# 2026 Summer Series of R&D Webinars
# Part I – Cardiometabolic

June 29, 2026

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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 |
|---|---|
| Overview of Cardiometabolic Pipeline | Vince Anzalone, CFA |
| Arrowhead's Technology and R&D Process | James Hamilton, M.D., MBA |
| Plozasiran (APOC3) | Jennifer Hellawell, M.D. |
| Zodasiran (ANGPTL3) | Jennifer Hellawell, M.D. |
| ARO-DIMER-PA (PCSK9/APOC3) | James Hamilton, M.D., MBA |
| Mixed Hyperlipidemia/ASCVD Treatment Landscape | Steven Nissen, M.D., Cleveland Clinic |
| Q&A | Panel |

# Cardiometabolic Key Opinion Leader

## **Steven Nissen, M.D.**
## Cleveland Clinic

Steven E. Nissen, MD, is Chief Academic Officer for the Heart and Vascular Institute at the Cleveland Clinic, the Lewis and Patricia Dickey Chair in Cardiovascular Medicine and Professor of Medicine at the Lerner College of Medicine. From 2006 to 2019, he served as Chair of the Department of Cardiovascular Medicine at the Cleveland Clinic. In 2006-2007 he served as President of the American College of Cardiology (ACC), the professional society representing American cardiologists.

He has served as Study Chair for large global cardiovascular outcomes trials, most studying lipid modifying therapies. He is directing clinical trials of several therapies for patients with elevated lipoprotein(a) including pelacarsen, zerlasiran, lepodisiran and muvalaplin. Dr. Nissen's contributions to scientific literature include more than 750 journal articles. He is co-author of a book for patients with heart disease, Heart411 published by Crown Books.

In 2007, Time Magazine selected Dr. Nissen as one of the world's 100 most influential people. Beginning in 2015, he was named by Thompson-Reuters as one of the world's most highly cited physician-scientists.

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# Overview of Cardiometabolic Pipeline

**Vince Anzalone, CFA**
Senior Vice President

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# Bringing RNA Interference to Patients

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

## First Commercial Launch in 2025

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

## Broad Pipeline

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

## Proprietary Platform

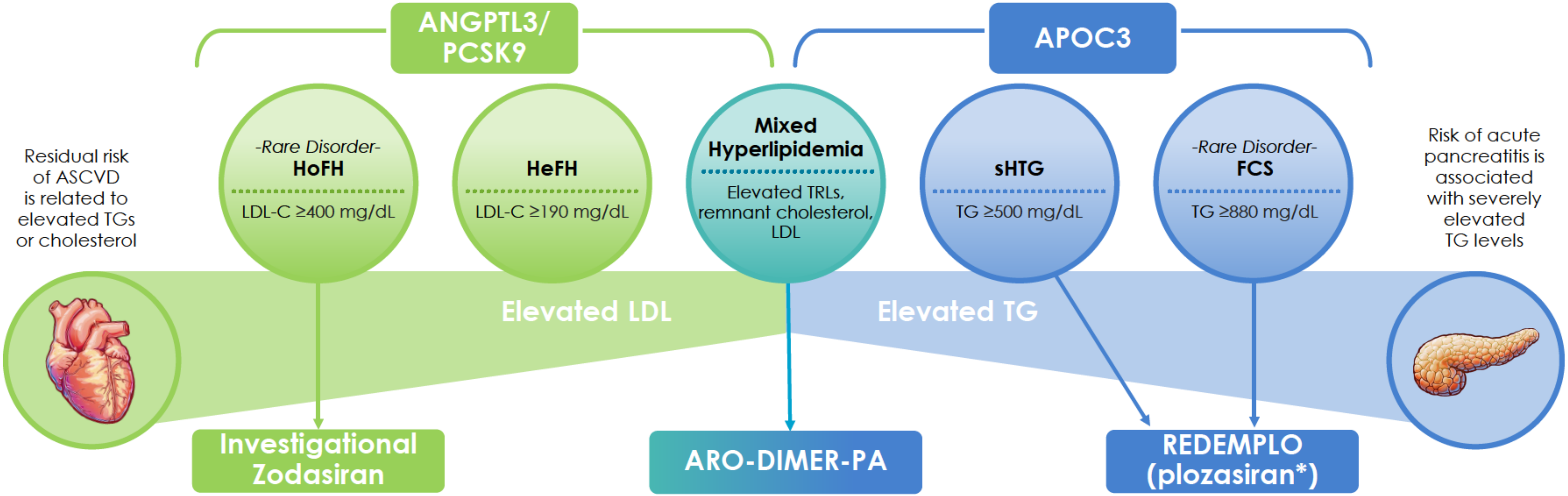
- **Targeted RNAi Molecules** platform (**TRiM™**) designed for **deep and durable gene silencing**
- **Fulfilling the promise** of bringing RNAi therapeutics to diseases **outside of the liver**
- Potential to be **best-in-class** across several tissue types

## Financial Resources

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

# Active Across Cardiometabolic and TG/LDL Spectrum

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

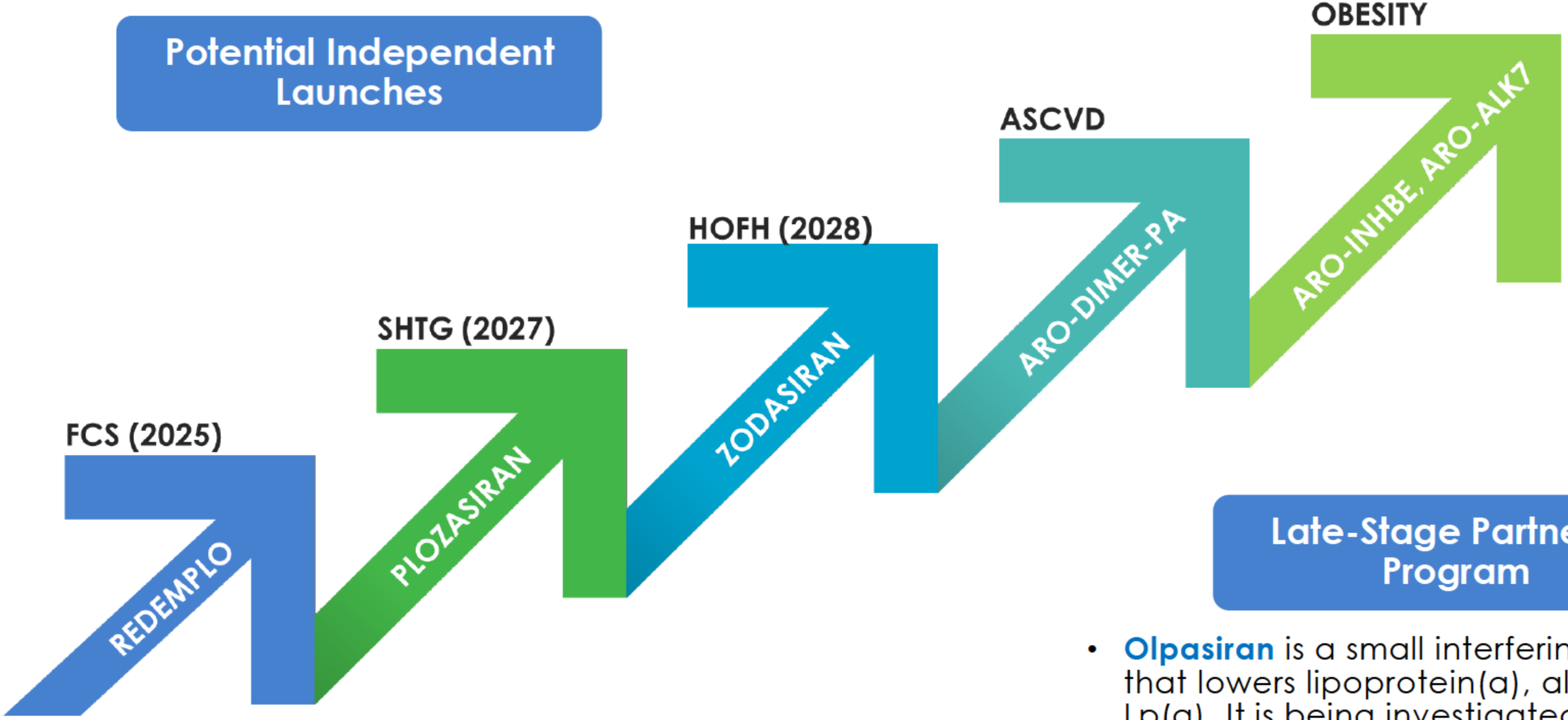



ASCVD, atherosclerotic cardiovascular disease; FCS, familial chylomicronemia syndrome; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; sHTG, severe hypertriglyceridemia; TG, triglyceride; TRL, triglyceride-rich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

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


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

# Potential Upcoming Commercial Launches in Cardiometabolic




**Late-Stage Partnered Program**

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

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# Arrowhead's Technology and R&D Process

**James Hamilton MD, MBA**
Chief Medical Officer and Head of R&D

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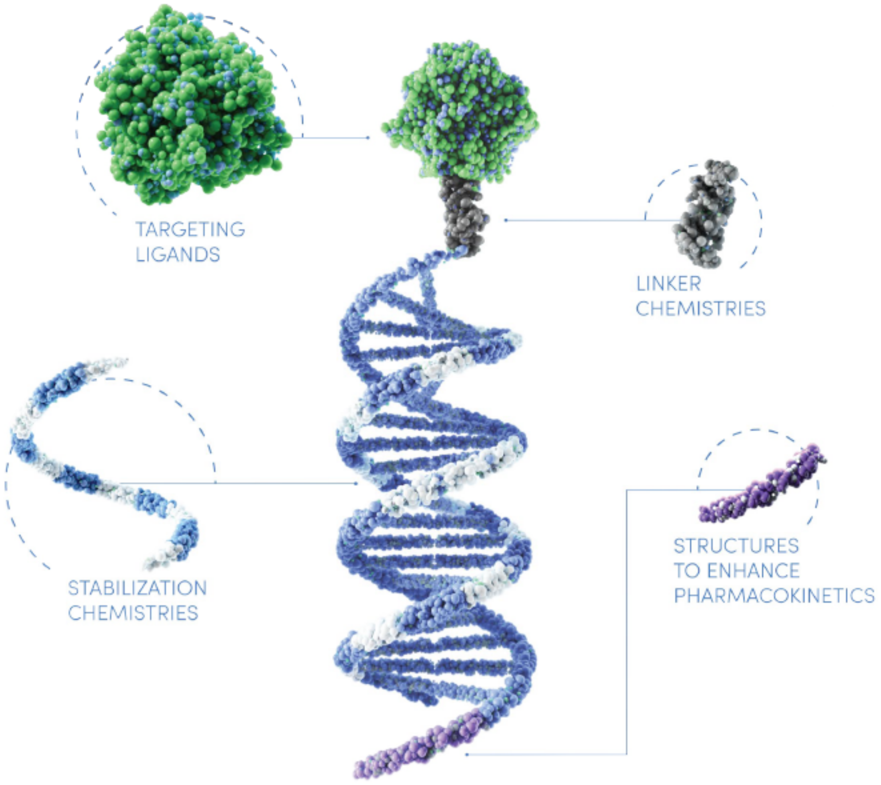
# Arrowhead's Targeted RNAi Molecule (TRiM™) Platform: The Broadest and Most Versatile in the Field




**Optimized Delivery of siRNA to Multiple Cell Types**

## TRiM™ also has rules and algorithms to optimize trigger sequence and modification patterns

**Activity**

Characterized by depth & duration of effect

- Ability to unlock previously undruggable targets

**Specificity**

To maximize activity and innate stability with the potential for reduced off-target effects

**Versatility**

In structure and design offers multiple routes of administration and access to multiple tissues

- Facilitates rapid drug development and speed to patients

**Simplicity**

In design translates to relatively lower costs, and production at scale

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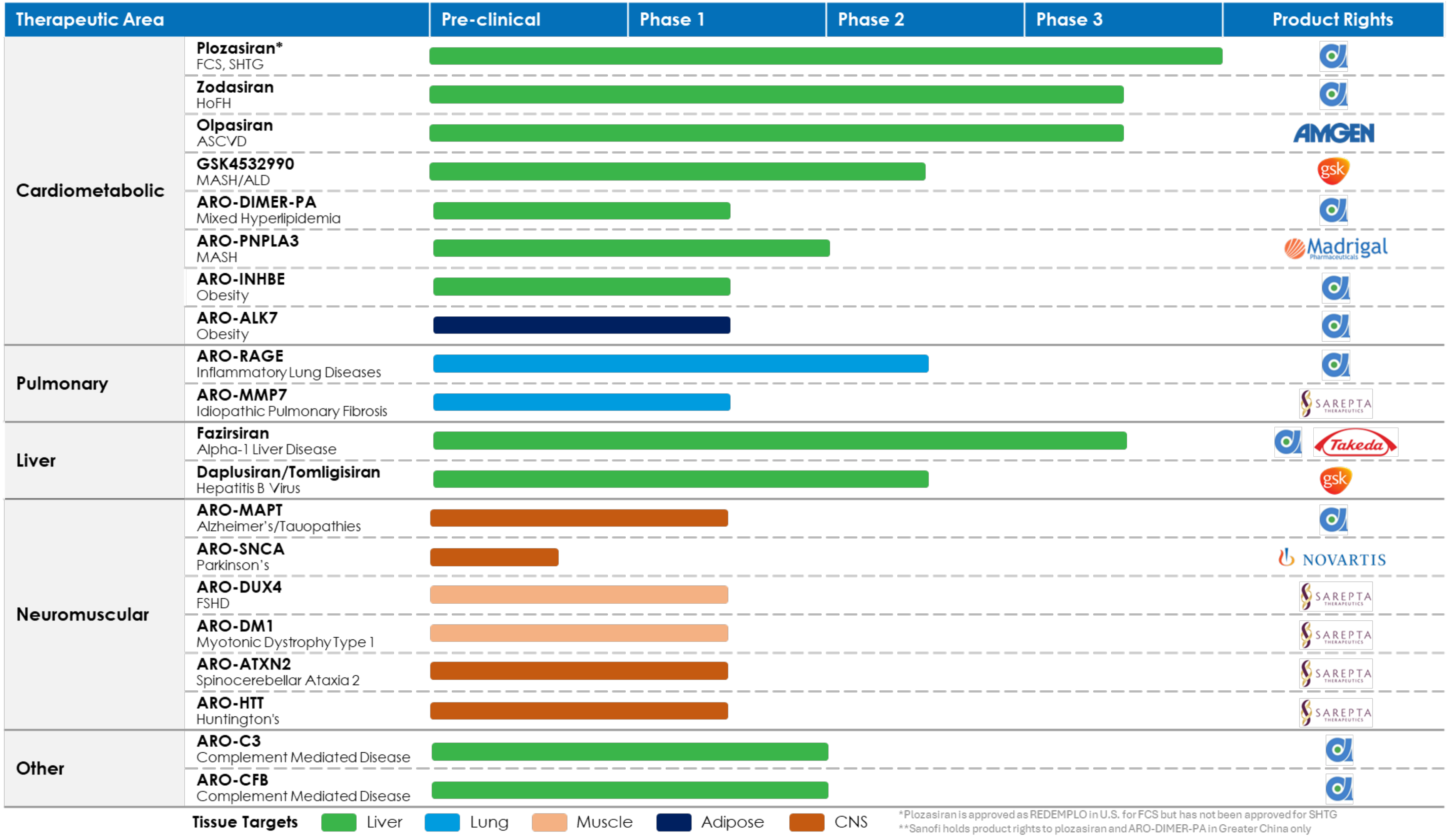
# TRiM™ Platform Enables Delivery to Seven Cell Types

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

**Arrowhead is Fulfilling the Promise of Bringing RNAi Throughout the Body**

# Robust Pipeline with Near-term Commercial Opportunities and Long-term Growth Opportunities




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

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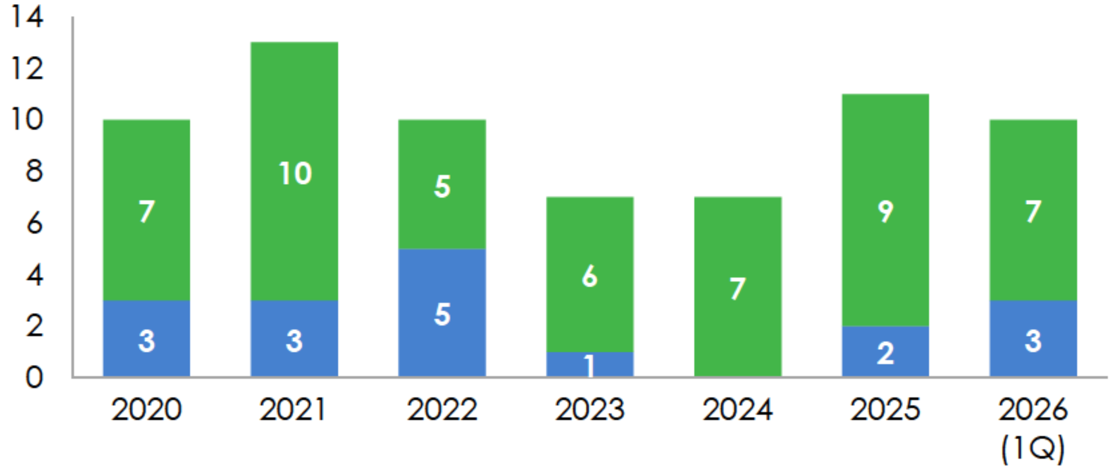
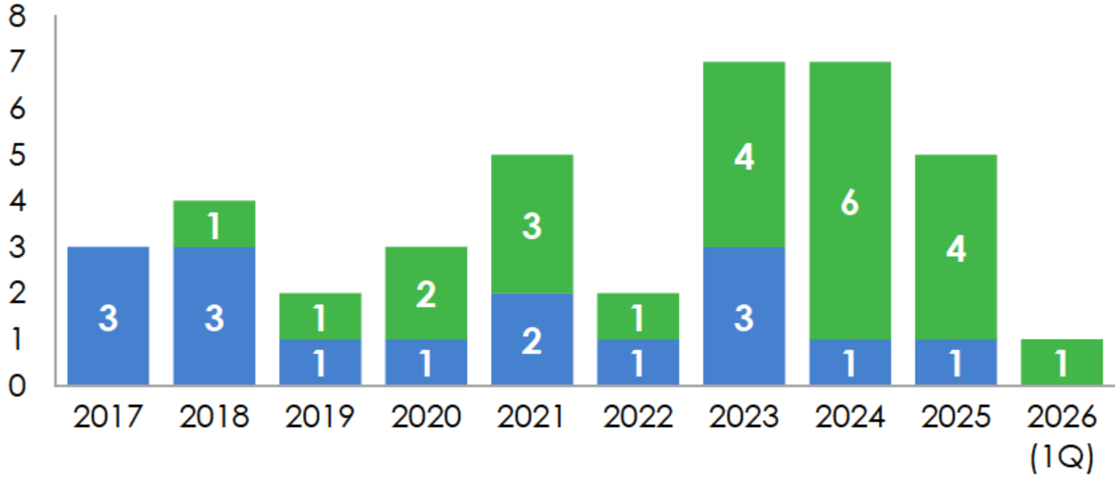
# Discovery Capacity Supports Consistent Pipeline Growth
# Concept to CTA Goal of **12 Months**

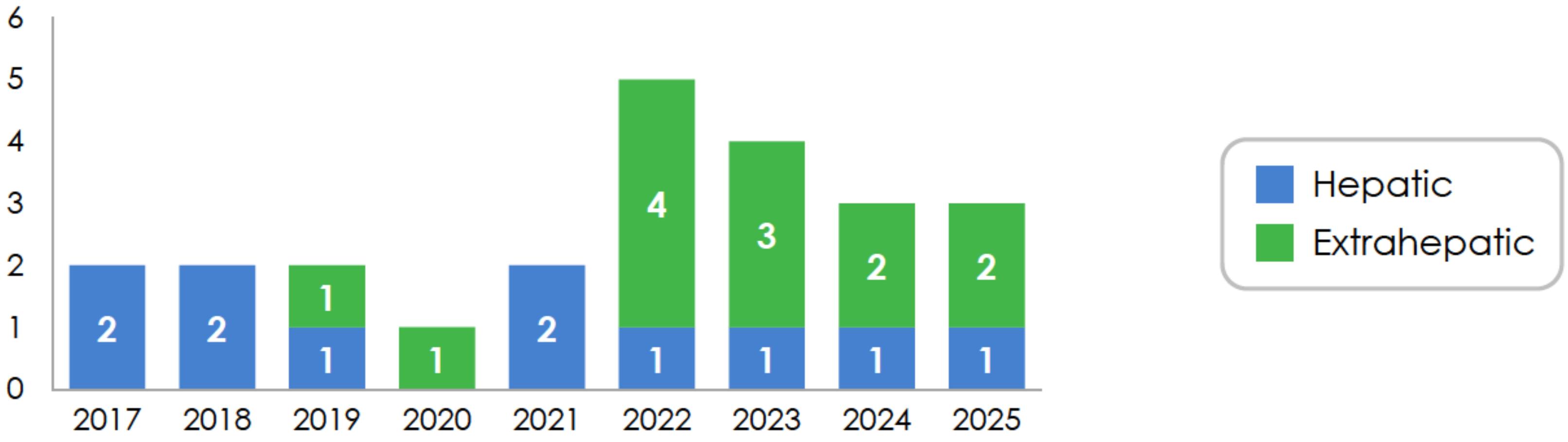
## New Discovery Programs Initiated




## Candidate Nominations




## CTA or IND Filings



# Translational Genetics is Leveraging Large-Scale Data and AI for Target Identification and Prioritization

## Data Identification and Curation

>45 genetics and biology dataset/database

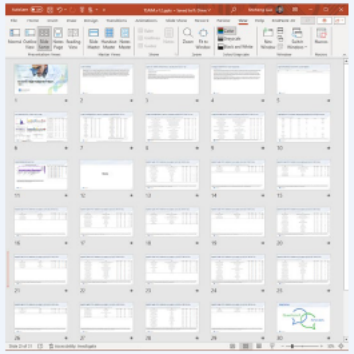
## Statistic Modelling

- GWAS
- PheWAS
- Colocalization
- MendeRand
- Phe-MR
- DiffEG
- Pathway
- Enrich
- Alt Splicing
- Meta Analysis

>9 statistical tests

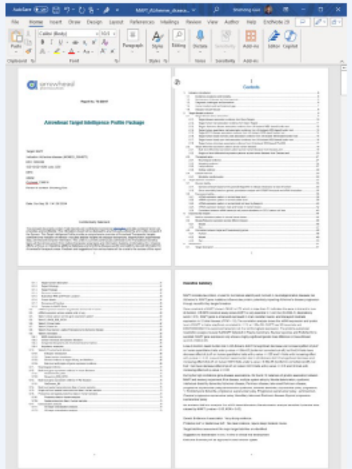
## Arrowhead Target Knowledge Database

## Automatic Target Assessment Report System



- High Efficiency
- Multi-Omics data
- Rigorous Data Quality
- High Level of Automation
- Comprehensive Disease Coverage
- User-Friendly Presentation Format

## Target Intelligence Profile Generation System



- Standard Format
- Multi-Omics data
- Flexible Expansion
- Deep interpretation
- Rigorous Data Quality
- High Level of Automation
- Comprehensive Disease Coverage
- User-Friendly Presentation Format

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# Plozasiran

**Jennifer Hellawell, MD**
Vice President, Clinical Development

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# Multiple Segments of Patients with Elevated TGs Being Studied

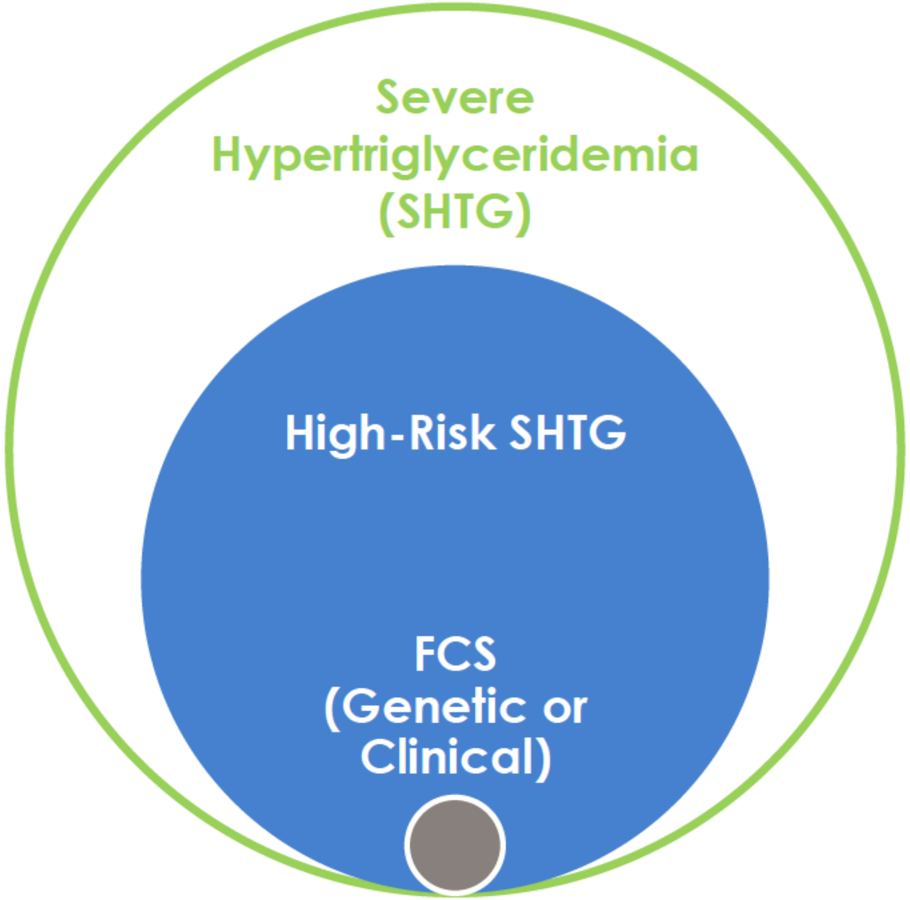


Figure Not to Scale

## SHTG

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

## High-Risk SHTG

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

## FCS (Genetic or Clinical)

- Persistently Elevated TGs ≥ 880 mg/dL
- Prevalent Prior History of AP
- Potentially 6500 to over 10,000 people
- Extremely High Risk of AP

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

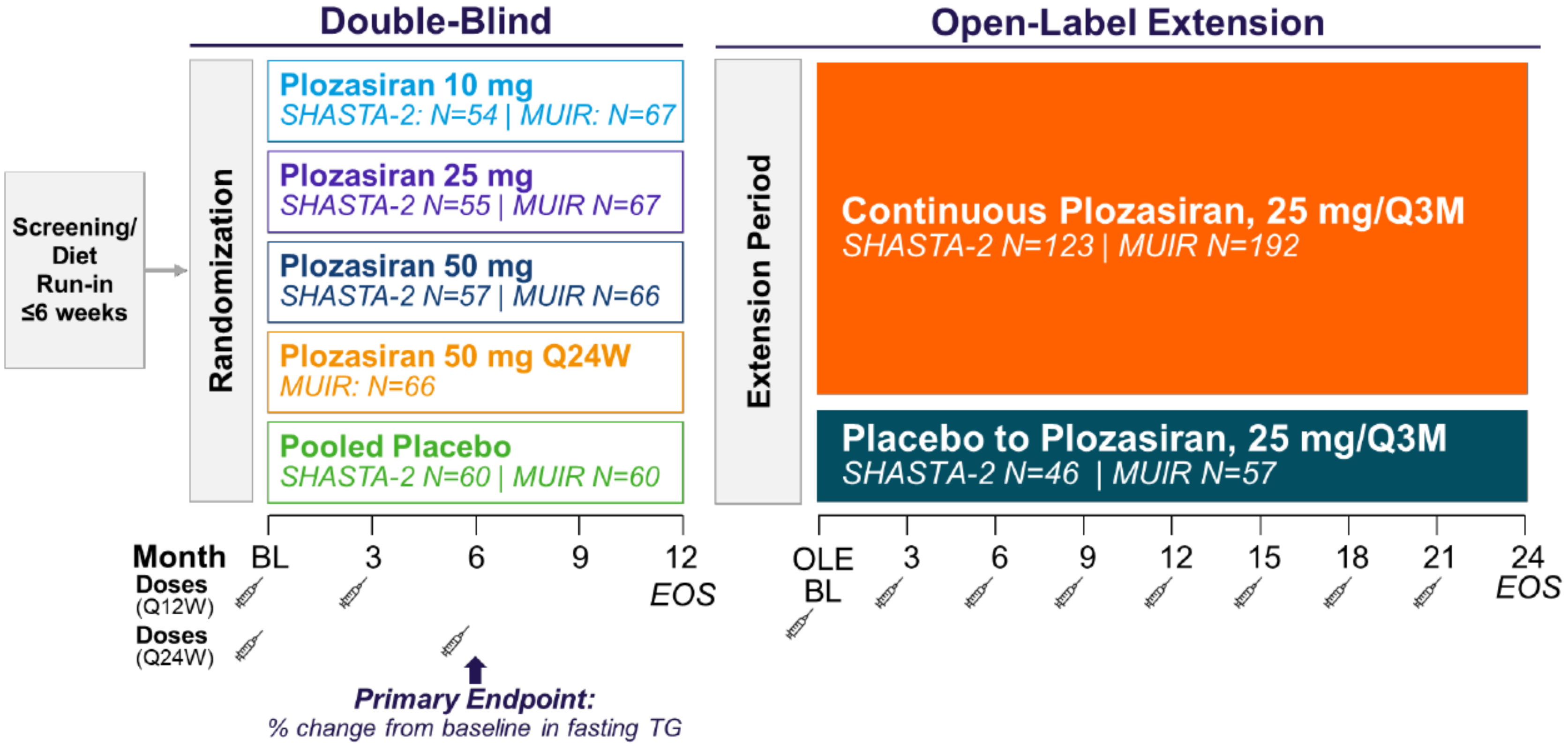
# Overview of Plozasiran Development Program

## SUMMIT PROGRAM: PLOZASIRAN *(APOC3-targeted siRNA)*

| Patient Population | Study Name | Study Objective | Status | Phase |
|---|---|---|---|---|
| Familial Chylomicronemia Syndrome (FCS) | PALISADE | In adults with **FCS and TG ≥880 mg/dL (≥10 mmol/L) (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 (≥5.65 mmol/L) (N=226)**, the primary endpoint was to evaluate change in TG levels at Month 6* | Study Completed | Phase 2 |
| | SHASTA-3 | In adults with **TG ≥500 mg/dL (≥5.65 mmol/L) (N=405)**, the primary endpoint is to evaluate the change in TG levels at Month 12*‡ | Near Completion | Phase 3 |
| | SHASTA-4 | In adults with **TG ≥500 mg/dL (≥5.65 mmol/L) (N=300)**, the primary endpoint is to evaluate change in TG levels at Month 12* | Near Completion | Phase 3 |
| | SHASTA-5 | In adults with a history of **fasting TG ≥880 mg/dL (≥10 mmol/L) and at least 1 acute pancreatitis event within the last 5 years (N=288)**, the primary endpoint will be to evaluate the time to first occurrence of positively adjudicated acute pancreatitis event* | Currently Enrolling | Phase 3 |
| Mixed Hyperlipidemia | MUIR | In adults with **TG 150-499 mg/dL (1.69-5.65 mmol/L) and non-HDL-C ≥100 mg/dL (≥2.59 mmol/L) or LDL-C ≥70 mg/dL (≥1.8 mmol/L) (N=353)**, the primary endpoint was to evaluate change in TG levels at Month 6* | Study Completed | Phase 2 |
| | MUIR-3 | In adults with **TG 150-499 mg/dL (1.69-5.65 mmol/L) (N=1328)**, the primary endpoint is to evaluate change in TG levels at Month 12 | Near Completion | Phase 3 |

*Open-label extension period or study is available for patients who participate in the clinical trial program. †Primary analysis completed, open-label extension ongoing. ‡A subset of patients enrolled in SHASTA-3 will undergo serial MRI-PDFF in a substudy to assess change in LFC. FCS, familial chylomicronemia syndrome; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LFC, liver fat content; MRI-PDFF, magnetic resonance imaging proton density fat fraction; TEAE, treatment-emergent adverse event; TG, triglyceride.

# SHASTA-2 and MUIR Open-Label Extension (OLE) Study Design




| OLE Primary Endpoint | OLE Secondary Endpoints | OLE Exploratory Endpoints | OLE Exploratory Safety Endpoints |
|---|---|---|---|
| Incidence of TEAEs through end-of-study | Change in TGs, ApoC3, non-HDL-C, HDL-C, total ApoB, and LDL-C | Change in total chol, VLDL-C, ApoB-48, ApoB-100, adjudicated AP events | Change in fasting glucose and HbA1c |

Ballantyne CM, et al. *Am J Prev Cardiol*. 2026 Mar 24:27:101523. doi: 10.1016/j.ajpc.2026.101523

# SHASTA-2 and MUIR OLE Baseline Characteristics

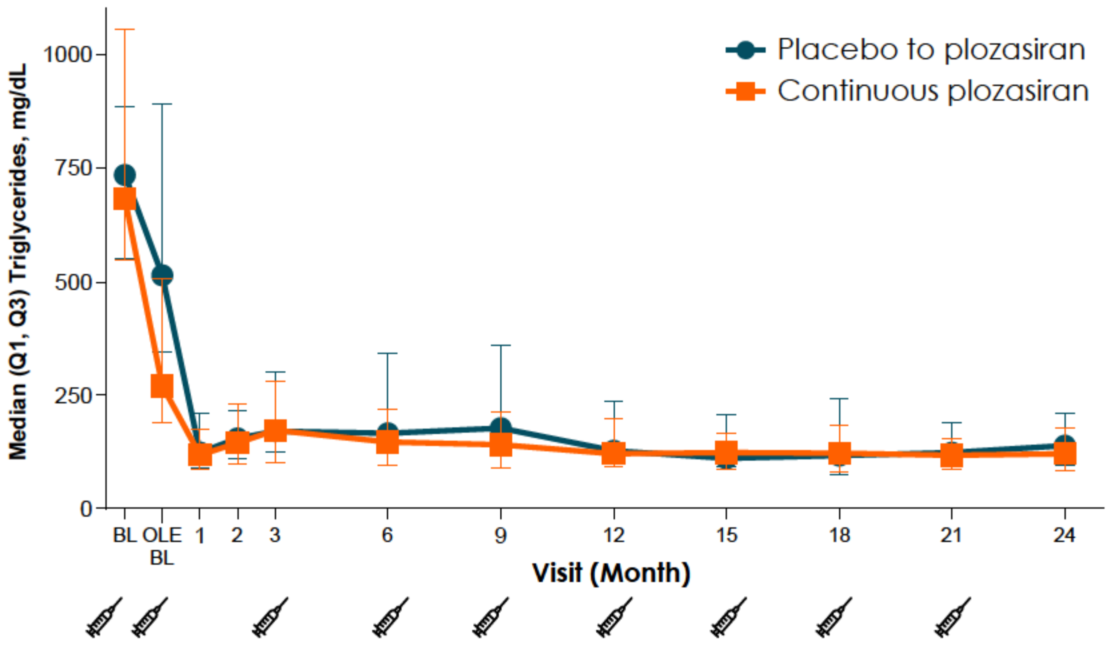
| | SHASTA-2 | | MUIR | |
|---|---|---|---|---|
| | Placebo to Plozasiran (N=46) | Continuous Plozasiran (N=123) | Placebo to Plozasiran (N=57) | Continuous Plozasiran (N=192) |
| **Age (years), mean (SD)** | 56.4 (10.8) | 55.8 (11.2) | 60.5 (10.1) | 63.3 (11.0) |
| **Male, n (%)** | 33 (71.7) | 97 (78.9) | 32 (56.1) | 108 (56.3) |
| **Race, White, n (%)** | 42 (91.3) | 111 (90.2) | 51 (89.5) | 178 (92.7) |
| **BMI (kg/m$^2$), mean (SD)** | 30.3 (3.7) | 31.7 (4.6) | 30.7 (5.5) | 32.1 (6.4) |
| **TGs, mg/dL, median (Q1, Q3)** | 735.9 (551.0, 885.3) | 684.7 (549.8, 1057.0) | 231.0 (196.9, 279.9) | 228.3 (184.2, 309.9) |
| **ApoC-III, mg/dL, mean (SD)** | 32.6 (16.6) | 33.9 (16.4) | 15.0 (4.8) | 15.3 (5.50) |
| **HDL-C, mg/dL, mean (SD)** | 28.6 (11.5) | 29.4 (10.5) | 41.4 (10.9) | 43.4 (11.9) |
| **Non-HDL-C, mg/dL, mean (SD)** | 187.0 (81.5) | 211.1 (91.9) | 147.0 (40.9) | 152.1 (47.3) |
| **VLDL-C (calc), mg/dL, mean (SD)** | 122.4 (85.0) | 138.9 (100.3) | 47.9 (16.7) | 49.7 (21.5) |
| **LDL-C (Martin-Hopkins), mg/dL, median (Q1, Q3)** | 79.0 (48.0, 114.0) | 93.5 (60.0, 128.0) | 103.0 (84.0, 125.0) | 107.0 (84.5, 142.5) |
| **ApoB, mg/dL, mean (SD)** | 95.4 (29.6) | 107.1 (47.7) | 102.0 (27.6) | 102.1 (26.0) |
| **Receiving statins, n (%)** | 33 (71.7) | 84 (68.3) | 55 (96.5) | 177 (92.2) |
| **Type 2 diabetes, n (%)** | 29 (63.0) | 63 (51.2) | 26 (45.6) | 107 (55.7) |
| **Receiving GLP-1R agonists, n (%)** | 5 (10.9) | 23 (18.7) | 6 (10.5) | 18 (9.4) |
| **Medical History of Pancreatitis, n (%)** | 11 (23.9) | 24 (19.5) | | |

Ballantyne CM, et al. *Am J Prev Cardiol*. 2026 Mar 24:27:101523. doi: 10.1016/j.ajpc.2026.101523

# Median Absolute Values in TG in SHASTA-2 and MUIR OLE

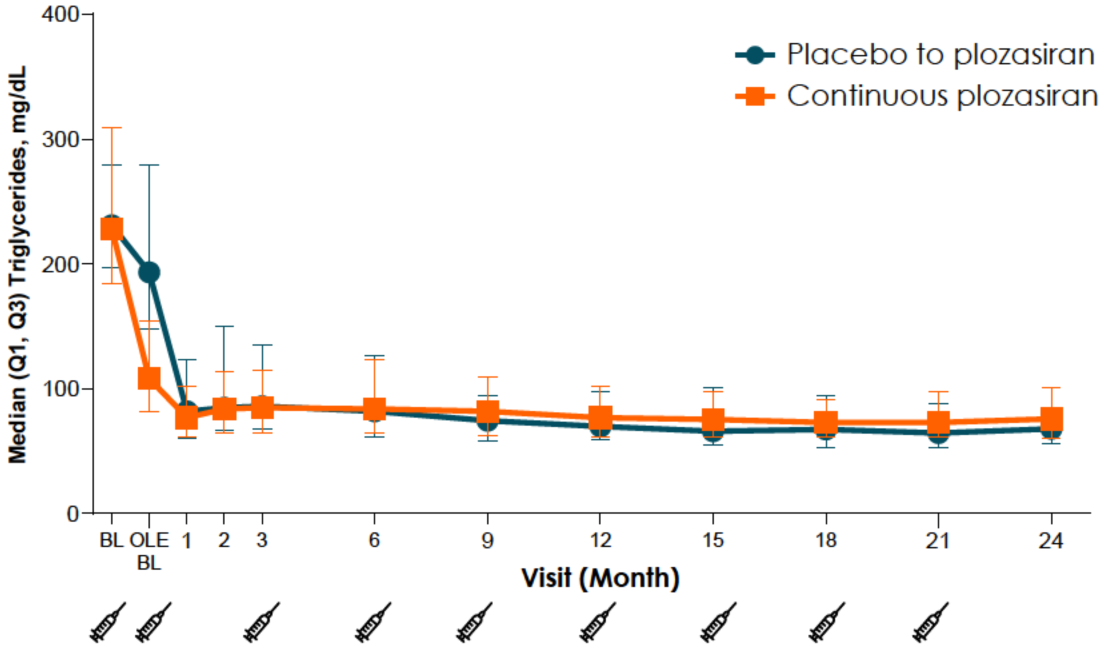
## SHASTA-2

**96% of patients achieved TG<500 mg/dL and 63% of patients achieved TG<150 mg/dL***




## MUIR

**93% of patients achieved TG <150 mg/dL***




**In SHASTA-2, Median TG Continued to Fall by -83 % (-89.5, -73.5)***
**In MUIR, Median Reductions in TG of -67 % (-73.8, -56.2)****

All graphs show median (Q1,Q3) levels or mean (± SE) % change from baseline (inset). Syringe represents dosing schedule. *Relative to Baseline, at Month 24 OLE.
Ballantyne CM, et al. *Am J Prev Cardiol*. 2026 Mar 24:27:101523. doi: 10.1016/j.ajpc.2026.101523

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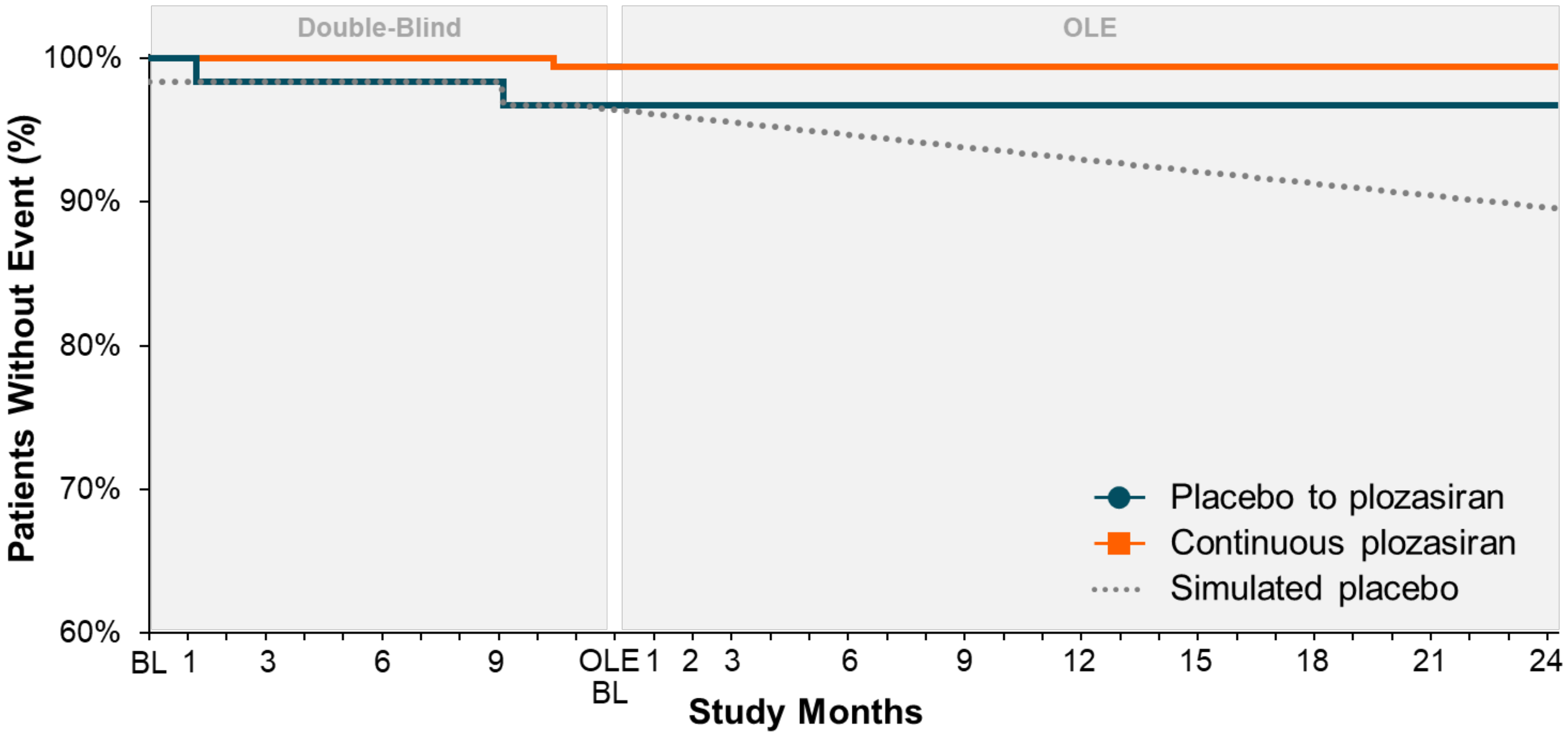
# Kaplan Meier Plot of Time to First Adjudicated AP Event in the SHASTA-2 OLE

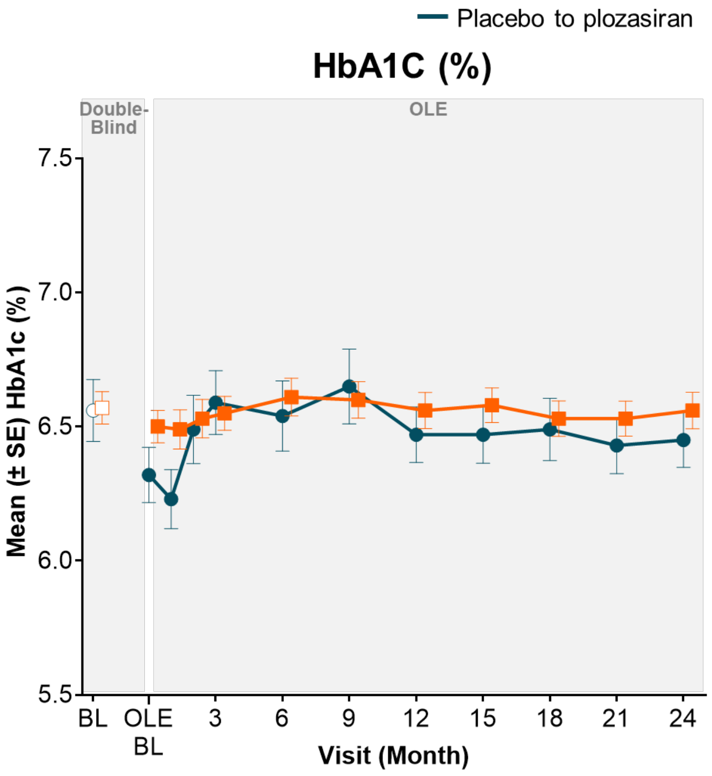
**Longer duration on plozasiran was associated with lower risk of AP events over time**

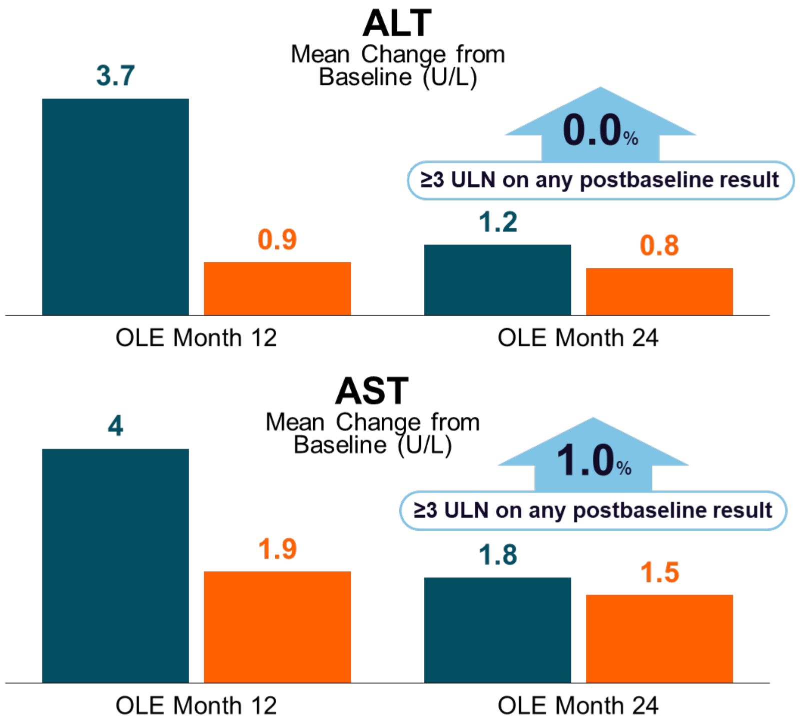



**No Positively Adjudicated AP Events in the OLE Out to 24 Months**

Ballantyne CM, et al. *Am J Prev Cardiol*. 2026 Mar 24:27:101523. doi: 10.1016/j.ajpc.2026.101523

# SHASTA-2 & MUIR OLE Safety Findings




| SHASTA-2 + MUIR, n (%) | Plozasiran Pooled (N=418) |
|---|---|
| **All TEAEs** | 310 (74.2) |
| Type 2 diabetes mellitus | 40 (9.6) |
| COVID-19 | 34 (8.1) |
| Diabetes mellitus | 28 (6.7) |
| URTI | 24 (5.7) |
| Back pain | 22 (5.3) |
| **Treatment-related TEAEs** | 72 (17.2) |
| **Serious TEAEs** | 60 (14.4) |
| **TEAEs leading to study drug discontinuation** | 26 (6.2)* |
| **Deaths** | 2 (0.5)† |

Data reported as n (%) TEAEs occurring >5%. *Drug discontinuations in the OLE due to: diabetes mellitus (9), type 2 diabetes mellitus (5), glycosylated hemoglobin increased (4), sudden cardiac death (1), bladder neoplasm (1), cholangiocarcinoma (1), colorectal cancer metastatic (1), small intestine adenocarcinoma (1), drug abuse (1), renal impairment (1), rash (1).
†OLE deaths: sudden cardiac death, cholangiocarcinoma; were not deemed to be related to study drug.

**OLE Safety Consistent With Index Studies, No Clinically Meaningful Changes in HbA1c or Liver Function**

Ballantyne CM, et al. *Am J Prev Cardiol*. 2026 Mar 24:27:101523. doi: 10.1016/j.ajpc.2026.101523

# SHASTA-2 & MUIR OLE Takeaways

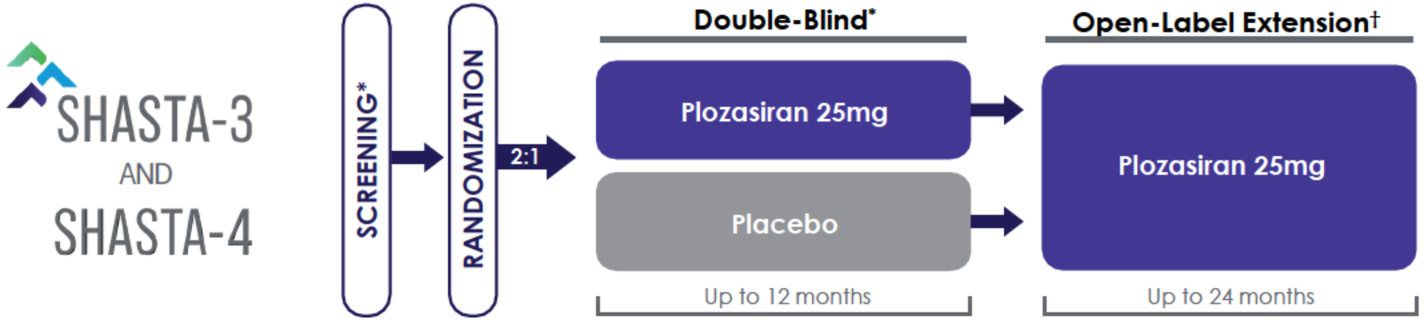
- Long-term treatment with 25 mg Q3M of plozasiran resulted in sustained and clinically meaningful reductions in TG across a broad spectrum of HTG through 24 months
- Majority of patients achieved TG levels below thresholds for AP risk or below normal thresholds
- There was a reduction in AP events, with no APs occurring in both studies in the OLE
- Plozasiran demonstrated a consistent long-term safety and tolerability profile with stable glycemic parameters, no clinically meaningful liver/renal function changes and no new safety signals

# SHASTA-3 and -4 Study Design

Two Double-Blind, Placebo-Controlled Phase 3 Studies to Evaluate the Efficacy and Safety of **Plozasiran (ARO-APOC3)** in Adults With **Severe Hypertriglyceridemia (SHTG)**

**Key Eligibility Criteria**

- 18 years or older
- Diagnosis of SHTG and prior medical history of fasting TG levels of ≥500 mg/dL (≥5.65 mmol/L)
- Mean fasting TG level ≥500 mg/dL (≥5.65 mmol/L) collected at 2 separate and consecutive visits at least 7 days apart and no more than 17 days apart during the screening period
- Screening HbA1c ≤9.0%
- Fasting LDL-C ≤130 mg/dL (≤3.37 mmol/L) at screening
- Agree to diet counseling and maintaining a stable low-fat diet
- Receiving standard of care (SOC) lipid-lowering medications per local guidelines, unless intolerant




Each participant will receive an SC injection of plozasiran or placebo every 3 months, for a total of 4 doses.

**Near Completion**

**ClinicalTrials.gov**

| SHASTA-3 | SHASTA-4 |
|---|---|
| NCT06347003 | NCT06347016 |

**Primary Endpoint**

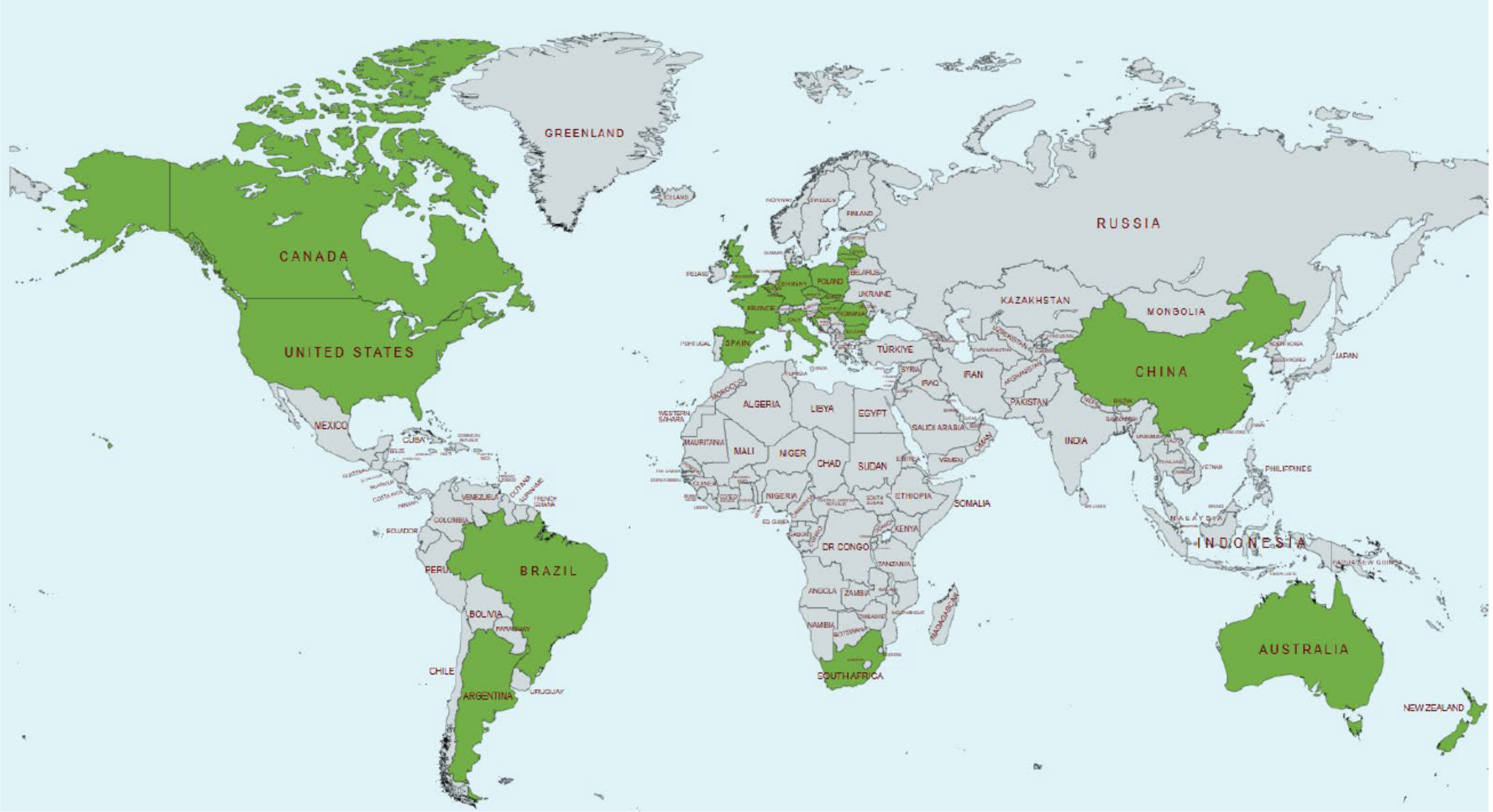
Percent change in fasting serum TG levels from baseline to Month 12

**Key Secondary & Safety Endpoints**

- Percent change in fasting TG levels from baseline to Month 10
- Proportion of patients who achieve fasting TG levels of <500 mg/dL (<5.65 mmol/L) at Month 12
- Proportion of patients who achieve fasting TG levels of <150 mg/dL (<1.69 mmol/L) at Month 12
- Percent change in remnant cholesterol(VLDL-C) from baseline to Month 12
- Percent change in non-HDL-C from baseline to Month 12
- Adjudicated acute pancreatitis event rate from Day 1 to Month 12
- Frequency and severity of AEs and SAEs over time through Month 12

Lepor N, et al. *J Clin Lipidol*. 2026:20(6):e111. doi.org/10.1016/j.jacl.2026.05.170.

# SHASTA-3 and -4 Global Enrollment




**23 Unique Countries**
SHASTA-3: 17 countries
SHASTA-4: 16 countries

**351 Total Sites**
SHASTA-3: 200 sites
SHASTA-4: 151 sites

**757 Total Randomizations**
SHASTA-3: 446
SHASTA-4: 311

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# SHASTA-3 and -4 Baseline Characteristics

| | SHASTA-3 (N=446) | SHASTA-4 (N=311) | SHASTA-3 + SHASTA-4 (N=757) |
|---|---|---|---|
| **Age (Years), mean (SD)** | 51.9 (11.7) | 53.2 (11.6) | 52.4 (11.7) |
| **Sex at birth, male n (%)** | 369 (82.7) | 229 (73.6) | 598 (79.0) |
| **Race, n (%)** | | | |
| White | 331 (74.2) | 271 (87.1) | 602 (79.5) |
| Asian | 99 (22.2) | 17 (5.5) | 116 (15.3) |
| Black or African American | 3 (0.7) | 13 (4.2) | 16 (2.1) |
| Other | 17 (3.8) | 13 (4.2) | 30 (3.9) |
| **Ethnicity, n (%)** | | | |
| Hispanic or Latino | 91 (20.4) | 60 (19.3) | 151 (19.9) |
| Not Hispanic or Latino | 354 (79.4) | 249 (80.1) | 603 (79.7) |
| **Region, n (%)** | | | |
| North America | 128 (28.7) | 120 (38.6) | 248 (32.8) |
| Europe | 179 (40.1) | 142 (45.7) | 321 (42.4) |
| Asia | 85 (19.1) | 0 (0.0) | 85 (11.2) |
| Other | 54 (12.1) | 49 (15.8) | 103 (13.6) |
| **BMI (kg/m²), mean (SD)** | 30.5 (5.2) | 31.5 (5.1) | 30.9 (5.1) |
| **Lipid lowering therapy, n (%)** | 430 (96.4) | 297 (95.5) | 727 (96.0) |
| Statin | 298 (66.8) | 226 (72.7) | 524 (69.2) |
| Fibrate | 278 (62.3) | 180 (57.9) | 458 (60.5) |
| Omega-3 fatty acid | 65 (14.6) | 42 (13.5) | 107 (14.1) |
| Ezetimibe | 109 (24.4) | 64 (20.6) | 173 (22.9) |
| PCSK9 inhibitor | 20 (4.5) | 9 (2.9) | 29 (3.8) |
| Niacin | 8 (1.8) | 3 (1.0) | 11 (1.5) |
| Other lipid lowering therapies | 61 (13.7) | 54 (17.4) | 115 (15.2) |
| ≥2 therapies | 281 (63.0) | 198 (63.7) | 479 (63.3) |

| | SHASTA-3 (N=446) | SHASTA-4 (N=311) | SHASTA-3 + SHASTA-4 (N=757) |
|---|---|---|---|
| **TG at screening (mg/dL)*** | | | |
| Mean (SD) | 945.3 (535.4) | 995.5 (672.4) | 965.9 (595.6) |
| Median (Q1, Q3) | 758.5 (597.5, 1095.0) | 730.0 (588.5, 1119.0) | 741.5 (594.5, 1104.5) |
| **TG at baseline (mg/dL)*** | | | |
| Mean (SD) | 809.0 (491.3) | 941.2 (667.0) | 863.3 (573.3) |
| Median (Q1, Q3) | 657.2 (516.1, 950.3) | 725.5 (544.6, 1094.9) | 677.8 (530.9, 1012.5) |
| **TG ≥880 mg/dL, n (%)** | 164 (36.8) | 119 (38.3) | 283 (37.4) |
| **ApoC-III (mg/dL), mean (SD)†** | 32.2 (15.3) | 36.4 (17.2) | 33.9 (16.2) |
| **non-HDL-C (mg/dL), mean (SD)†** | 176.3 (72.4) | 194.2 (86.3) | 183.7 (78.8) |
| **HDL-C (mg/dL), mean (SD)†** | 28.8 (10.8) | 28.0 (10.9) | 28.5 (10.9) |
| **LDL-C (UC) (mg/dL), mean (SD)†** | 66.5 (32.8) | 62.5 (31.8) | 64.9 (32.4) |
| **ApoB (mg/dL), mean (SD)†** | 97.2 (27.3) | 99.1 (26.6) | 98.0 (27.0) |
| **HbA1c (%), mean (SD)‡** | 6.4 (1.1) | 6.5 (1.1) | 6.5 (1.1) |
| **Medical History** | | | |
| Diabetes mellitus | 273 (61.2) | 195 (62.7) | 468 (61.8) |
| Hypertension | 277 (62.1) | 219 (70.4) | 496 (65.5) |
| Coronary artery disease | 29 (6.5) | 32 (10.3) | 61 (8.1) |
| Pancreatitis | 90 (20.2) | 65 (20.9) | 155 (20.5) |

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Lepor N, et al. *J Clin Lipidol*. 2026:20(6):e111. doi.org/10.1016/j.jacl.2026.05.170.

# Plozasiran Timeline Considerations for sHTG

- Topline data release Q3 2026
- SHASTA-3/4 medical congress presentation and publication 2H 2026
- sNDA filing planned by end of 2026

Cardiometabolic R&D Webinar
June 2026

# Zodasiran

**Jennifer Hellawell, MD**
Vice President, Clinical Development

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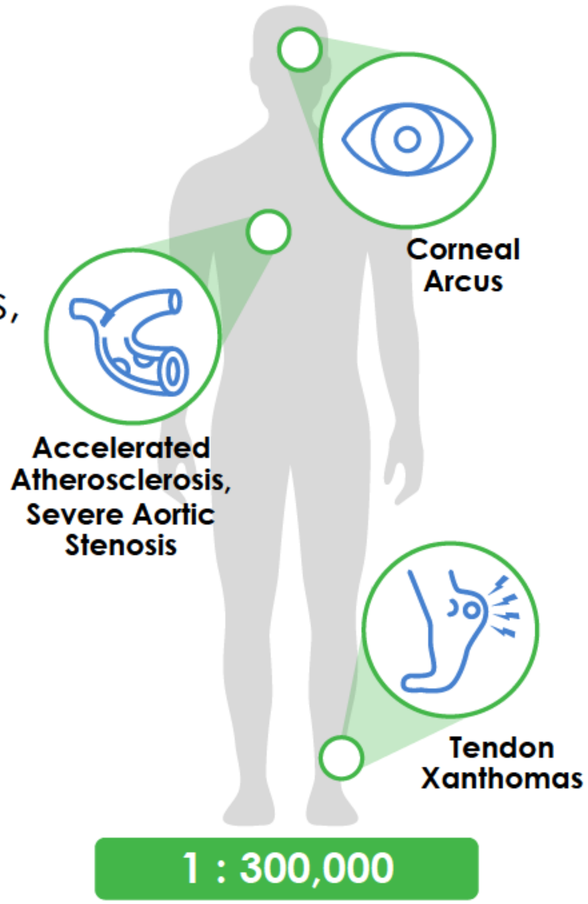
# HoFH is a Rare But Grievous Disease with High Unmet Need

## HoFH is a Rare But Grievous Disease

- HoFH patients have untreated LDL-C 400–1000 mg/dL, ~ four to 10 times normal
- Untreated, people with HoFH develop heart disease as teenagers, sometimes in early childhood
- Estimated HoFH prevalence ~ 1:300,000 worldwide
- HoFH patients often have suboptimal response to conventional lipid lowering therapies due to dysfunctional LDL receptor pathways

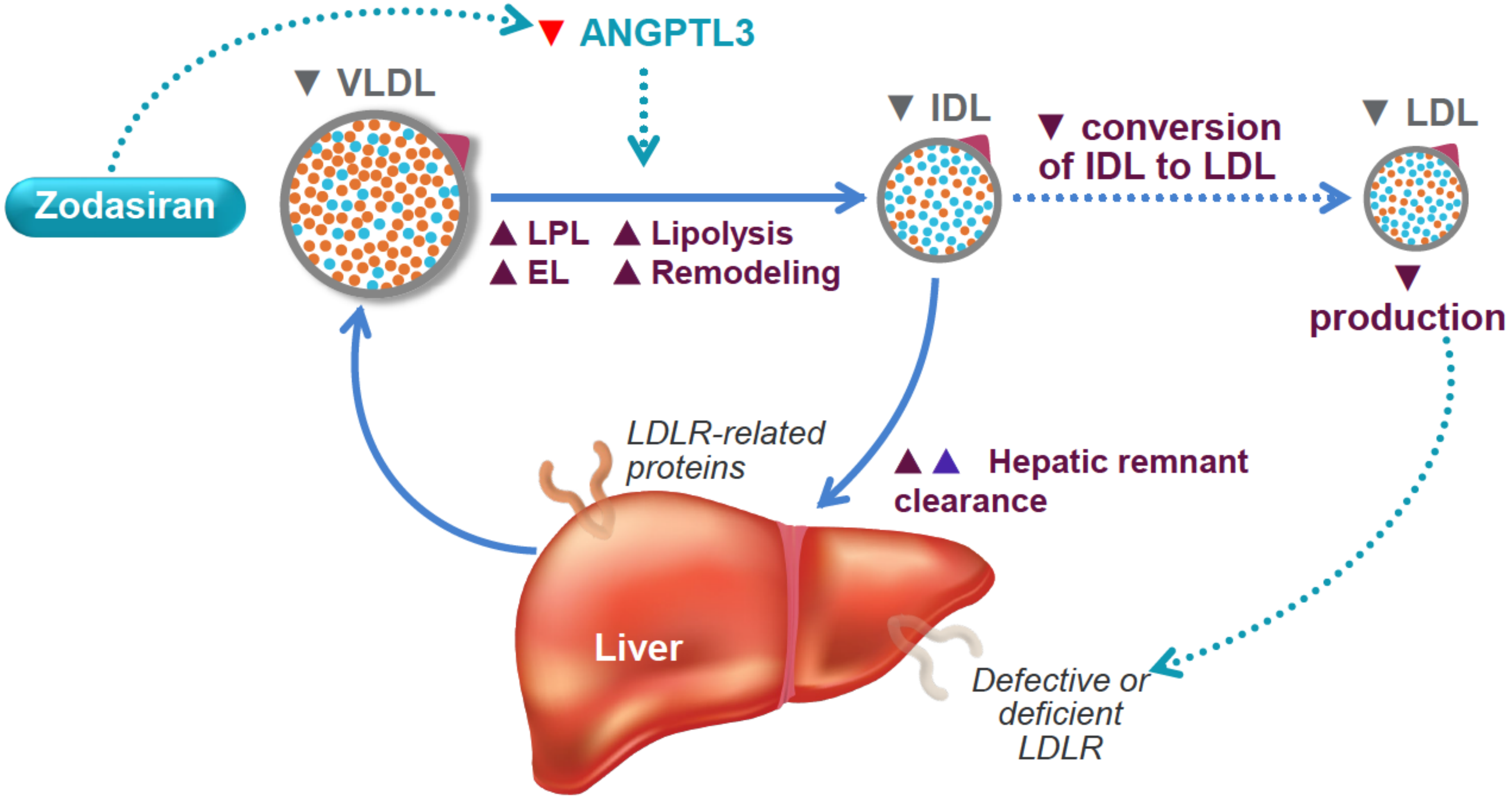



## HoFH Patients at Risk Despite Available Therapies

- In CASCADE FH registry, 78% of adults and 44% of children with HoFH had documented ASCVD
- Despite treatment with 3-6 LLTs in specialty lipid clinics, just 25% and 32% of adults and children reached LDL-C goals
- 40% of HoFH patients in the CASCADE FH registry are on no lipid lowering therapies

https://familyheart.org
Cuchel M, et al. *J Am Heart Assoc*. 2023 May 2;12(9):e029175. doi: 10.1161/JAHA.122.029175. LLT: lipid lowering therapy

# ANGPTL3 is a Key Regulator of Lipoprotein Metabolism and Clearance[1-6]




- *ANGPTL3* is a hepatocyte expressed regulator of lipid and lipoprotein metabolism with multiple potential modes of action, including inhibition of lipoprotein lipase (LPL) and endothelial lipase (EL)[1,2]
- *ANGPTL3* loss-of-function variants lead to enhanced LPL and EL activity, resulting in:
  - ▼ LDL-C, TG, VLDL-C/ remnant-C, and HDL-C[3-5]
  - ▼ Risk of ASCVD[3,4,6]
- No known adverse phenotype is associated with genetic deficiency in *ANGPTL3*[3,4]
- Mechanism is independent of LDL receptor and therefore promising target in HoFH

Figure adapted from: Watts G, et al. *Eur Heart J*. 2024;45:2435-2438.; 1. Adam, et al. *J Lipid Res*. 2020;61(9): 1271-86. 2. Rosenson. *J Lipid Res*. 2021:62:100060. 3. Dewey, et al. *N Engl J Med*. 2017;377 (3):211-21. 4. Minicocci, et al. *J Lipid Res*. 2013;54(12): 3481-90. 5. Musunuru, et al. *N Engl J Med*. 2010; 363(23):2220-7. 6. Stitziel, et al. *J Am Coll Cardiol*. 2017; 69(16):2054-63. ▼=Reductions in; ANGPTL3, angiopoietin-like protein 3; ASCVD, atherosclerotic cardiovascular disease; EL, endothelial lipase; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; remnant-C, remnant cholesterol; VLDL, very low-density lipoprotein.

# Overview of Zodasiran Development Program

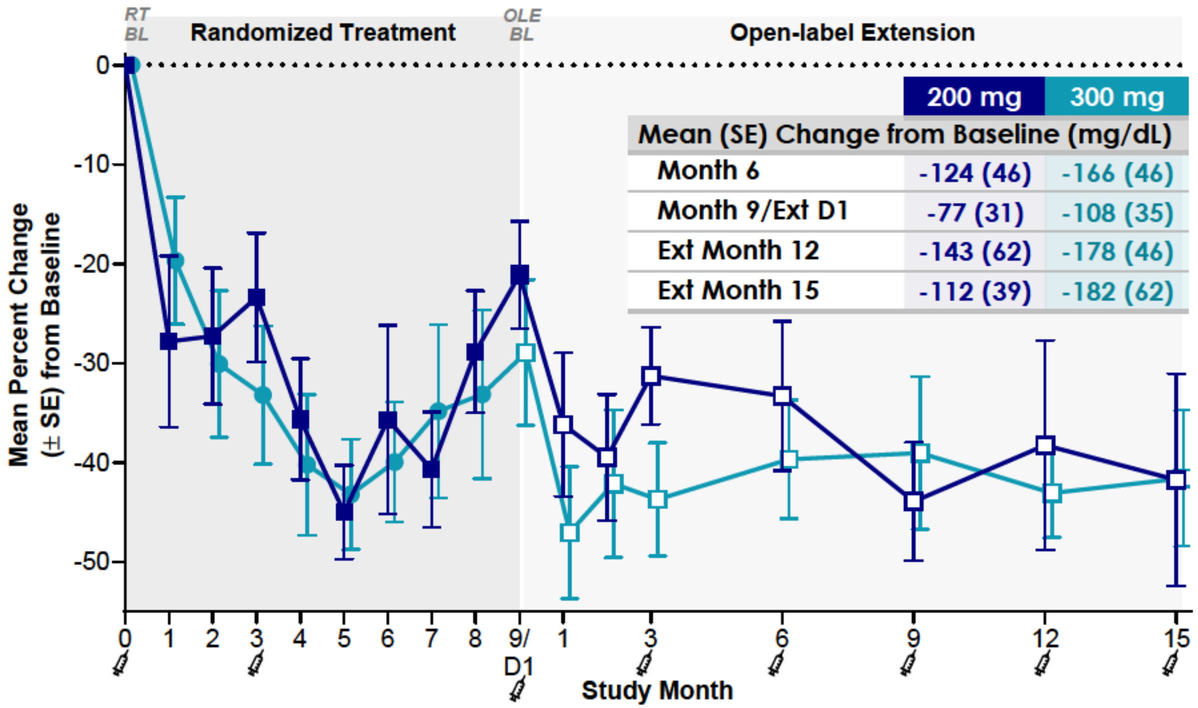
## VISTA PROGRAM: ZODASIRAN (ARO-ANG3)

| Patient Population | Study Name | Study Objective | Status | Phase |
|---|---|---|---|---|
| Mixed Hyperlipidemia | Arches-2 | In adults with **TG ≥1.69–5.65 mmol/L (≥150–499 mg/dL) and LDL-C ≥1.8 mmol/L (≥70 mg/dL) (N=204)**, the primary endpoint was to evaluate change in TG levels at Month 6* | Study Completed | Phase 2 |
| Familial Hypercholesterolemia | Gateway | In adults with **HoFH and LDL-C >2.59 mmol/L (>100 mg/dL) (N=18)**, the primary endpoint was to evaluate change in LDL-C levels at Month 6* | Study Completed | Phase 2 |
| | VSA003-3001 | In adults with **HoFH and LDL-C >2.59 mmol/L (>100 mg/dL) (N=45)**, the primary endpoint was to evaluate change in LDL-C levels at Month 6 | Study Completed | Phase 3 |
| | Yosemite | In adults and adolescents (ages 12 and up) with **HoFH and LDL-C ≥1.8 mmol/L (≥70 mg/dL)**, the primary endpoint will be to evaluate change from baseline in LDL-C levels at Month 12* | Currently Enrolling | Phase 3 |
| | Spruce | In adolescents (ages 12 to <18) with **HoFH and LDL-C ≥116 mg/dL (≥3 mmol/L) (N=12)**, the primary endpoint will be to evaluate change from baseline in LDL-C levels at Month 12* | Not Yet Enrolling | Phase 3 |

- Consistent reductions in ANGPTL3 (up to 96%), TG (up to 71%), LDL-C (up to 50%), non-HDL-C (up to 55%) and HDL-C (up to 47%) along with other lipid parameters in all patient populations studied (Phase 1-3)
- Reassuring safety profile with no changes in platelets and modest, non-progressive signal of worsening glycemia confined to mixed hyperlipidemia population with (pre)diabetes thus far

# GATEWAY Phase 2: Zodasiran Demonstrated Substantial and Durable Reductions in LDL-C and ApoB Throughout the Randomized Treatment Period and OLE

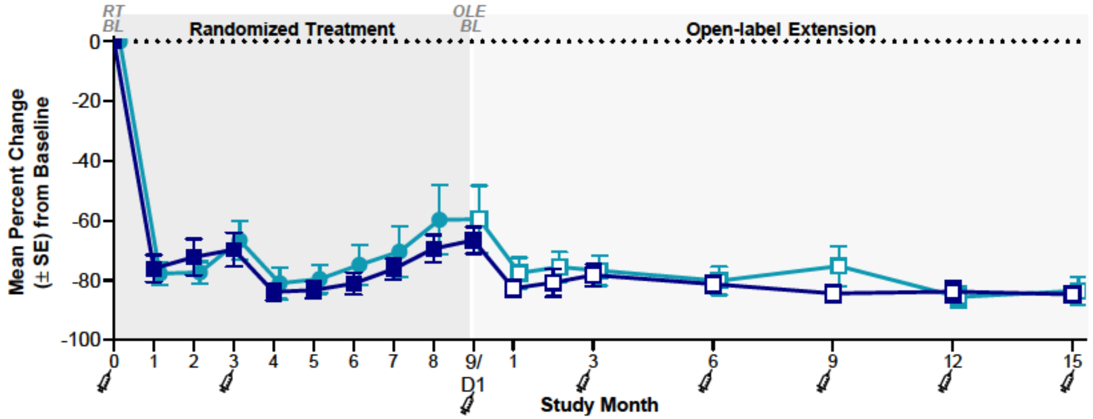
## LDL-C



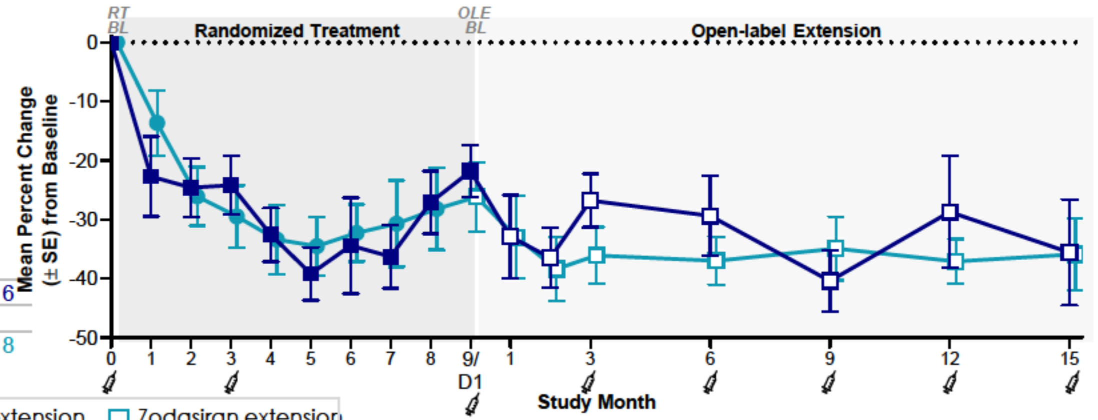

| | 200 mg | 300 mg |
|---|---|---|
| **Mean (SE) Change from Baseline (mg/dL)** | | |
| Month 6 | -124 (46) | -166 (46) |
| Month 9/Ext D1 | -77 (31) | -108 (35) |
| Ext Month 12 | -143 (62) | -178 (46) |
| Ext Month 15 | -112 (39) | -182 (62) |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 200 mg | 9 | 9 | 9 | 9 | 9 | 8 | 9 | 8 | 9 | 9 | | | | | | |
| 200 mg Ext | | | | | | | | | | 9 | 9 | 9 | 9 | 9 | 8 | 6 |
| 300 mg | 9 | 9 | 8 | 9 | 8 | 9 | 9 | 9 | 9 | 9 | | | | | | |
| 300 mg Ext | | | | | | | | | | 8 | 8 | 9 | 8 | 8 | 8 | 8 |

## ANGPTL3




## ApoB




■ Zodasiran 200 mg ● Zodasiran 300 mg □ Zodasiran extension 200 mg continuous □ Zodasiran extension 300 mg ⇨ 200 mg

Analysis of Covariance (ANCOVA) with repeated measures modeling was used for statistical modeling. ANGPTL3, angiopoietin-like protein 3; ApoB, apolipoprotein B; BL, baseline; D1, day 1 of OLE; Ext, extension; LDL-C, low-density lipoprotein cholesterol; LS, least squares; OLE, open-label extension; RT, randomized treatment period; SE, standard error of mean.

Raal FJ, et al. *Lancet Diabetes Endocrinol*. 2026 Feb;14(2):123-136. doi: 10.1016/S2213-8587(25)00290-6

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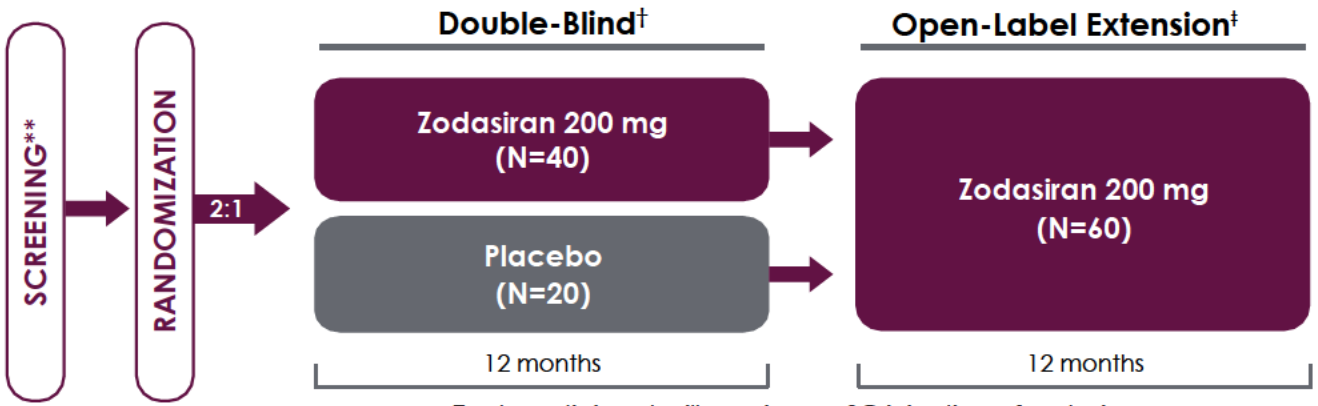
# YOSEMITE: Study Design

## Phase 3 Study to Evaluate the Efficacy and Safety of **Zodasiran (ARO-ANG3)** in Adolescents and Adults with **Homozygous Familial Hypercholesterolemia (HoFH)**

**Key Eligibility Criteria**

- ≥12 years of age with a genetic or clinical diagnosis of HoFH on standard of care, maximally tolerated lipid-lowering therapy
- Body weight ≥35 kg at screening
- Screening LDL-C ≥70 mg/dL (≥1.8 mmol/L); for adolescents 12 to <18 years of age, screening LDL-C ≥116 mg/dL (≥3 mmol/L)
- Screening HbA1c ≤9.5%
- Total bilirubin <2xULN, unless in previously confirmed cases of Gilbert's syndrome, ALT or AST<3xULN at screening
- Subjects with diabetes must have no events related to poor glycemic control* within 24 weeks of the screening period; if insulin dependent, subjects must be on a stable insulin regimen with no changes in basal insulin of more than ±10 units for at least 12 weeks from Day 1
- Subjects undergoing LDL apheresis must have initiated LDL apheresis ≥3 months before Screening Visit 2 and must have been on a stable schedule and settings for ≥8 weeks before Screening Visit 2

Yosemite




Each participant will receive an SC injection of zodasiran or placebo every 3 months, with a loading dose at Month 1

**Currently Enrolling**

**ClinicalTrials.gov**
NCT07037771

**Primary Endpoint**

- Percent change from baseline to Month 12 in fasting LDL-C levels (by the Martin-Hopkins formula)

**Key Secondary & Safety Endpoints**

- Change and percent change from baseline to Month 12 in fasting ApoB
- Change and percent change from baseline to Month 12 in fasting non-HDL-C
- Change from baseline to Month 12 in fasting LDL-C
- Area under the curve (AUC) from baseline to Month 12 for fasting LDL-C
- Change and percent change from baseline to Month 12 in fasting TGs
- Change and percent change from baseline to Month 12 in fasting ANGPTL3
- Change and percent change from baseline to Month 12 in fasting total cholesterol
- Change and percent change from baseline to Month 12 in fasting HDL-C
- Incidence and severity of treatment emergent adverse events (TEAEs)

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# YOSEMITE Global Enrollment


**21 Unique Countries Selected**

**47 Total Sites Activated**

**60 Randomizations Planned**

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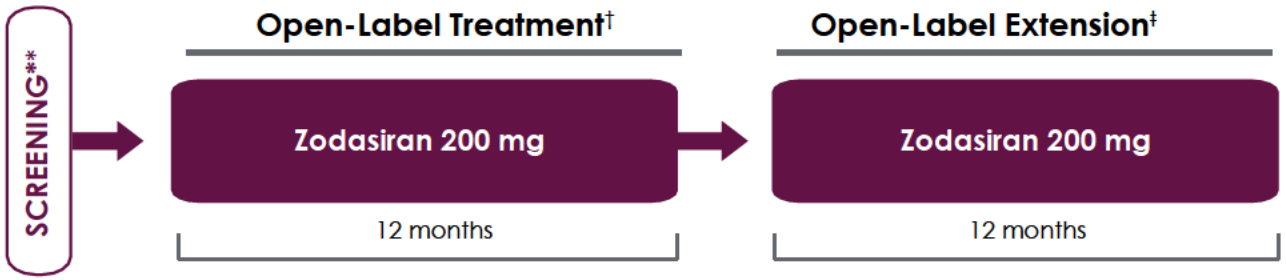
# SPRUCE: Study Design

## Phase 3 Single-Arm Open-Label Study to Evaluate the Efficacy and Safety of **Zodasiran (ARO-ANG3)** in Adolescents with **Homozygous Familial Hypercholesterolemia (HoFH)**

### Key Eligibility Criteria

- Adolescents 12 to <18 years of age who are nonpregnant, nonlactating, and do not plan to become pregnant during the study
- HoFH diagnosis based on a supportive genetic test (from a source-verifiable medical record or based on screening genotype) or clinical diagnosis
- Body weight ≥35 kg at screening
- Screening LDL-C ≥116 mg/dL (3 mmol/L)
- Screening HbA1c ≤9.5%
- Total bilirubin <2xULN, unless in previously confirmed cases of Gilbert's syndrome
- ALT or AST <3xULN
- Subjects with diabetes must have no events related to poor glycemic control* within 24 weeks of the screening period; if insulin dependent, subjects must be on a stable insulin regimen with no changes in basal insulin of more than ±10 units for at least 12 weeks from Day 1
- Subjects undergoing LDL apheresis must have initiated LDL apheresis ≥3 months before Screening Visit 2 and must have been on a stable schedule and settings for ≥8 weeks before Screening Visit 2
- Must be on available local standard of care, maximally tolerated lipid-lowering therapy

Spruce




Each participant will receive an SC injection of zodasiran every 3 months, with a loading dose at Month 1

**Not Yet Enrolling**

**ClinicalTrials.gov**
NCT07473843

### Primary Endpoint

- Percent change from baseline to Month 12 in fasting LDL-C (by the Martin-Hopkins formula)

### Key Secondary & Safety Endpoints

- Change and percent change from baseline to Month 12 in fasting ApoB, non-HDL-C, TG, ANGPTL3, total cholesterol, and HDL-C
- Change from baseline to Month 12 in fasting LDL-C
- Area under the curve (AUC) from baseline to Month 12 for fasting LDL-C
- Proportion of participants who meet European Union (EU) LDL-C apheresis eligibility criteria (per German Apheresis Working Group) at Month 12
- Proportion of participants who meet US apheresis eligibility criteria (per National Lipid Association) at Month 12
- Proportion of participants with fasting LDL-C <100 mg/dL (2.6 mmol/L) at Month 12
- Change and percent change from baseline in fasting LDL-C at each scheduled assessment
- Participant incidence and severity of TEAEs

# Zodasiran Next Steps

- Broader pediatric program in development with adolescent-focused study (SPRUCE) anticipated to randomize its first patient soon
- YOSEMITE full enrollment anticipated in Summer 2026
- Completion of 12 months double blind portion of study in Summer 2027
- Zodasiran NDA planned for 2H 2027

Cardiometabolic R&D Webinar
June 2026

# ARO-DIMER-PA

**James Hamilton MD, MBA**
Chief Medical Officer and Head of R&D

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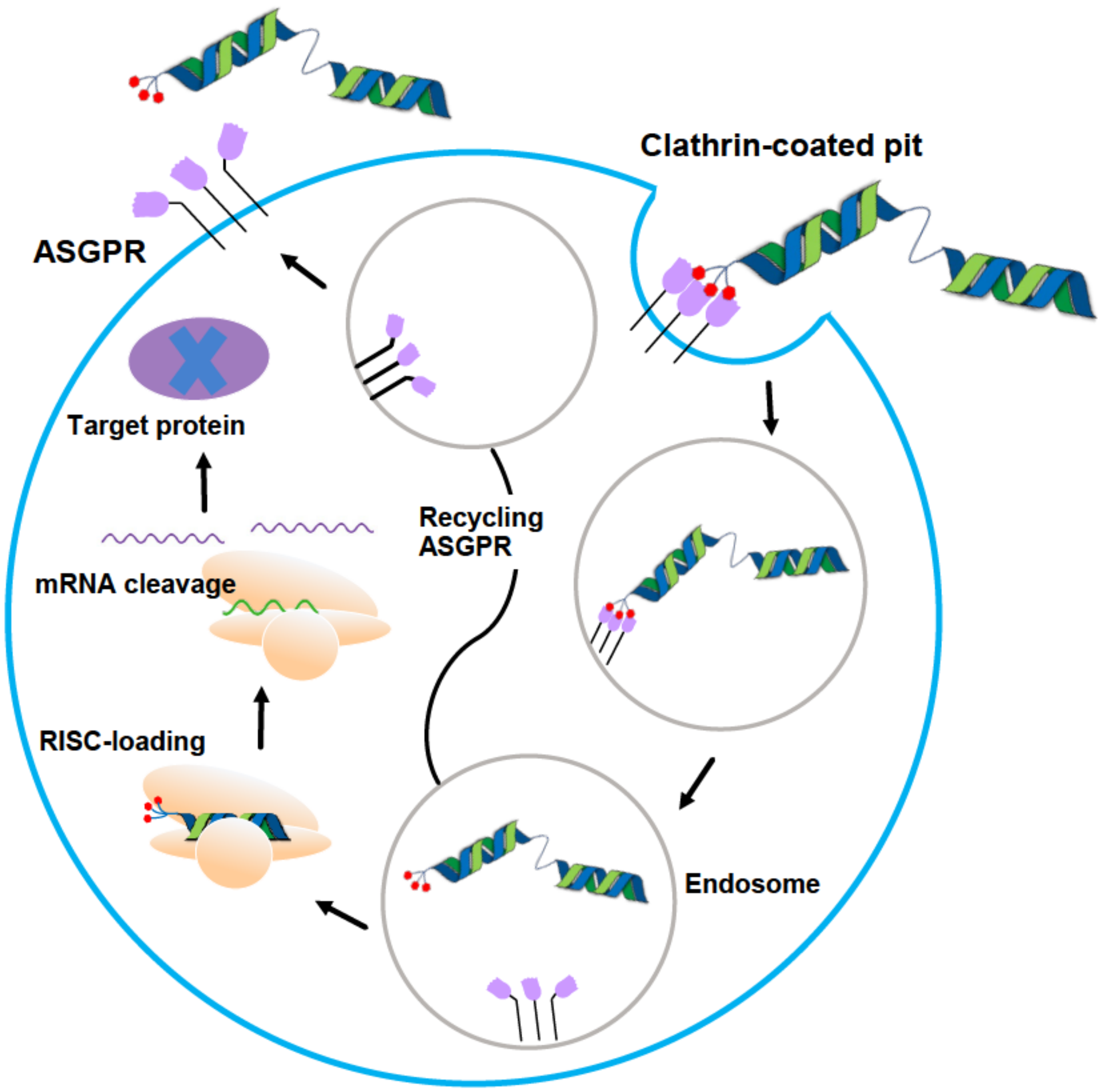
# Single RNAi Molecule to Silence Two Genes




## Single Chemical Entity to Silence Two Gene Targets

- Regulatory advantages over two co-dosed drugs
- Two siRNAs internalized during one receptor turnover

# ApoC3/PCSK9 siRNA Dimer for Lowering CVD Risk in Mixed Hyperlipidemia Patients

### APOC3 regulates triglyceride transport and uptake

- Competitively inhibits lipoprotein lipases
- Inhibits uptake of TG-rich particles

### KD of *APOC3*

- Increase uptake and lipolysis of circulating TG-rich particles
- Lower risk of CVD

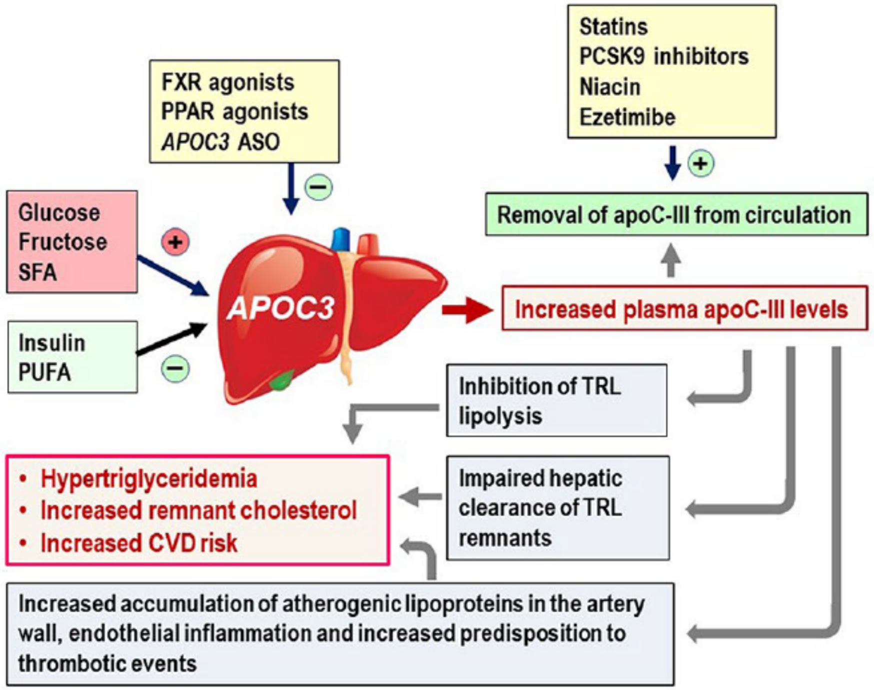
### PCSK9 binds LDL-R in liver

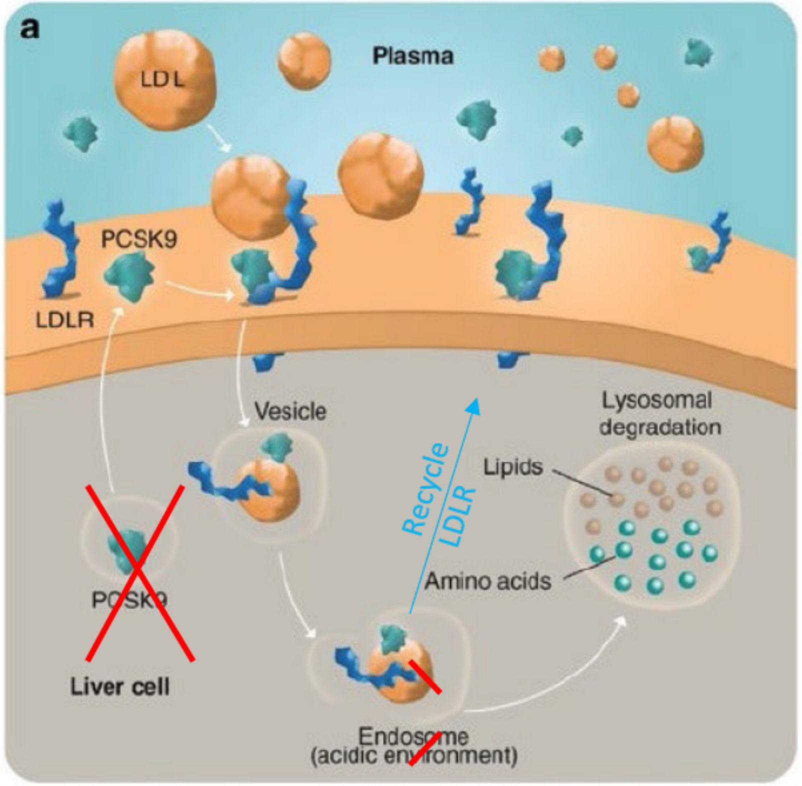
resulting in lysosomal degradation of LDL-R with LDL

- Removal of LDL-R leads to reduced LDL uptake by liver

### KD of *PCSK9*

- Prevent degradation of LDL-R with LDL
- Maintain LDL uptake by recycling LDL-R to PM




a) Secreted PCSK9 binds to LDLR on the liver cell surface and mediates the lysosomal degradation of the complex formed by PCSK9 - LDLR - LDL.

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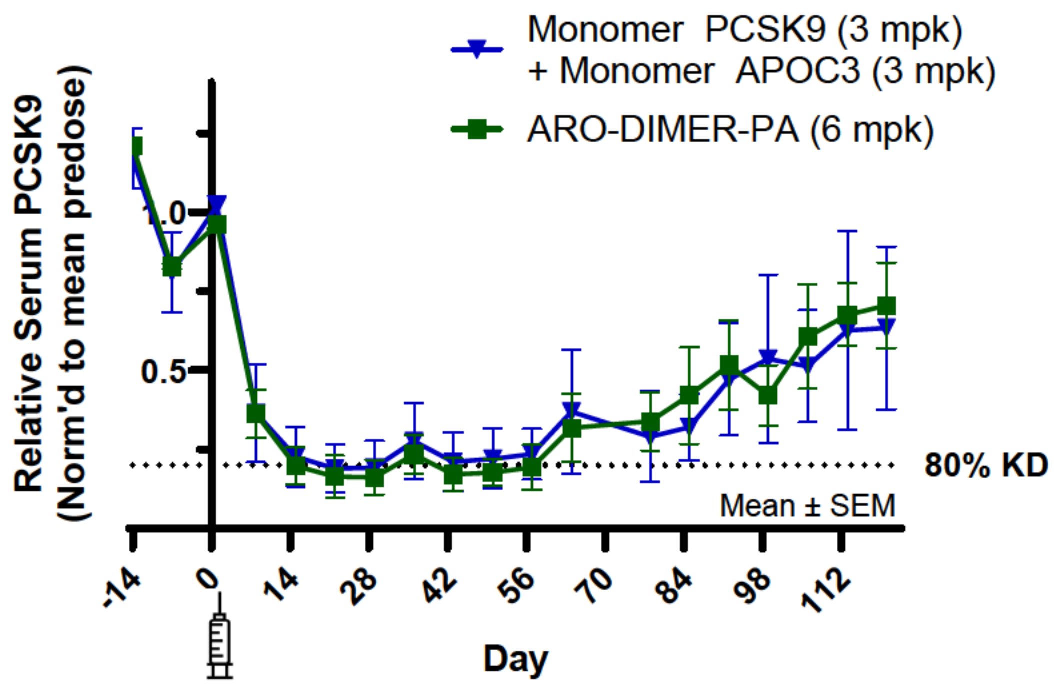
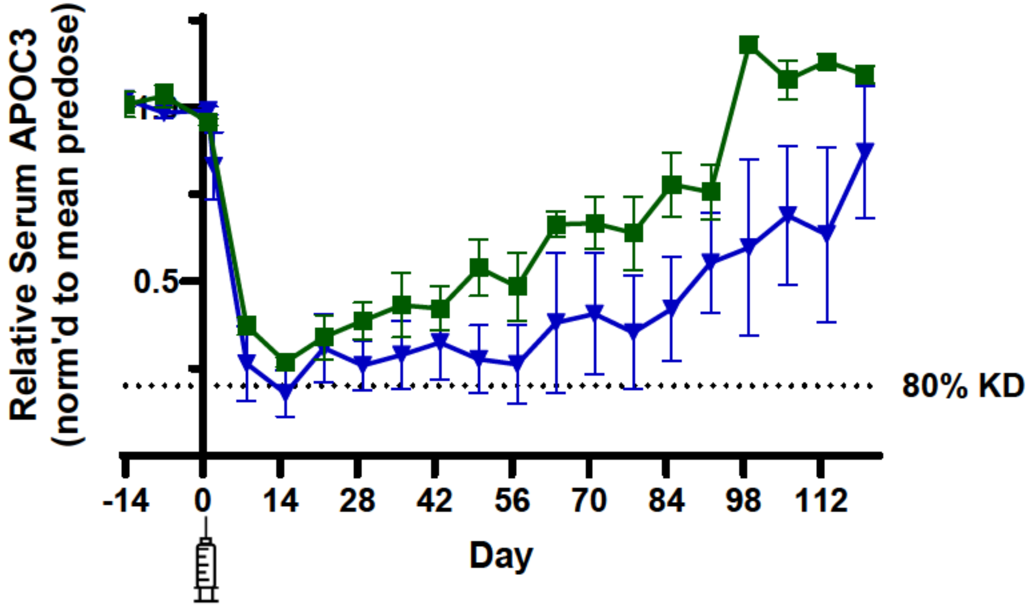
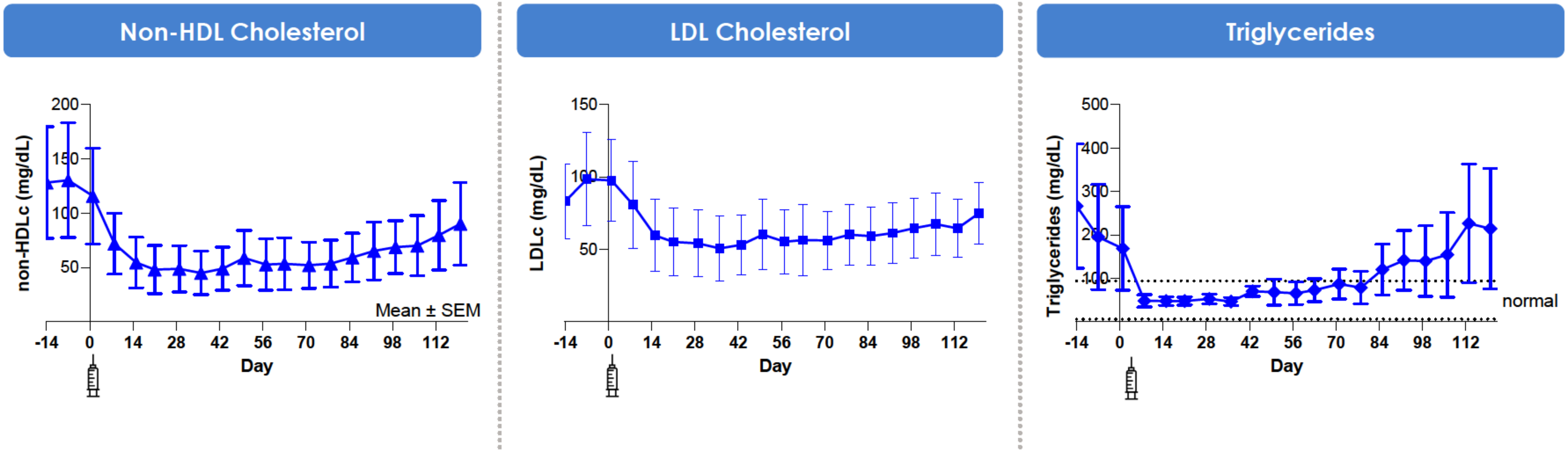
# ARO-DIMER-PA to Silence PCSK9 and APOC3



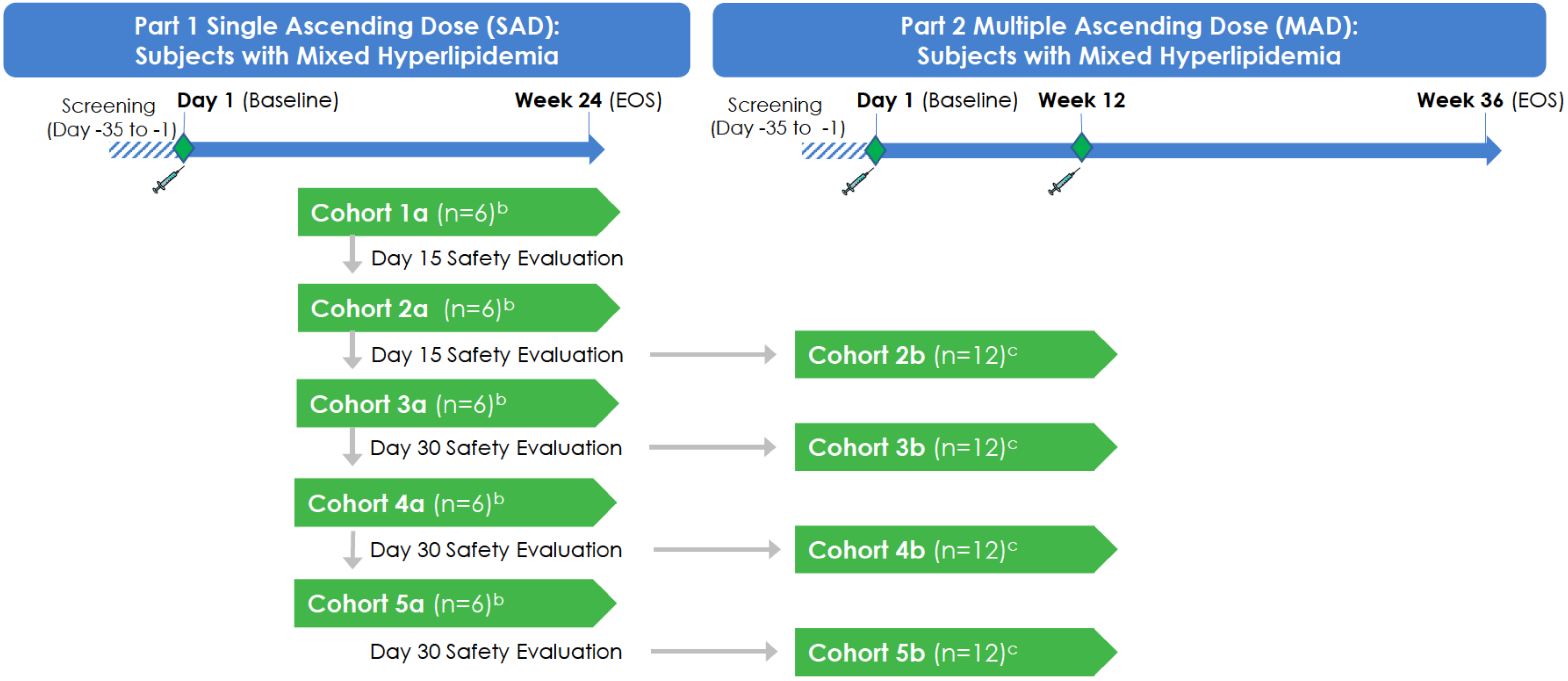

- Cynomolgus monkeys were administered ARO-DIMER-PA via subcutaneous injection on D1 at 6 mg/kg
- ARO-DIMER-PA exhibited similar potency in lowering serum PCSK9 and APOC3 levels, respectively, when compared to equivalent monomeric therapeutics (targeting only *PSCK9* or *APOC3*)

# Pharmacologic Effects of ARO-DIMER-PA Lowering Lipids in Dyslipidemic Cynomolgus Monkeys




- Spontaneously dyslipidemic monkeys were identified and administered a single 6 mg/kg subcutaneous dose of ARO-DIMER-PA on D1
- A single dose of ARO-DIMER-PA was sufficient to reduce non-HDL cholesterol, LDL cholesterol and triglyceride levels by ~ 50%

# ARODIMERPA-1001 Study Design (Part 1/Part 2)




[b] 4:2 ARO-DIMERPA:placebo [c] 6:2 ARO-DIMERPA:placebo

# ARO-DIMER-PA Progress and Timelines

- SAD cohorts fully enrolled by mid to late summer
- Full enrollment in Q3 2026
- Anticipate topline data release in Q3 2026

Cardiometabolic R&D Webinar
June 2026

# Mixed Hyperlipidemia, ASCVD, and the Promise of ARO-DIMER-PA

**Steven Nissen, MD**
Cleveland Clinic

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# Mixed Hyperlipidemia

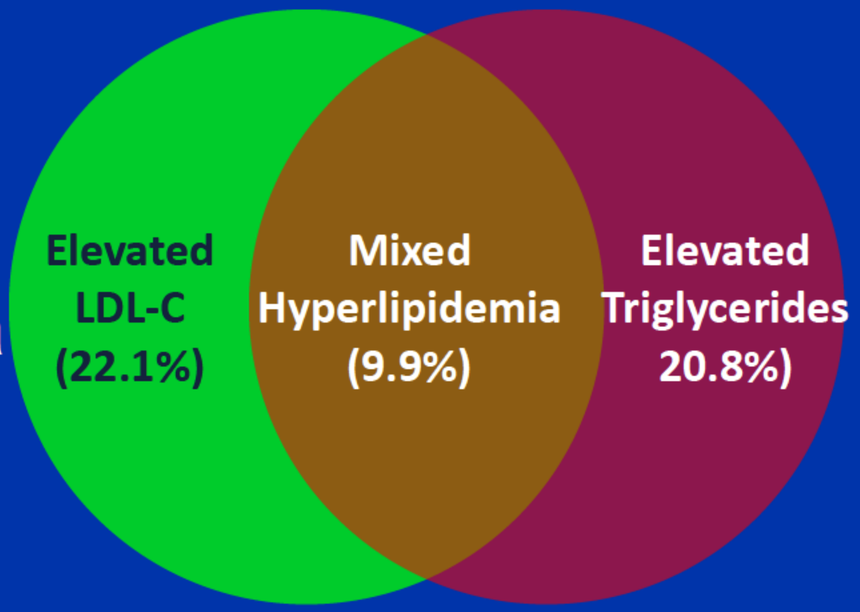
Steven E. Nissen MD MACC
Chief Academic Officer, Heart, Vascular and Thoracic Institute
Cleveland Clinic

C5Research

# What Is Mixed Hyperlipidemia?

**Mixed hyperlipidemia** is the simultaneous elevation of LDL-C and triglycerides — frequently accompanied by reduced HDL-C.

- Distinct from isolated hypercholesterolemia (LDL-C alone) or isolated hypertriglyceridemia (TG alone).
- Clinical hallmark: increased number of circulating apoB-containing particles (LDL + VLDL/remnants) - a more atherogenic burden than either abnormality alone.




EURIKA European Study on Cardiovascular Risk Prevention and Management in Usual Daily Practice

# The Atherogenic Lipid Triad

### TG-Rich Remnants

Hepatic VLDL overproduction and chylomicron remnants accumulate; small enough to penetrate the arterial wall and are readily retained.

### Small, Dense LDL

CETP-mediated exchange of triglyceride for cholesteryl ester yields LDL particles that are more easily oxidized and arterial-wall retained.

### Low HDL-C

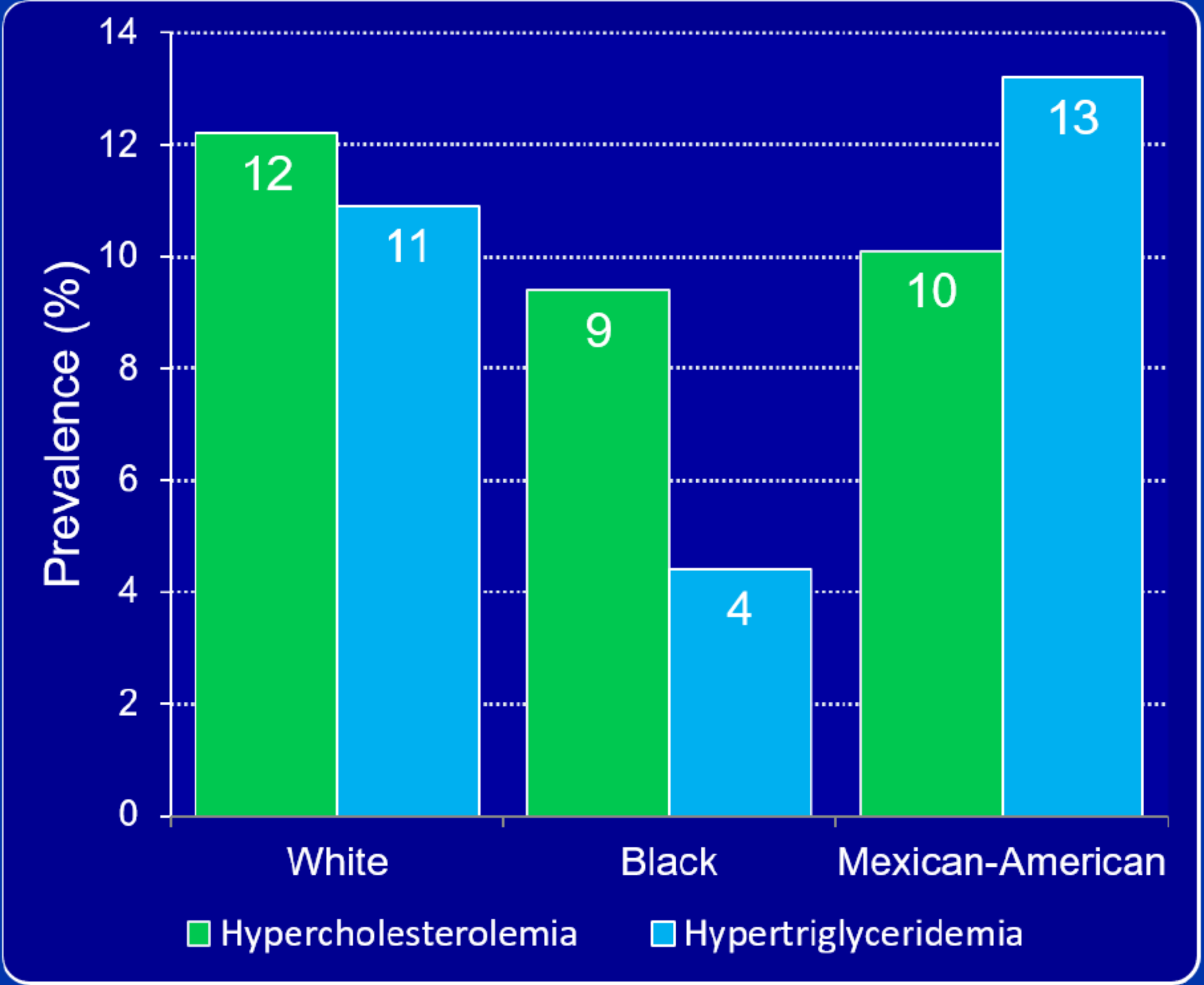
Reciprocal depletion of HDL cholesterol impairs reverse cholesterol transport, removing a key antiatherogenic counterweight.

**COMMON UPSTREAM DRIVER**

Insulin resistance / metabolic syndrome → Hepatic VLDL overproduction → **Impaired lipoprotein lipase clearance** → **Atherogenic lipid triad**

# Prevalence — General Population

| Hypercholesterolemia (TC ≥240 mg/dL) | Hypertriglyceridemia (TG ≥200 mg/dL) |
| --- | --- |
| 11.5% | 10.4% |
| ~12.05M U.S. adults | ~10.84M U.S. adults |




**NHANES 2007–2018 representing 104.4M U.S. residents.**

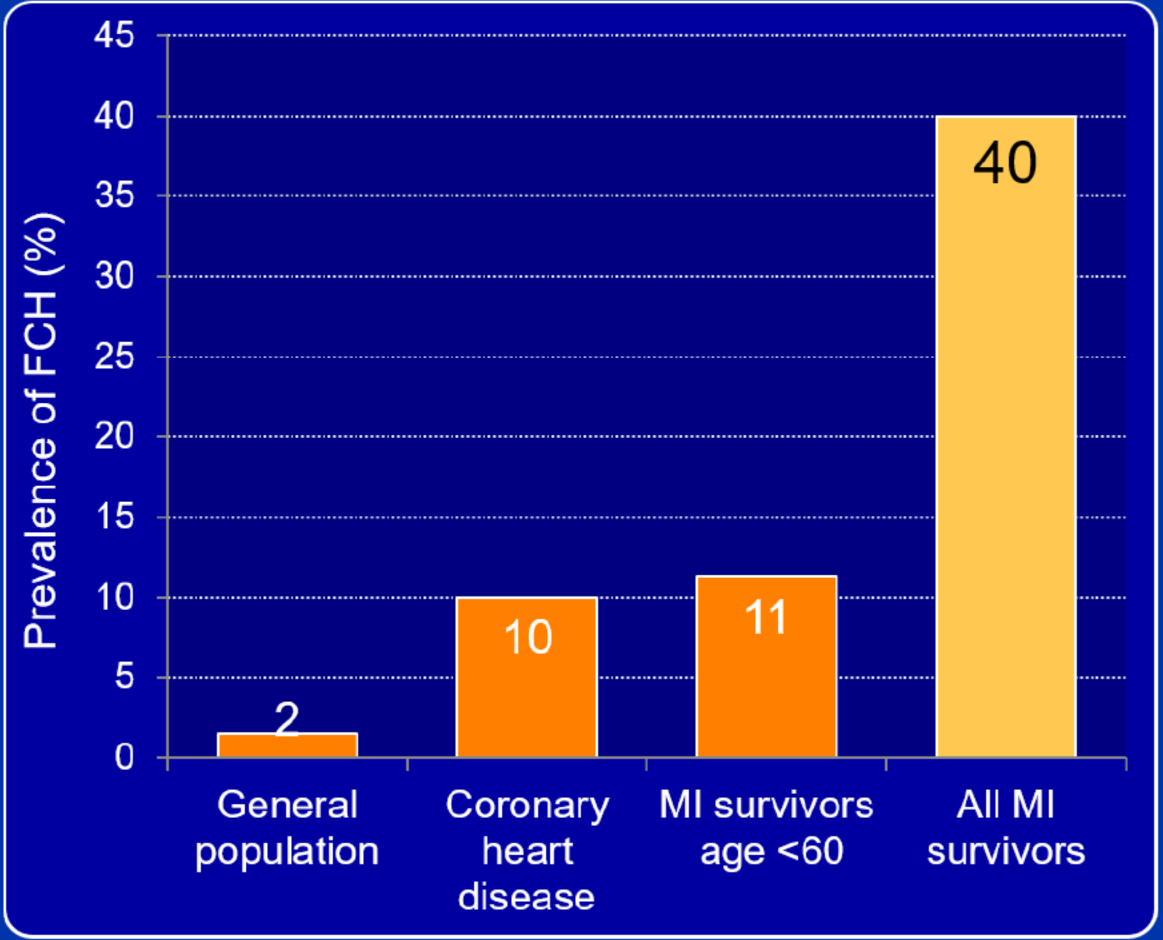
- Prevalence varies by race, ethnicity and sex
- Mexican-American highest hypertriglyceridemia (13.2%)
- Blacks: lower hypercholesterolemia (9.4%) and hypertriglyceridemia (4.4%)

*Source: Li Z, et al. Distribution of lipid levels and prevalence of hyperlipidemia: NHANES 2007–2018. Lipids Health Dis. 2022;21:111.*

# Prevalence — Genetic & High-Risk Subgroups

**Familial combined hyperlipidemia (FCH):** The most common inherited dyslipidemia - the genetic form of mixed hyperlipidemia — more common than familial hypercholesterolemia (~0.3–0.4% of the population).

- Polygenic disorder driven by hepatic overproduction of apoB-containing (VLDL/LDL) particles.
- Phenotype is variable within the same family and even within the same individual over time.
- Enriched among patients with premature coronary heart disease.
- Frequently overlaps with — and is often mistaken for — metabolic syndrome.




***Genetic dyslipidemias are commonly underdiagnosed** in routine practice because the phenotype fluctuates and overlaps with common metabolic risk factors.*

*"up to 40%" reflects pooled estimates across MI-survivor cohorts of any age*

Sources: Sniderman AD, et al. (FCH reviews); Gaddi A, et al. 2007; De Bruin TW, et al. 1996; JACC 2020 (FH prevalence meta-analysis).

# Residual ASCVD Risk Despite Statin Therapy

**48%**
not at LDL-C goal

**38%**
elevated triglycerides

**26%**
low HDL-C

*DYSlipidemia International Study (DYSIS) — >22,000 statin-treated patients with established or high-risk CVD (Europe & Canada)*

## EURIKA (primary prevention)

**>20%** of patients with ≥1 CV risk factor have markers of atherogenic dyslipidemia (high TG and/or low HDL-C) — higher still among those with diabetes or elevated calculated risk.

**~55% of patients with these markers receive no lipid-lowering therapy at all.**

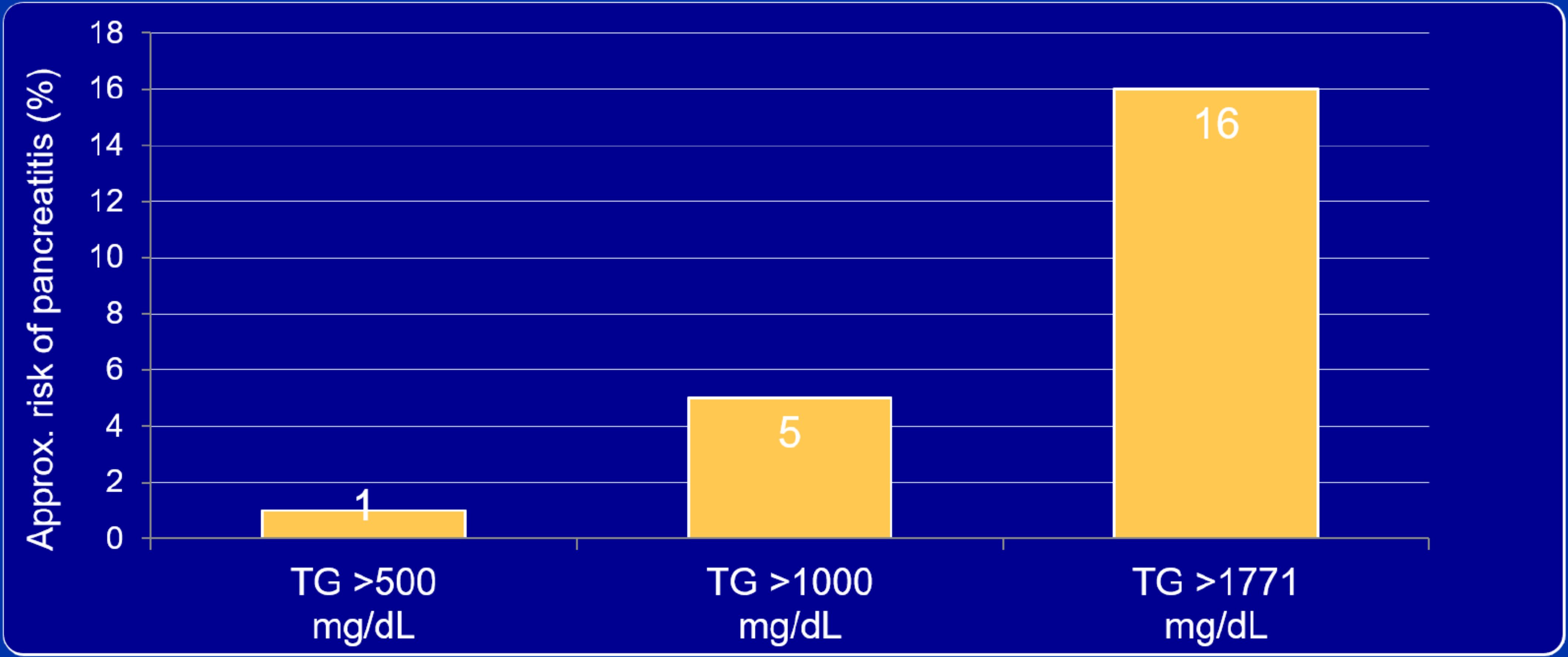
## Why LDL-C control isn't enough

Even with intensive statin therapy, 5-year major vascular events exceed 20% among patients with established coronary disease — residual risk substantially attributable to triglyceride-rich remnant lipoproteins and low HDL-C that statins address only partially.

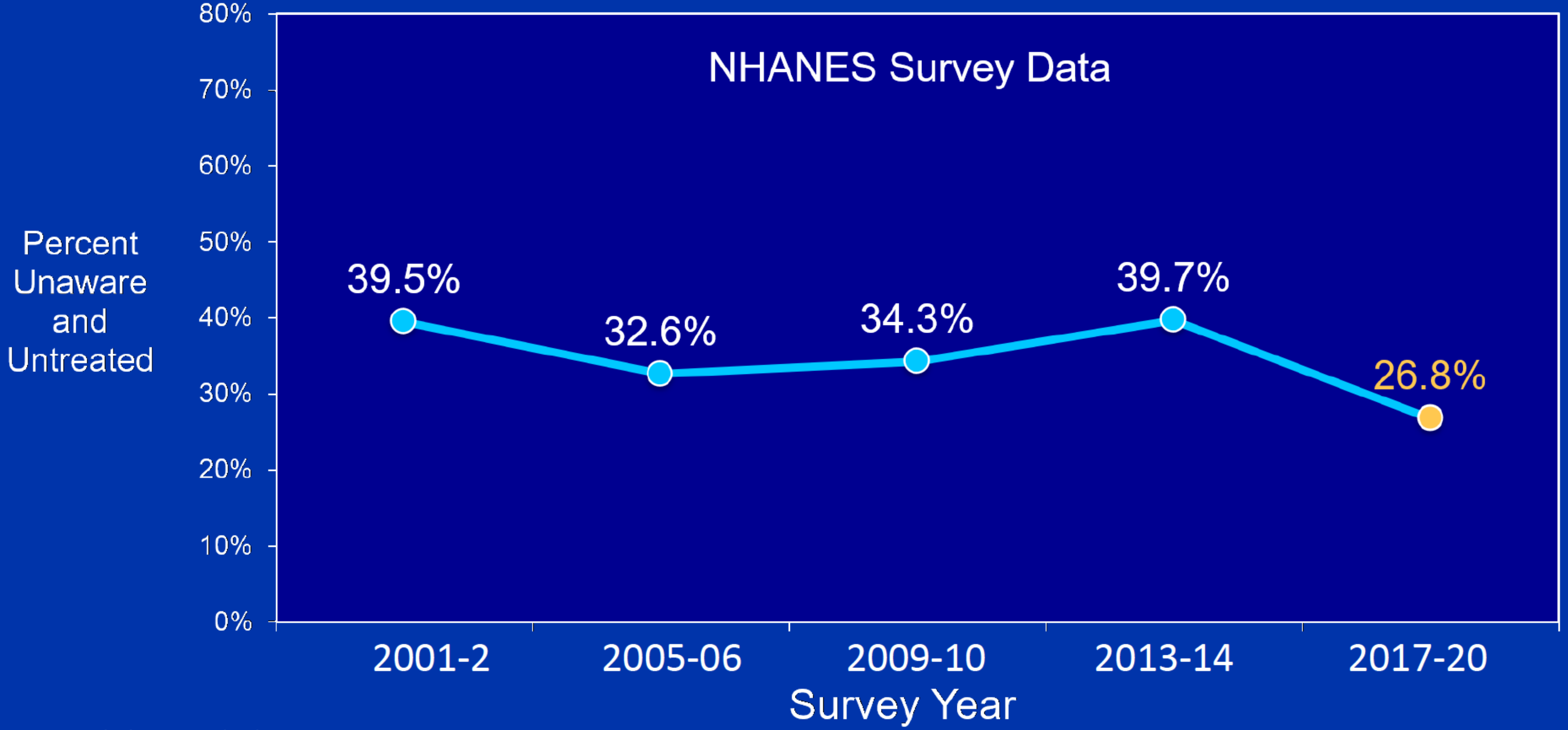
Sources: DYSIS (South Africa cohort, Raal FJ et al.); Sazonov V, et al. EURIKA study; PROMINENT trial protocol background.

# Acute Pancreatitis Risk

**Severe hypertriglyceridemia (TG ≥500 mg/dL)** occurs in roughly 1–1.7% of the population and is the third most common cause of acute pancreatitis, after gallstones and alcohol.



# Percent of Population with LDL-C >190 mg/dL Untreated and Unaware




*JAMA Cardiol.* 2023;8(12):1185–1187.

# Potential Role of Arrowhead SiRNA Dimer for PCSK9 and ApoC3

- Both PCSK9 (e.g. inclisiran) and ApoC3 (e.g. plozasiran) validated targets for LDL-C and triglycerides, respectively.

- Simultaneous and durable reductions in LDL-C ~50% and triglycerides ~70% with infrequent injections (enhanced adherence).

- Tolerability of the class has been excellent with few AEs (only minor injection site reactions).

- Potential to reduce cardiovascular morbidity and mortality very high with potential for additional event reduction by combing triglyceride lowering with established benefits of LDL-C reduction

# CLINICAL TAKE-HOME POINTS

## 01 Common, underrecognized

Co-elevated LDL-C and TG affect roughly 1 in 10 U.S. adults at the population level, and the genetic phenotype (FCH) reaches 10–40% in coronary and MI cohorts.

## 02 Drives residual ASCVD risk

TG-rich remnants and small dense LDL continue to promote atherosclerosis even when LDL-C is at goal on statin therapy — a major contributor to residual cardiovascular risk.

## 03 High pancreatitis risk

Severe hypertriglyceridemia (≥500, especially ≥1000 mg/dL) carries a separate, threshold-driven risk of acute pancreatitis

## 04 Current TG-lowering inadequate

Omega 3 fatty acids and fibrates lower triglycerides by <25% and do not substantially lower LDL-C, not enough to make a major difference in outcomes.

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# Key Takeaways

**Vince Anzalone, CFA**
Senior Vice President

arrowhead pharmaceuticals

# Key Takeaways

- Arrowhead's cardiometabolic pipeline includes **multiple promising programs across the TG/LDL spectrum** and building commercial to support complementary assets with **similar call points**
- Potential for **multiple independent and partner launches** over coming years
- **Building on the momentum** of REDEMPLO in FCS to **potentially address high prevalence sHTG population**, pending clinical data and regulatory submission and review
- **Zodasiran** targeting genetically validated **ANGPTL3**
- **Promising dual-functional siRNA** ARO-DIMER-PA with potential to address **large mixed hyperlipidemia population with high unmet need**
- **Several key potential catalysts** in cardiometabolic on the horizon, including:
  - SHASTA-3/4 topline data in Q3 2026 and potential sNDA by YE 2026
  - YOSEMITE full enrollment summer 2026 and potential completion summer 2027
  - ARO-DIMER-PA first data in Q3 2026

# Questions?

# Answers.