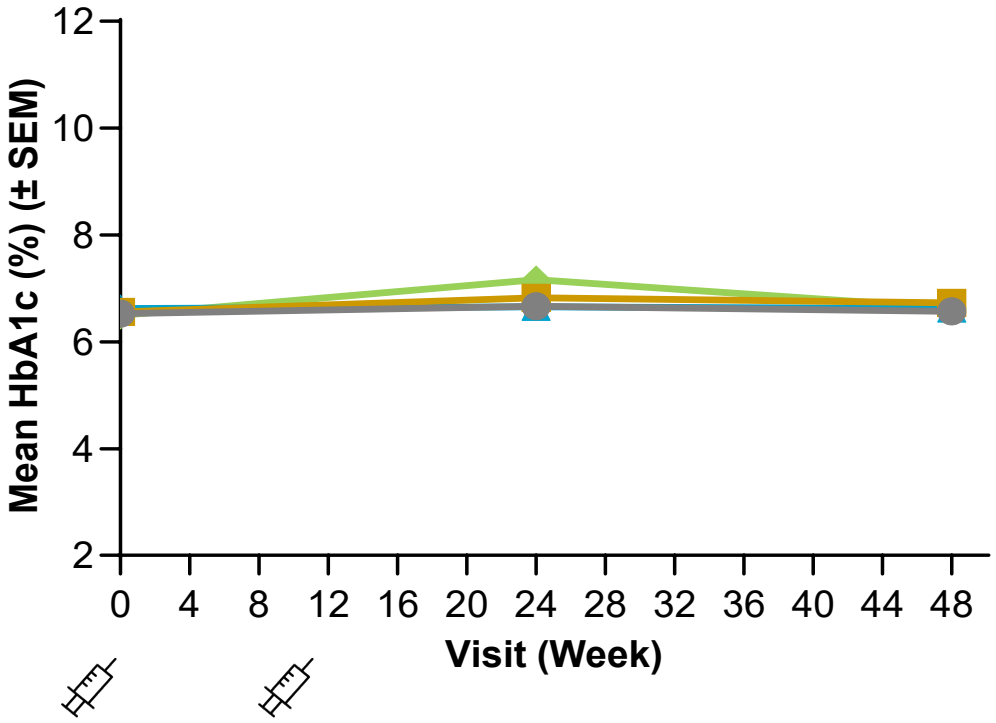
- TEAEs reflect the comorbidities and underlying conditions of the study population
- Serious TEAEs were deemed not related to Plozasiran
- All serious TEAEs resolved without sequelae (except 2 subjects with malignancies), with no deaths
- Data includes exposure out to 48 weeks

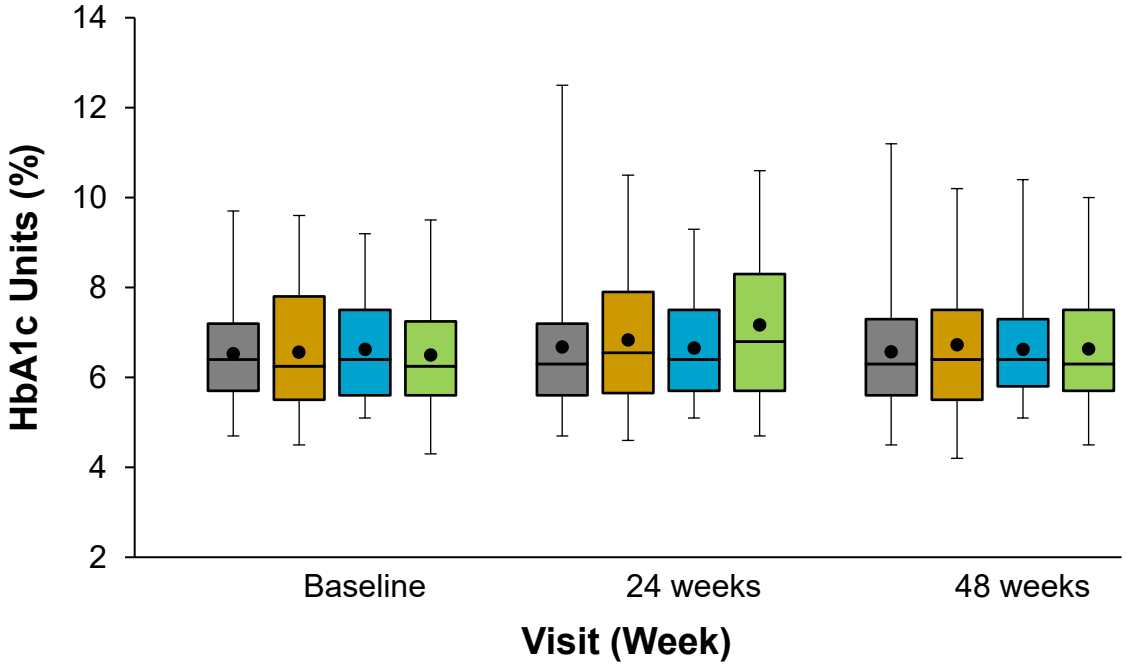
Gaudet D, et al. JAMA Cardiol. Published online April 7, 2024. doi:10.1001/jamacardio.2024.0959

TEAEs, treatment emergent adverse events.

Minimal Change in Mean HbA1C in sHTG

Glycemia: HbA1C, All Patients





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

Cardiometabolic Webinar – June 25, 2024

Plozasiran Proves Itself in Mixed Hyperlipidemia – MUIR

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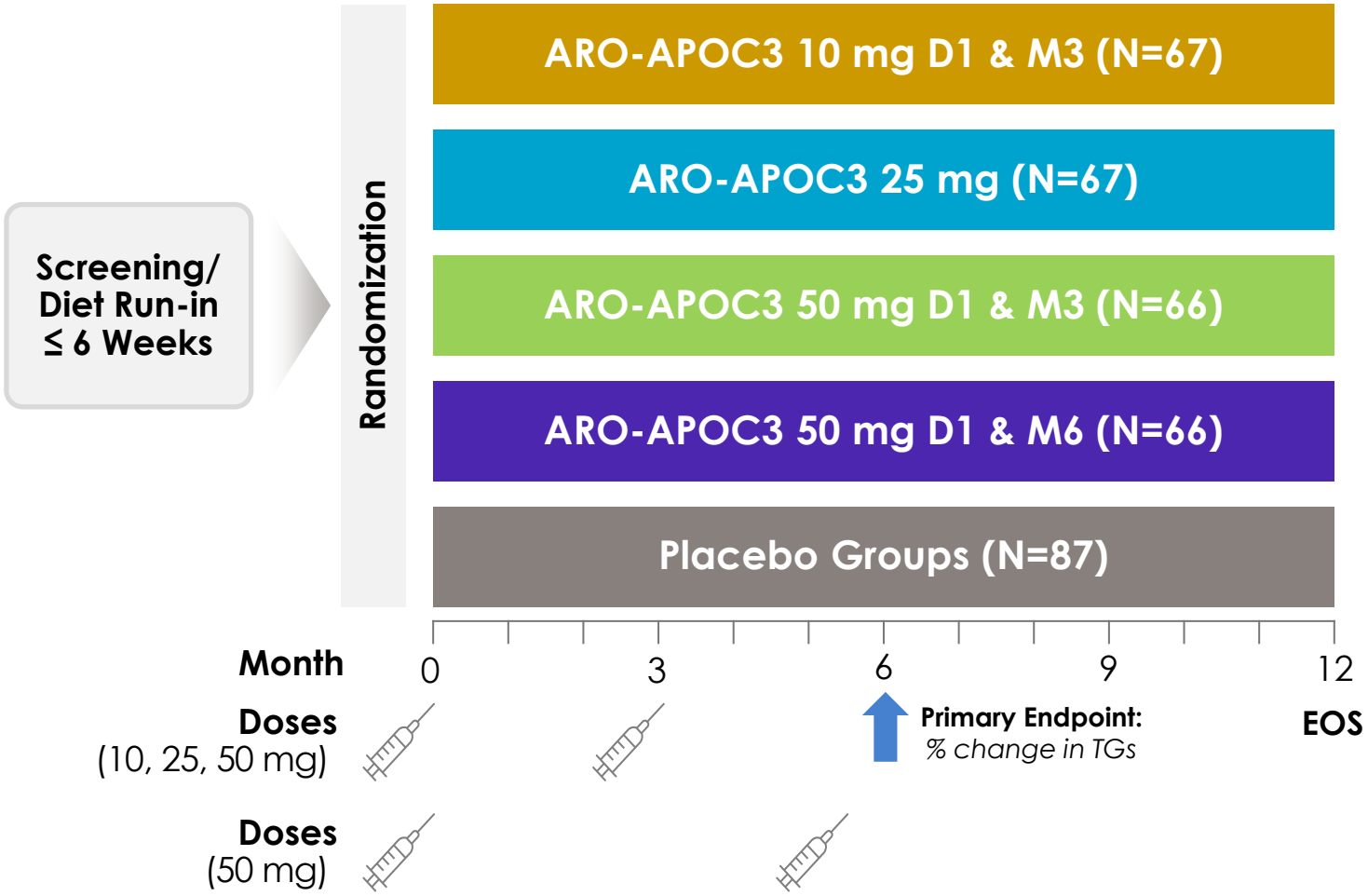
Plozasiran for the Treatment of Mixed Hyperlipidemia: MUIR Study Design



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

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Baseline Characteristics: MUIR

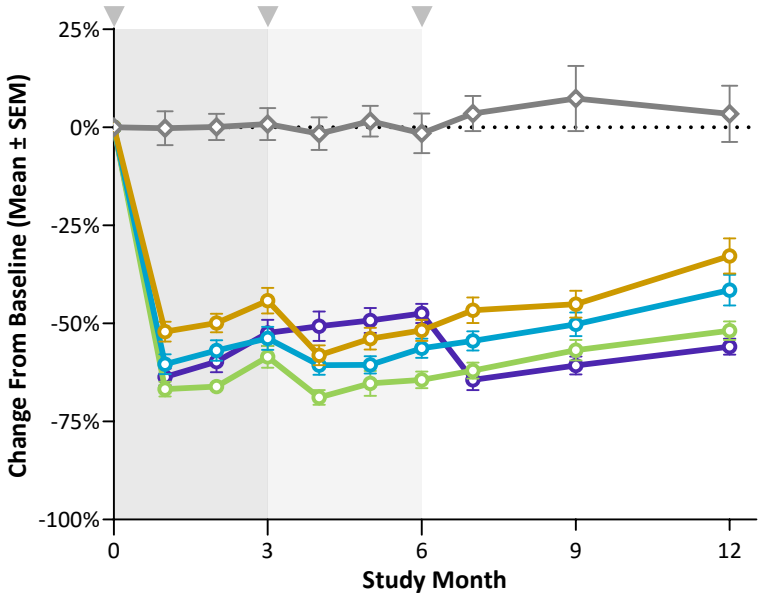
	Pooled Placebo (N=87)	Plozasiran 10 mg Q12W (N=67)	Plozasiran 25 mg Q12W (N=67)	Plozasiran 50 mg Q12W (N=66)	Plozasiran 50 mg Q24W (N=66)
Mean (SD) Age, years	58.9 (9.7)	60.2 (11.7)	61.3 (11.3)	62.6 (10.5)	61.3 (11.8)
Female, n (%)	41 (47.1)	31 (46.3)	30 (44.8)	29 (43.9)	23 (34.8)
White, n (%)	79 (90.8)	62 (92.5)	60 (89.6)	63 (95.5)	62 (93.9)
Mean (SD) BMI, kg/m^2	31.2 (5.4)	30.5 (5.7)	32.4 (6.7)	32.6 (6.5)	32.0 (5.6)
Mean (SD) APOC3,[a] mg/L	14.6 (4.7)	15.5 (5.5)	15.6 (5.5)	15.0 (5.7)	15.0 (5.5)
Mean (SD) Remnant cholesterol[b], mg/dL	45.0 (18.9)	48.3 (20.5)	46.1 (20.3)	48.8 (27.2)	47.4 (23.1)
Mean (SD) Triglyceride, mg/dL	237.2 (76.2)	253.2 (81.4)	234.1 (72.7)	250.3 (81.3)	248.0 (80.6)
Median (Q1, Q3) Triglyceride, mg/dL	217.2 (182.7, 275.9)	222.9 (192.4, 323.1)	213.9 (180.2, 275.0)	228.9 (187.3, 296.4)	232.7 (182.1, 298.7)
Mean (SD) Non-HDL-C, mg/dL	148.3 (43.4)	153.5 (42.0)	147.7 (48.4)	151.8 (49.3)	153.0 (42.7)
Mean (SD) ApoB, mg/dL	102.3 (29.6)	102.6 (23.0)	100.9 (27.2)	100.6 (27.6)	104.5 (24.2)
Mean (SD) HDL-C, mg/dL	42.1 (11.1)	42.2 (11.1)	44.7 (13.6)	42.7 (11.7)	40.8 (12.6)
Mean (SD) LDL-C (UC), mg/dL	101.6 (38.7)	105.1 (37.0)	101.6 (43.4)	103.0 (39.7)	105.6 (31.8)

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

Plozasiran Lowers APOC3, TGs, and Remnant Cholesterol in MUIR (Mixed Hyperlipidemia)

Triglycerides

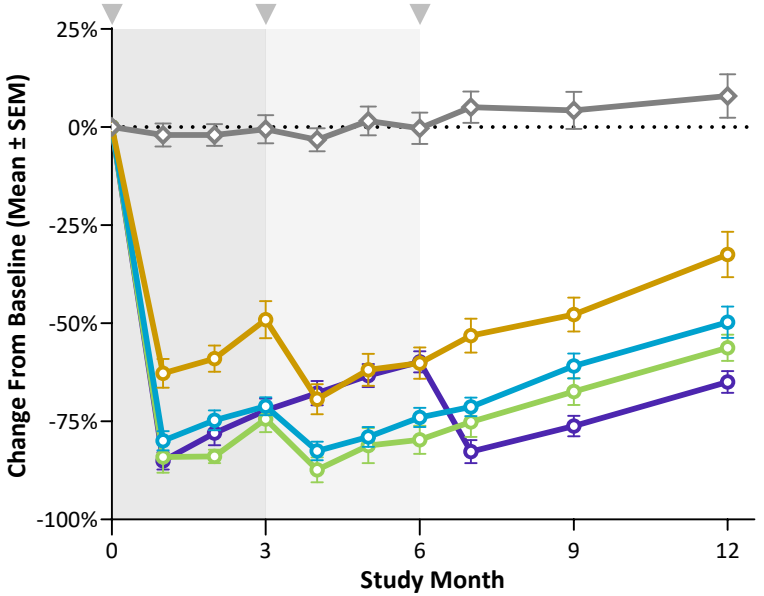
Primary Endpoint:
% change in TG at 24 weeks



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

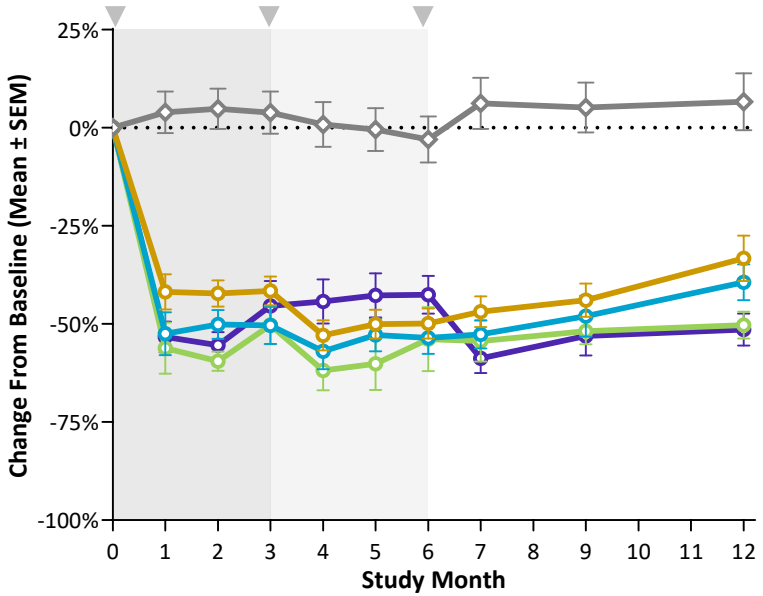
APOC3



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*)

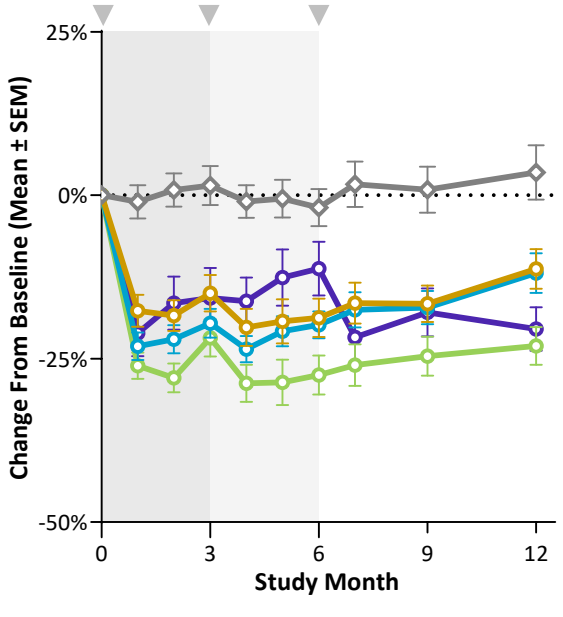
24 Weeks	**-5%**	**-48%** p<0.0001	**-54%** p<0.0001	**-53%** p<0.0001	**-42%** p<0.0001

Plozasiran
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

Plozasiran Impact on Lipids: MUIR (Mixed Hyperlipidemia)

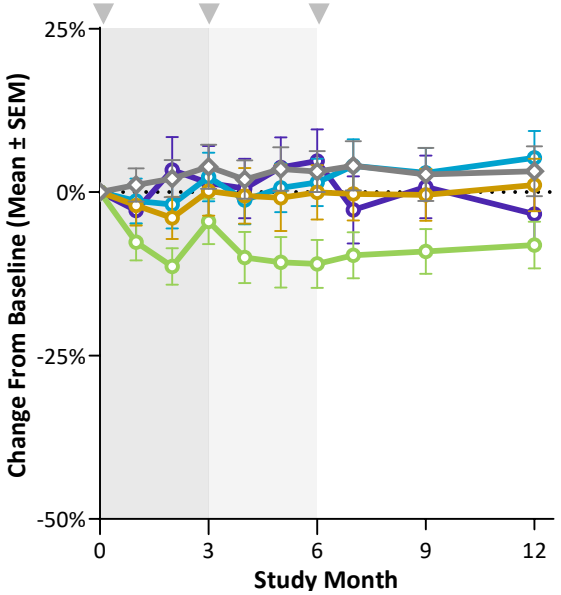
Non-HDL-C



Change from Baseline (LS Mean)

24 Weeks	-3%	-19%	-20%	-27%	-10%

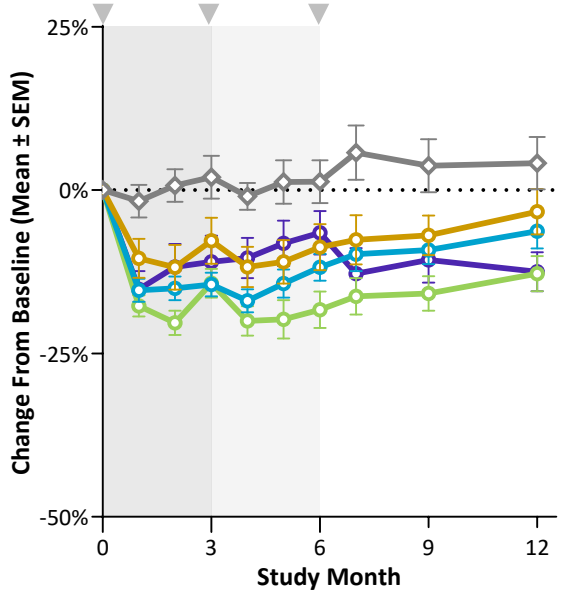
LDL-C



Change from Baseline (LS Mean)

24 Weeks	3%	-1%	1%	-10%	6%

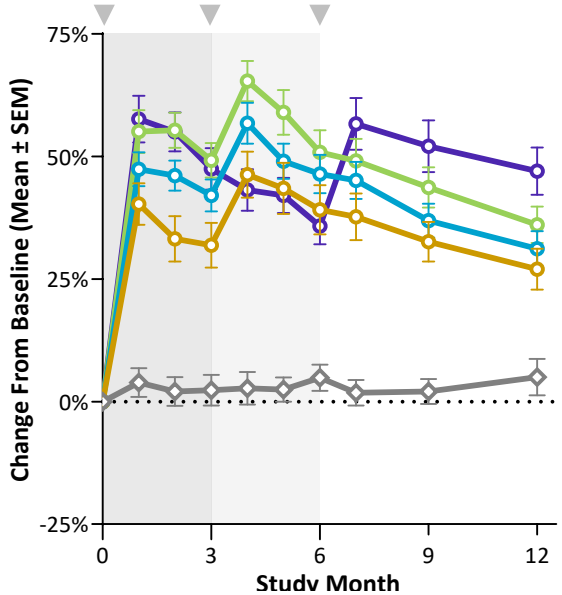
ApoB



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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Changes in Remnant Cholesterol According to Tertiles of Baseline TG: MUIR

	Pooled Placebo (N=87)	Plozasiran 10 mg Q3M (N=67)	Plozasiran 25 mg Q3M (N=67)	Plozasiran 50 mg Q3M (N=66)
Remnant Cholesterol, mg/dL			**Mean (SD)**	
1st Tertile (Triglycerides: < 195 mg/dL)				
n at baseline	34	17	25	19
Baseline RC, mg/dL	34 (10)	31 (8)	33 (13)	32 (13)
Week 24 RC, mg/dL	28 (10)	15 (7)	18 (8)	16 (9)
Week 24 % Change	-14 (40)	-47 (26)	-41 (37)	-25 (114)
2nd Tertile (Triglycerides: 195 - < 267 mg/dL)				
n at baseline	27	26	25	23
Baseline RC, mg/dL	40 (12)	43 (10)	48 (19)	44 (15)
Week 24 RC, mg/dL	45 (20)	21 (12)	18 (11)	16 (9)
Week 24 % Change	22 (65)	-49 (30)	-56 (34)	-62 (17)
3rd Tertile (Triglycerides: ≥ 267 mg/dL)				
n at baseline	26	24	17	24
Baseline RC, mg/dL	64 (19)	67 (21)	64 (18)	67 (34)
Week 24 RC, mg/dL	50 (17)	29 (16)	20 (9)	19 (9)
Week 24 % Change	-15 (46)	-52 (32)	-68 (13)	-69 (15)

Changes in Non-HDL-C According to Tertiles of Baseline TG: MUIR

Non-HDL-C Levels, mg/dL	Pooled Placebo (N=87)	Plozasiran 10 mg Q3M (N=67)	Plozasiran 25 mg Q3M (N=67)	Plozasiran 50 mg Q3M (N=66)
	Mean (SD)			
1st Tertile (Triglycerides: < 195 mg/dL)				
n at baseline	34	17	25	19
Baseline Non-HDL-C, mg/dL	136 (40)	137 (36)	144 (57)	144 (46)
Week 24 Non-HDL-C, mg/dL	126 (39)	110 (37)	117 (43)	116 (34)
Week 24 % Change	-5 (19)	-21 (17)	-16 (15)	-15 (17)
2nd Tertile (Triglycerides: 195 - < 267 mg/dL)				
n at baseline	27	26	25	23
Baseline Non-HDL-C, mg/dL	145 (44)	162 (45)	145 (40)	151 (50)
Week 24 Non-HDL-C, mg/dL	146 (52)	131 (59)	114 (38)	111 (48)
Week 24 % Change	6 (36)	-18 (24)	-22 (17)	-28 (21)
3rd Tertile (Triglycerides: ≥ 267 mg/dL)				
n at baseline	26	24	17	24
Baseline Non-HDL-C, mg/dL	169 (41)	156 (41)	156 (49)	159 (52)
Week 24 Non-HDL-C, mg/dL	158 (35)	124 (44)	121 (48)	89 (31)
Week 24 % Change	-6 (17)	-18 (27)	-23 (18)	-37 (27)

Ballantyne CM, et al. N Engl J Med. Published online May 28, 2024. doi:10.1056/NEJMoa2404143APOC3

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MUIR

MUIR Safety Summary

	Pooled Placebo (N=67)	Plozasiran 10 mg Q3M (N=67)	Plozasiran 25 mg Q3M (N=67)	Plozasiran 50 mg Q3M (N=66)	Plozasiran 50 mg Q6M (N=66)
TEAEs	55 (63)	46 (69)	45 (67)	47 (71)	49 (74)
• COVID-19	11 (13)	7 (10)	10 (15)	8 (12)	5 (8)
• Type 2 diabetes mellitus	4 (5)	5 (8)	4 (6)	8 (12)	11 (17)
• Upper respiratory tract infection	7 (8)	3 (4)	7 (10)	1(2)	9 (14)
• Urinary tract infection	6 (7)	3 (5)	4 (6)	4 (6)	0 (0)
• Bronchitis	1(1)	4 (6)	2 (3)	2 (3)	5 (8)
• Headache	3 (3)	1 (2)	2 (3)	4 (6)	5 (8)
Severe TEAEs	4 (5)	1 (2)	3 (5)	4 (6)	3 (5)
Serious TEAEs	5 (6)	2 (3)	5 (8)	7 (11)	5 (8)
Deaths	0 (0)	0 (0)	1 (2)	2 (3)	1 (2)
Premature Discontinuations (Randomized Period)	9 (10)	7 (10)	3 (5)	5 (8)	5 (8)

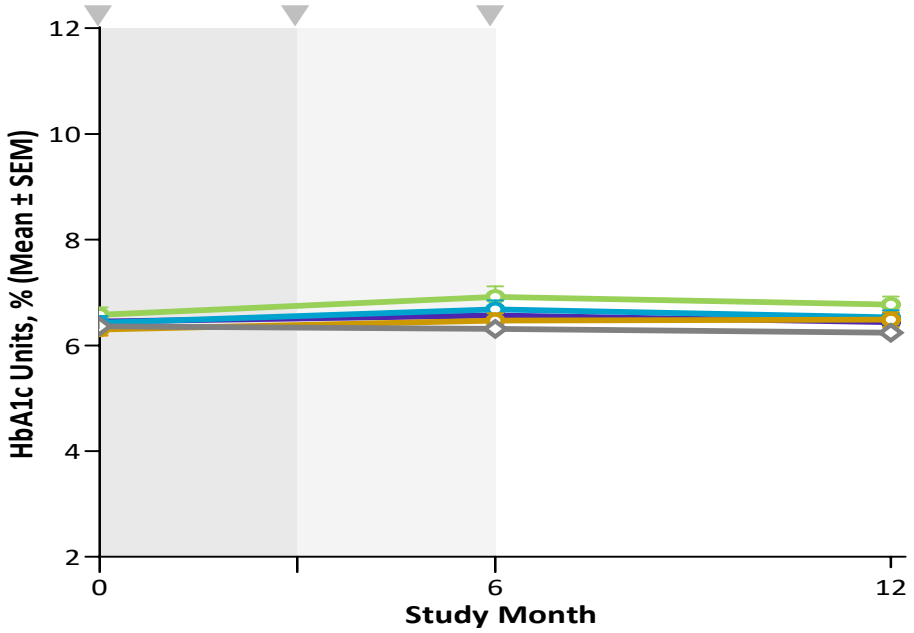
TEAEs, treatment emergent adverse events; **W,** week.

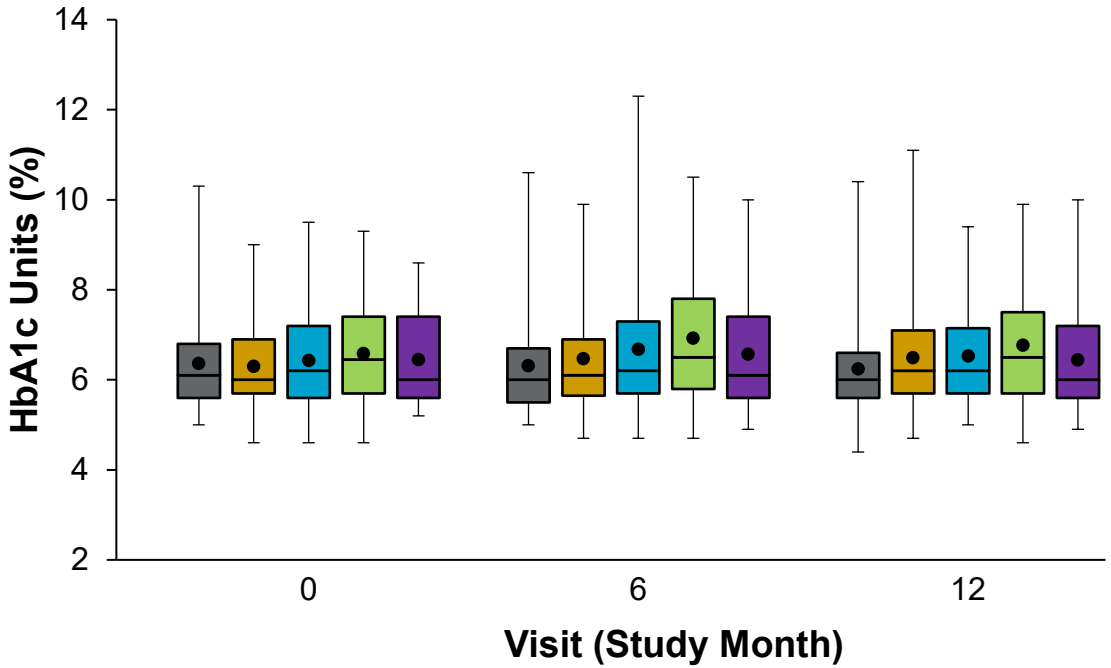
Ballantyne CM, et al. N Engl J Med. Published online May 28, 2024. doi:10.1056/NEJMoa2404143

- TEAEs reflect comorbidities and underlying conditions of the study population
- Platelets unchanged
- Worsened glycemic control reported at 50 mg
- Data includes exposure out to 48 weeks

Minimal Change in Mean HbA1C

Glycemia: HbA1C, All Patients





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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Cardiometabolic Webinar – June 25, 2024

Meeting the Triglyceride Challenge Beyond FCS

Bruce D. Given, M.D.
Chief Medical Scientist

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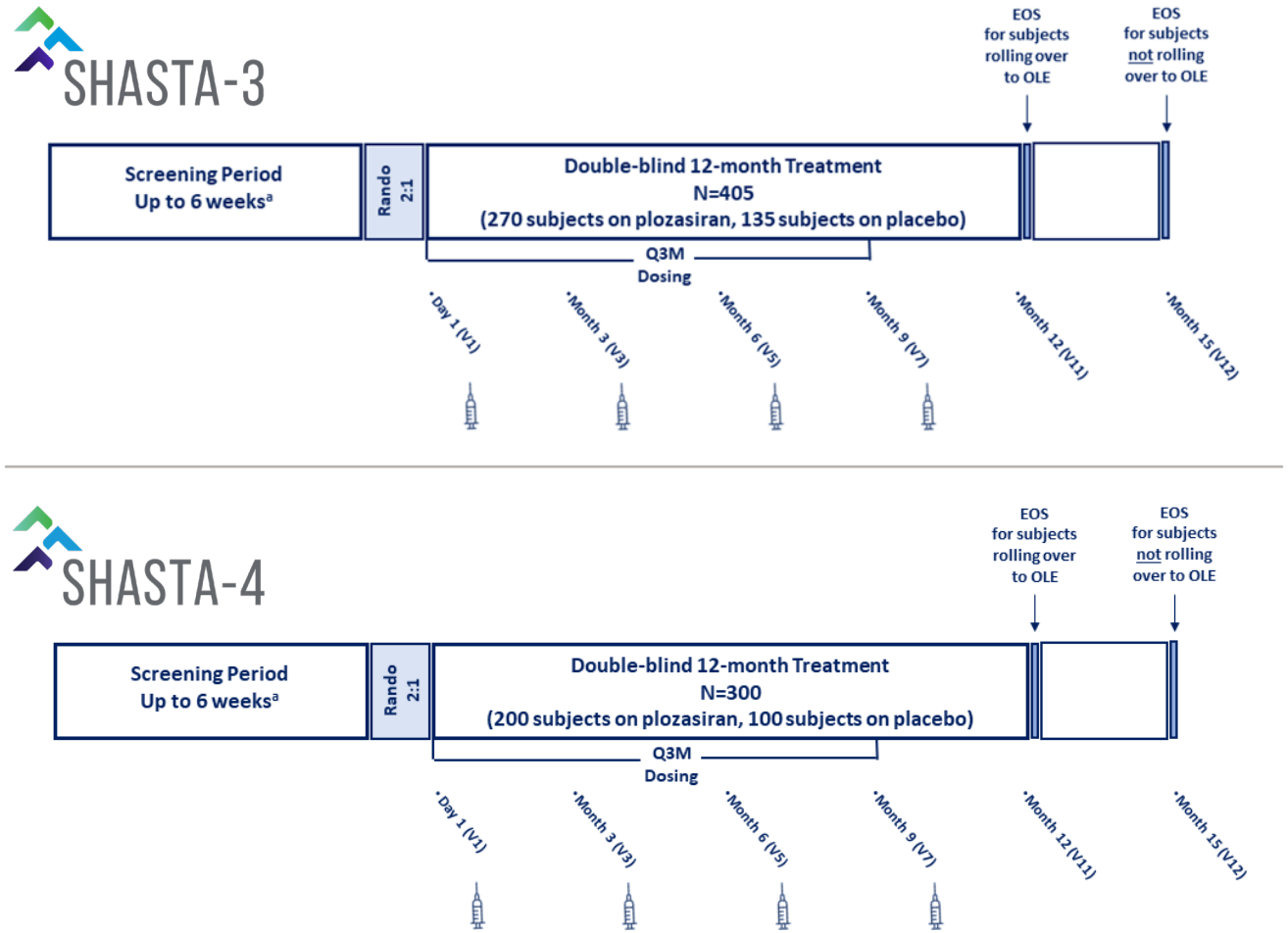
Expansion Across the Triglyceridemia Landscape

Program	Study	Indication	Study Title	Status
SUMMIT PROGRAM	SHASTA-3	sHTG	Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Plozasiran in Adults with Severe Hypertriglyceridemia	Enrolling
	SHASTA-4	sHTG	Double-blind, Placebo-controlled, Phase 3 Study to Evaluate The Efficacy and Safety of Plozasiran in Adults with Severe Hypertriglyceridemia	Enrolling
	MUIR-3	HTG	Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Plozasiran in Adults with Hypertriglyceridemia	Enrolling
	SHASTA-5	Acute Pancreatitis	Double-blind, Placebo-Controlled, Phase 3 Study To Evaluate The Efficacy And Safety Of Plozasiran In Adults With Severe Hypertriglyceridemia At High Risk Of Acute Pancreatitis	Coming Soon
	CAPITAN	ASCVD	A Cardiovascular Outcomes Trial (CVOT) Comparing Plozasiran with Placebo	Coming Soon

SHASTA-3 and SHASTA-4 Studies in Patients with sHTG



Study Population:

- Fasting TG ≥ 500 mg/dL

Primary Endpoints:

- % change from baseline in TG at month 12

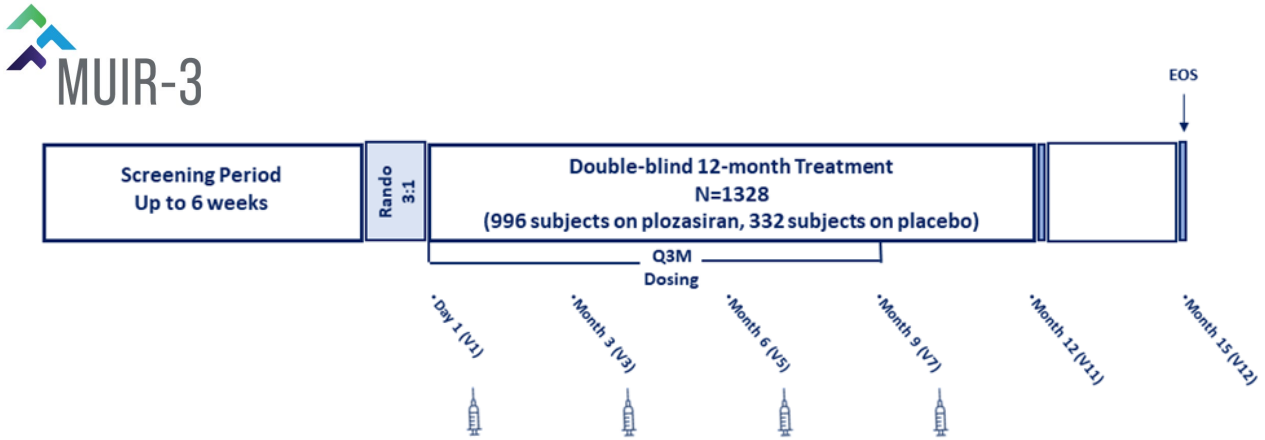
Secondary Endpoints:

- % change from baseline in TG at month 10
- Proportion of participants who achieve TG < 500 mg/dL at Month 10 and Month 12
- Adjudicated abdominal clinical event rate during the treatment period compared to placebo at Month 12 including:
  - ER visits or hospitalizations for abdominal pain attributed to hypertriglyceridemia
  - Events of documented pancreatitis
- Proportion of participants who achieve TG <150 mg/dL at Month 10 and Month 12

Abbreviations: **EOS**=end of study; **OLE**=open-label extension; **Q3M**=every 3 months; **rando**=randomization; **V**=visit.

[a] For subjects with suspected diagnosis of familial chylomicronemia syndrome, the screening period may be extended to up to 8 weeks to allow genetic testing.

MUIR-3 Study in Patients with HTG to Support sHTG NDA



Study Population:

- Fasting TG 150–499 mg/dL

Primary Endpoint:

- % change from baseline in TG at month 12

Secondary Endpoints:

- % change from baseline in TG at month 10
- Proportion of participants who achieve TG <150 mg/dL at Month 10 and Month 12

Abbreviations: **EOS**=end of study; **Q3M**=every 3 months; **rando**=randomization; **V**=visit.

CAPITAN: A Cardiovascular Outcomes Trial (CVOT) Comparing Plozasiran with Placebo

Study Population:

- 2° prevention cohort:
  - TG 200 -800 mg/dl
  - Non-HDL-C >100 mg/dl
- 1° prevention cohort:
  - TG 250-800 mg/dl
  - Non-HDL-C >130 mg/dL
- Stable optimal statin therapy

Primary Endpoint: time from randomization to 1st occurrence of any component of the clinical composite endpoint of:

- Cardiovascular death
- Nonfatal MI
- Nonfatal ischemic stroke
- Coronary revascularization
- Major adverse limb events

Cardiometabolic Webinar – June 25, 2024

Arrowhead's Future in Cardiometabolic Disease

Bruce D. Given, M.D.
Chief Medical Scientist

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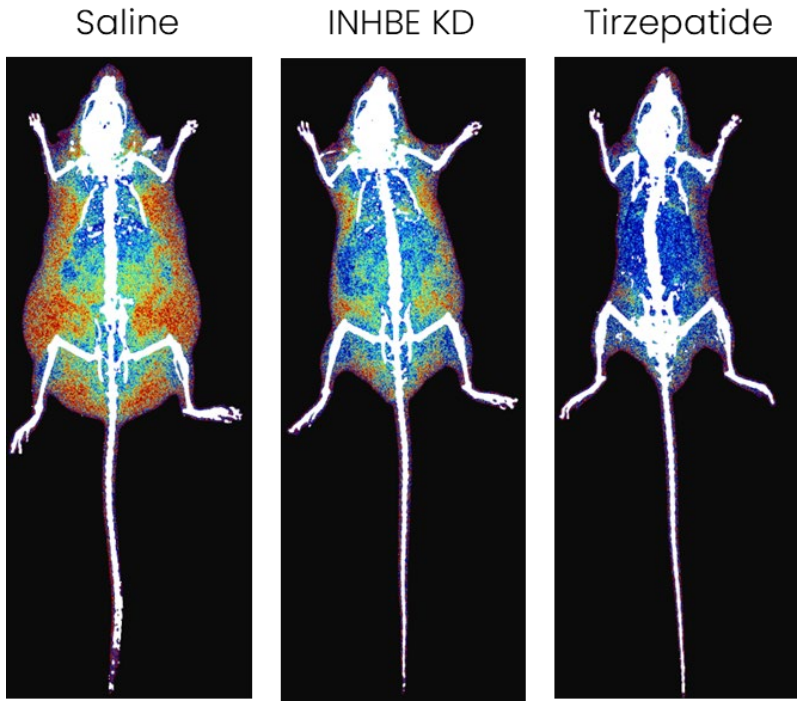
ARO-INHBE for Obesity and Metabolic Diseases

Knockdown of hepatic INHBE mRNA expression results in an improved body composition with: 1) Body weight suppression, 2) fat mass loss, 3) lean mass retention

- DIO mice were administered with saline (weekly), mouse surrogate ARO-INHBE (9 mpk, weekly), or tirzepatide (0.48 mpk, daily)
- INHBE mRNA expression reduced by ~95%
- INHBE silencing led to a 19% suppression of body weight compared to saline controls
- Body composition analysis through DEXA imaging indicates a 26% loss of fat mass and preservation of lean mass with INHBE silencing



Poster presented at ADA July 24, 2024. Additional INHBE data and new adipose targeted program to be discussed at Arrowhead Obesity/Metabolic R&D Webinar August 15, 2024

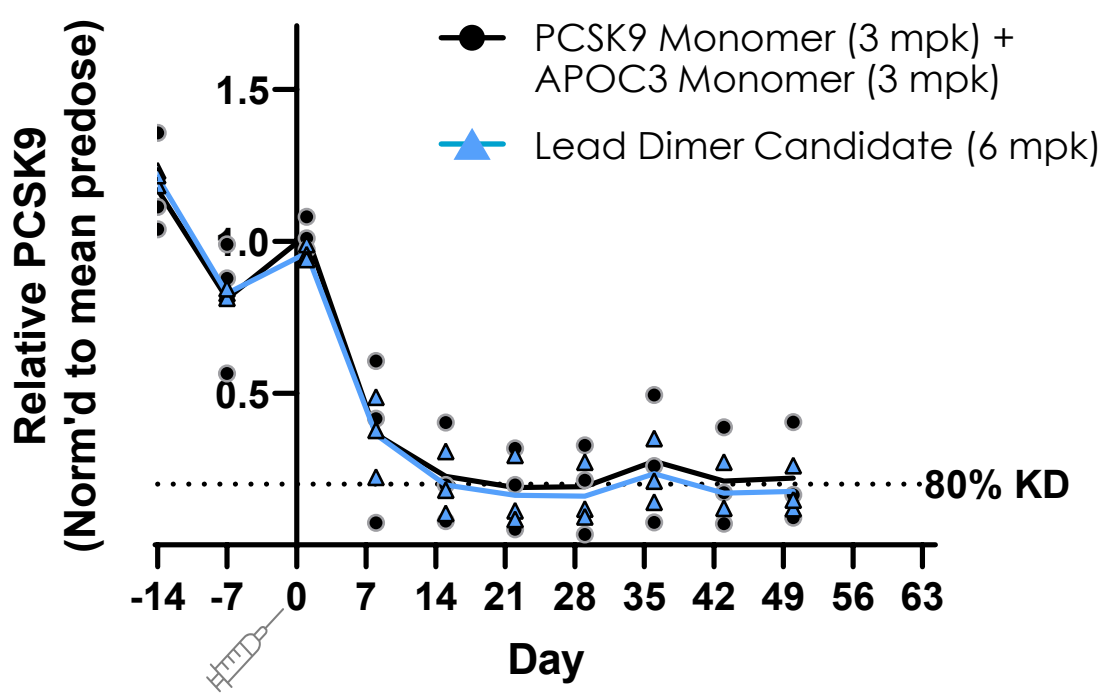
Advances Enable Hepatic Delivery of Two Therapeutic siRNAs

TRiM™ Hepatic-Targeted Dimer

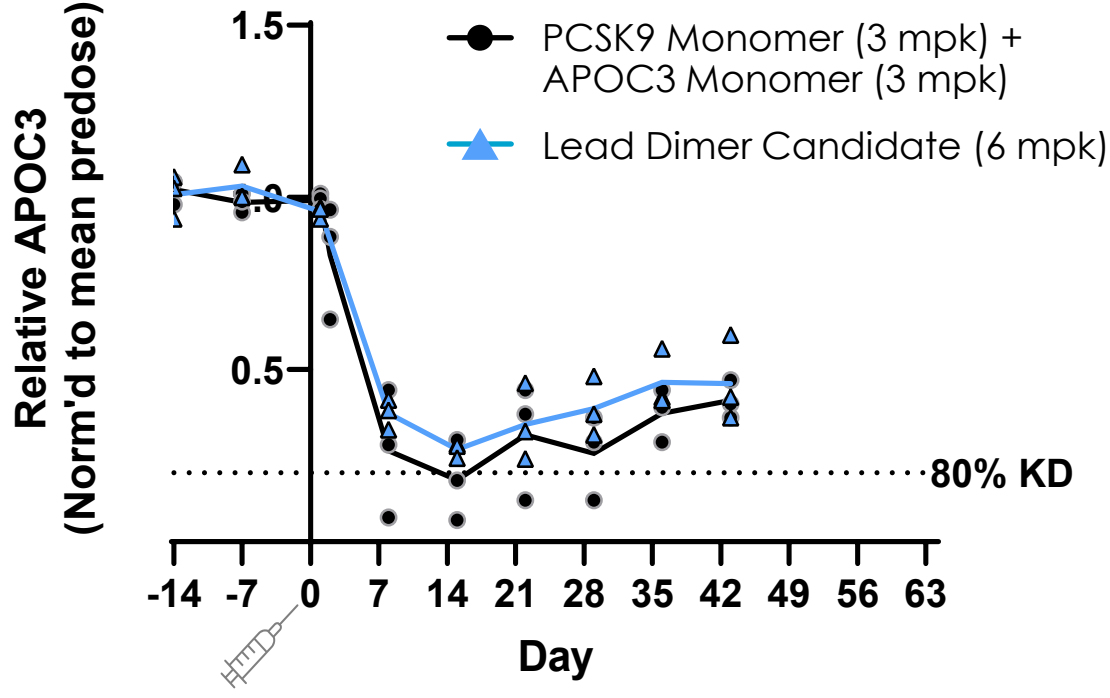
APOC3/PCSK9 Dimer Achieves KD Equivalent to Monomers

Dimer KD of NHP Serum APOC3 and PCSK9 is Equivalent to Monomers in NHP Following a Single SQ Dose Administered on Day 1

NHP Relative Serum APOC3



NHP Relative Serum PCSK9



Cardiometabolic Webinar – June 25, 2024

Our Take on the Triglyceride Market and Opportunity

Vince Anzalone, CFA
Vice President, Finance and IR

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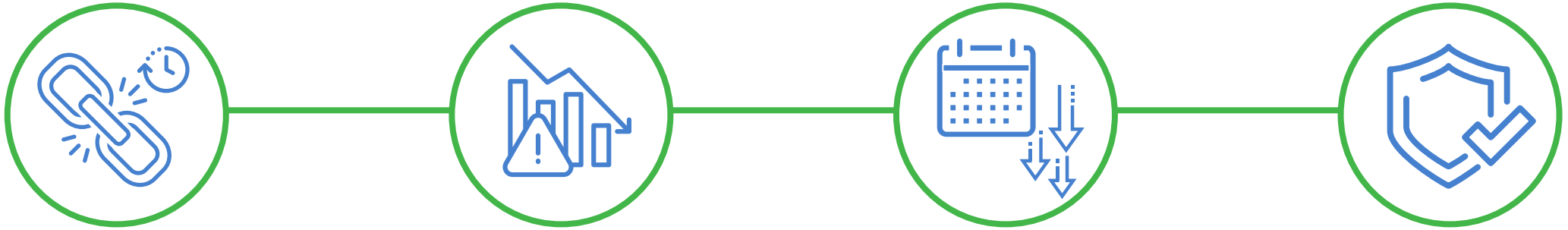
Plozasiran Profile Potentially Best in Class in FCS



Activity/ Durability

TG reductions of 80%
APOC3 reductions 94%
Long duration of effect

Acute Pancreatitis Reduction

Achieved statistical significance

Infrequent Dosing

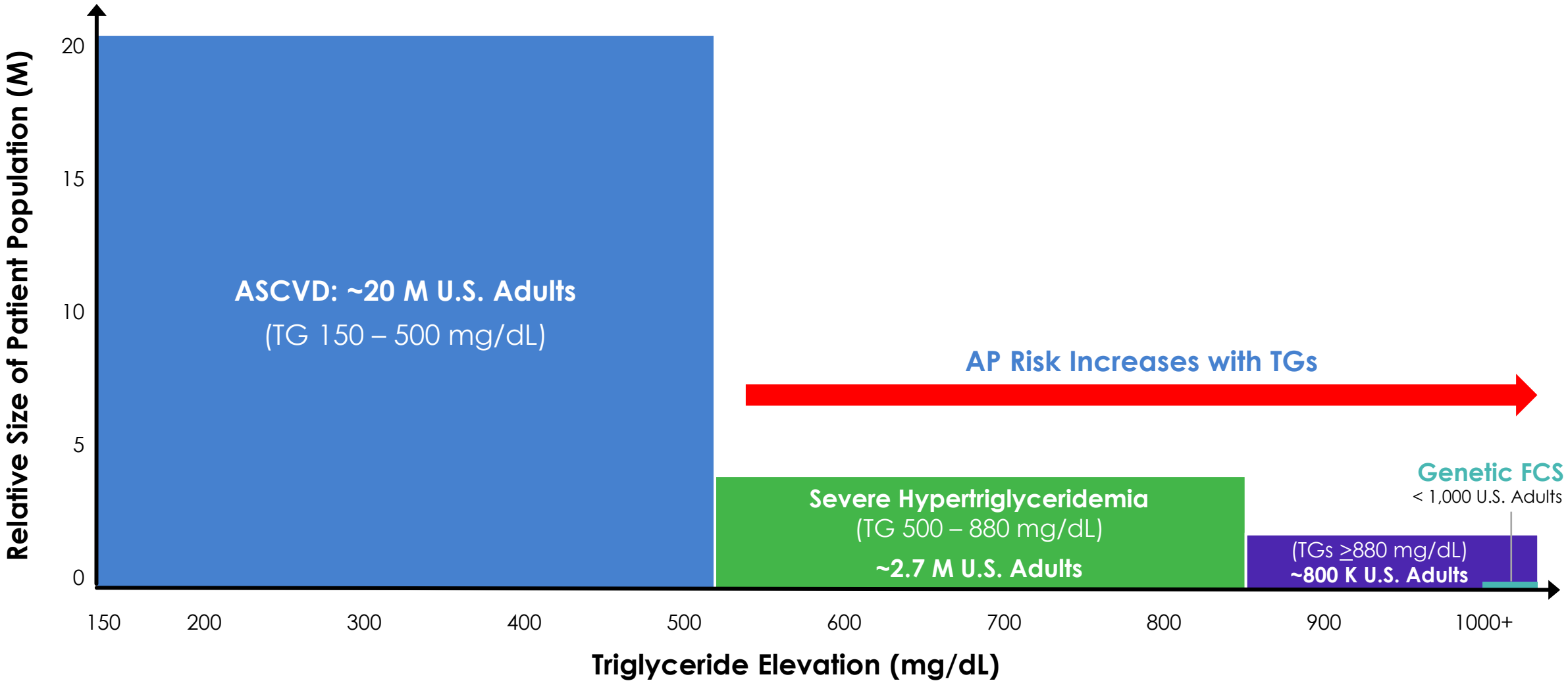
Convenient every 3-month (4/year) patient self injection

Safety/ Tolerability

Favorable safety/ tolerability profile demonstrated to date

Pipeline-in-a Molecule - Promising results also in sHTG and Mixed Hyperlipidemia

Progressively Larger Triglyceride Segments



Patients, HCPs, Payers Have Been Clear On FCS Unmet Need

1 Patients

- Reduction in abdominal pain and acute pancreatitis
- Favorable safety and tolerability profile
- Less burdensome dosing regimen
- To live life with fewer restrictions

> The pancreatitis is what had happened that led to all this...One time I was really, really ill. It was worse than childbirth. It hurt so bad.

2 HCPs

- Deep and durable triglyceride lowering below key risk thresholds (<500 mg/dL)
- Reduction in acute pancreatitis
- Favorable safety and tolerability profile
- Infrequent dosing regimen that supports patient compliance/ adherence

> I think we need help with current treatments. […] it'd be great if there was something specific. […] but anything that's easy for the patient, anything that's better access, anything that would help these people in the future would be great.

3 Payers

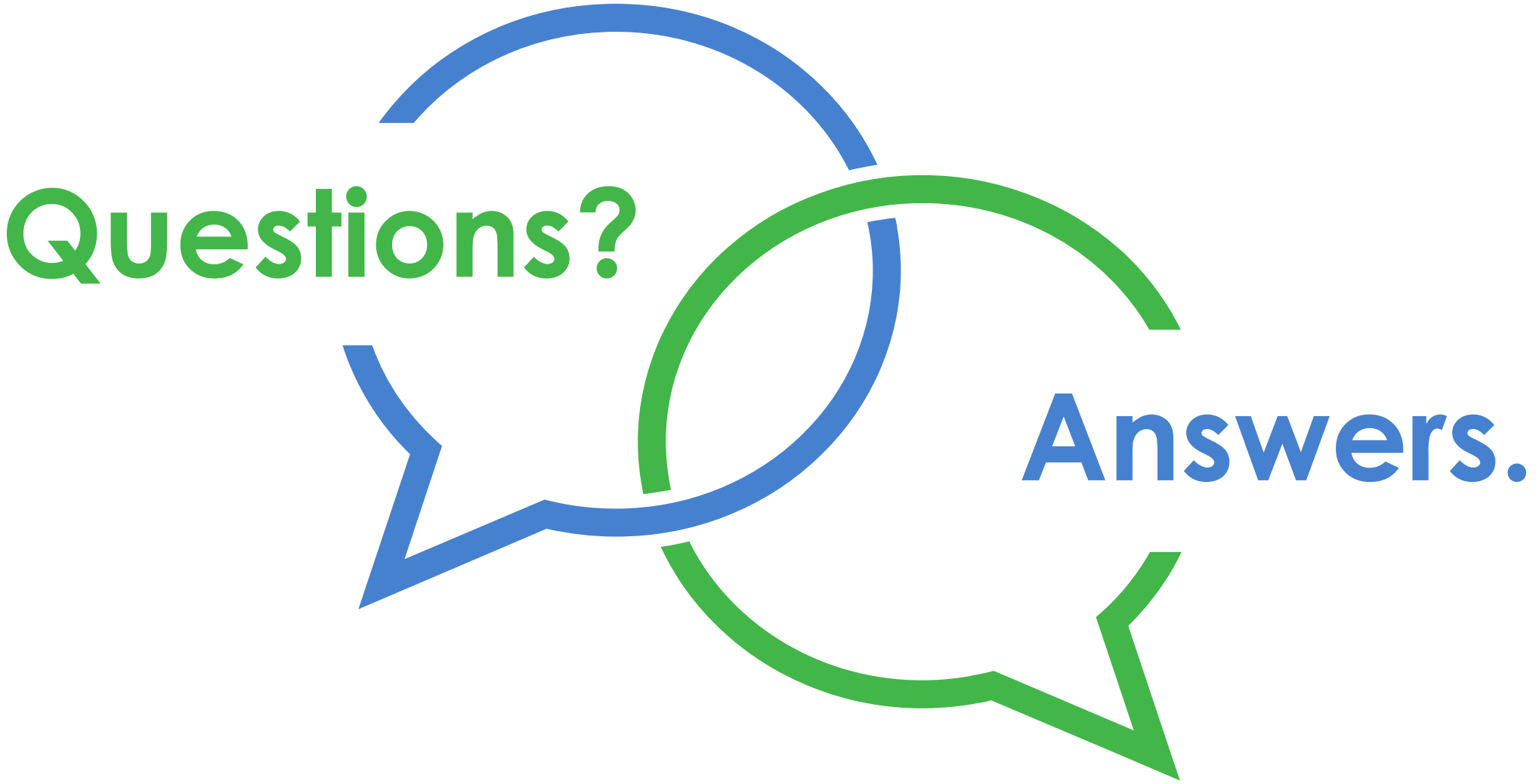
- Reduction in incidence of acute and chronic pancreatitis and ER visits
- Favorable safety profile
- Reduction in cost of care and manageable budget impact

> We are responsible for patients' long-term medical care, so we are looking for a long-term outcome. We want to see the impact in decreased episodes and total cost of care.

Source: Arrowhead Confidential Patient/HCP/Payer Market Research

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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