Cardiometabolic Virtual Investor Event
November 9, 2022

arrowhead pharmaceuticals

Welcome and Introductions

Vince Anzalone, CFA

Vice President, Finance & Investor Relations
Arrowhead Pharmaceuticals

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, enter into collaborations and achieve other projected milestones, rapid technological change 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

10:00-10:10	Welcome and Introductions – Vince Anzalone
10:10-10:20	ARO-ANG3 ARCHES-2 AHA Encore – Robert Rosenson
10:20-10:30	ARO-APOC3 SHASTA-2 AHA Encore – Christie Ballantyne
10:30-10:40	FCS, SHTG, and Pancreatitis – Christie Ballantyne
10:40-10:50	Cardiometabolic/Lipid Treatment Landscape and Residual Risk – Robert Rosenson
10:50-11:15	Journey From Early Development to Registration Path – Javier San Martin
11:15-11:25	Concluding Remarks – Chris Anzalone
11:25-11:45	Q&A – Panel

Panelists

Robert Rosenson, MD
Director, Metabolism and Lipids Unit,
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Marie-Josee and Henry R. Kravis Center for Cardiovascular Health,
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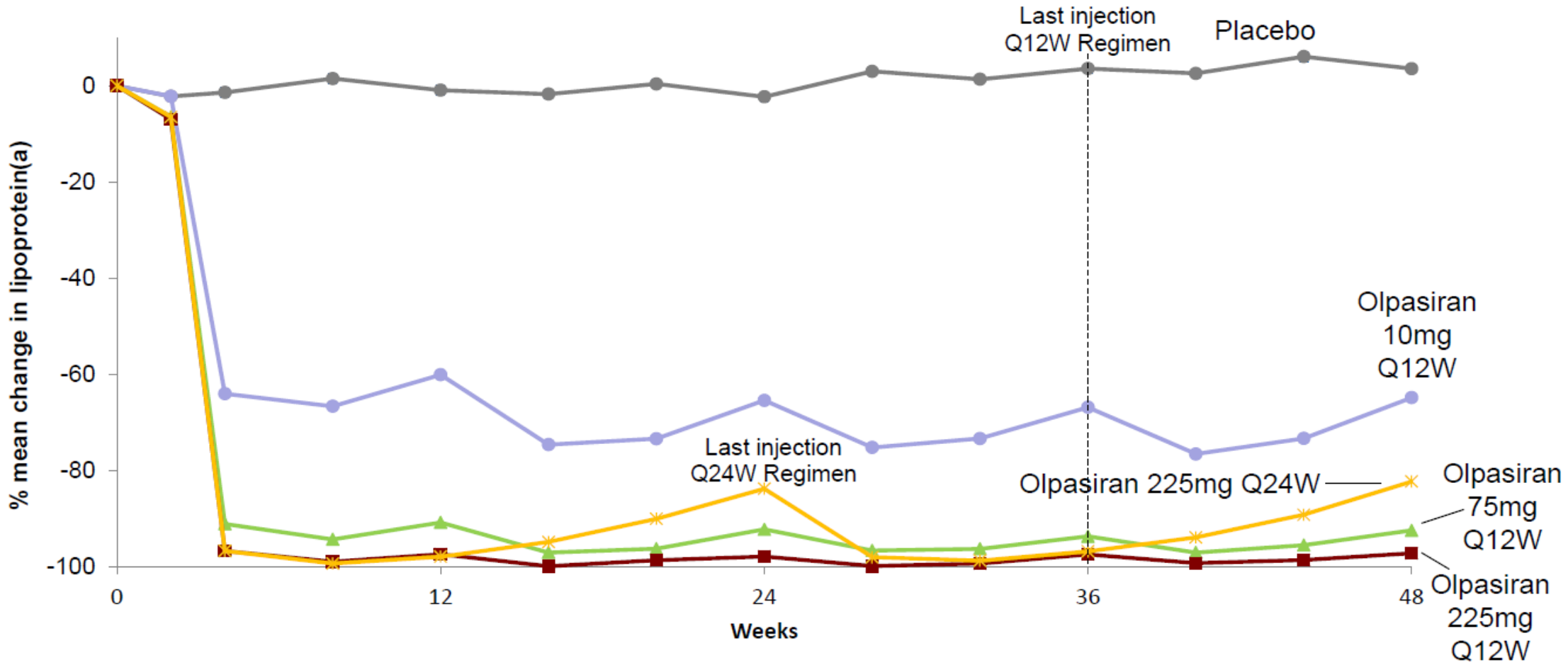
Arrowhead Pharmaceuticals

Javier San Martin, MD
Chief Medical Officer
Arrowhead Pharmaceuticals

Royalty Sale Allows Arrowhead to Invest in High Value Opportunities

- Receive $250 million upfront from Royalty Pharma for olpasiran royalty stream
- Eligible to receive additional:
  - $100 million in development and regulatory milestones
  - $60 million in sales milestones
- Retain ownership of all $400 million in remaining development, regulatory, and sales milestones from Amgen
- Immediate cash to reinvest in our business and up to $560 million additional cash as olpasiran progresses

Olpasiran Data Potentially Best in Class



An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Lp(a)= Lipoprotein(a); Q12W = every 12 weeks; Q24W = every 24 weeks.

Means reported as least-square means

Ongoing Cardiometabolic Studies

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	Active, Recruiting
	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	Fully Enrolled
	MUIR	Mixed Dyslipidemia	A Double-Blind, Placebo-controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-APOC3 in Adults with Mixed Dyslipidemia and open-label extension	Fully Enrolled
Vista Program	Gateway	HoFH	Phase 2 Study to Evaluate the Safety and Efficacy of ARO-ANG3 in Subjects with Homozygous Familial Hypercholesterolemia (HoFH) and open-label extension	Fully Enrolled
	Arches-2	Mixed Dyslipidemia	A Double-blind, Placebo-controlled Phase 2b Study to Evaluate the Efficacy and Safety of ARO-ANG3 in Adults with Mixed Dyslipidemia and open-label extension	Fully Enrolled

American Heart Association Encore

Robert Rosenson, MD
Mount Sinai Icahn School of Medicine, New York, New York, USA

#AHA22

ARO-ANG3, an Investigational RNAi Therapeutic, Decreases Serum Angiopoietin-like Protein 3, Triglycerides, and Cholesterol in Patients With Mixed Dyslipidemia

Robert S Rosenson, M.D.

Icahn School of Medicine at Mount Sinai, New York

On behalf of the ARCHES-2 Study Team

Cardiometabolic Virtual Investor Event November 9, 2022

Financial Disclosure

Presenter

RS Rosenson reports grant/research support from (all paid to institution, not individual): Amgen, Arrowhead, Novartis, Eli Lilly, Regeneron; consulting fees from Amgen, Arrowhead, CRISPR Therapeutics, Eli Lilly, Lipigon, Novartis, Precision Biosciences, Regeneron, UltraGenyx, Verve; non-promotional speaking fee from Amgen and Kowa; and other support from MediMergent, LLC (significant); UpToDate, Inc. stock shareholder (significant).

Co-Authors

GF Watts reports grants and/or honoraria from Amgen, Novartis, and Sanofi-Regeneron.

D Gaudet reports grants and/or honoraria from Acasti, Akcea, Allergan, Amryt pharma, Amgen, Applied Therapeutics, Arrowhead, AstraZeneca, Boehringer-Ingelheim, Dalcor Pharma, Eli Lilly, Esperion, Institut de cardiologie de Montréal, Ionis, Kowa, the Medicine Company, NovoNordisk, Pfizer, Regeneron, UniQure, and Verve Therapeutics.

D Altamirano has no disclosures

R Fu, T Chang and J San Martin are all current employees of Arrowhead Pharmaceuticals

RA Hegele reports honoraria and/or speaker's fees from Acasti, Akcea/Ionis, Amgen, HLS Therapeutics, and Sanofi

CM Ballantyne reports grants and/or honoraria from Abbott Diagnostic, Akcea, Althera, Amarin, Amgen, Arrowhead, AstraZeneca, Denka Seiken, Esperion, Genentech, Gilead, Illumina, Ionis, Matinas BioPharma Inc, Merck, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic, and Sanofi-Synthelabo.

SJ Nicholls reports grants and/or honoraria from Akcea, Amarin, Amgen, Anthera, Arrowhead Pharmaceuticals Inc, AstraZeneca, Boehringer Ingelheim, Cerenis, CSL Behring, Eli Lilly, Esperion, InfraReDx, LipoScience, The Medicines Company, Merck, New Amsterdam Pharma, Novartis, Omthera, Resverlogix, Roche, Sanofi-Regeneron, and Takeda.

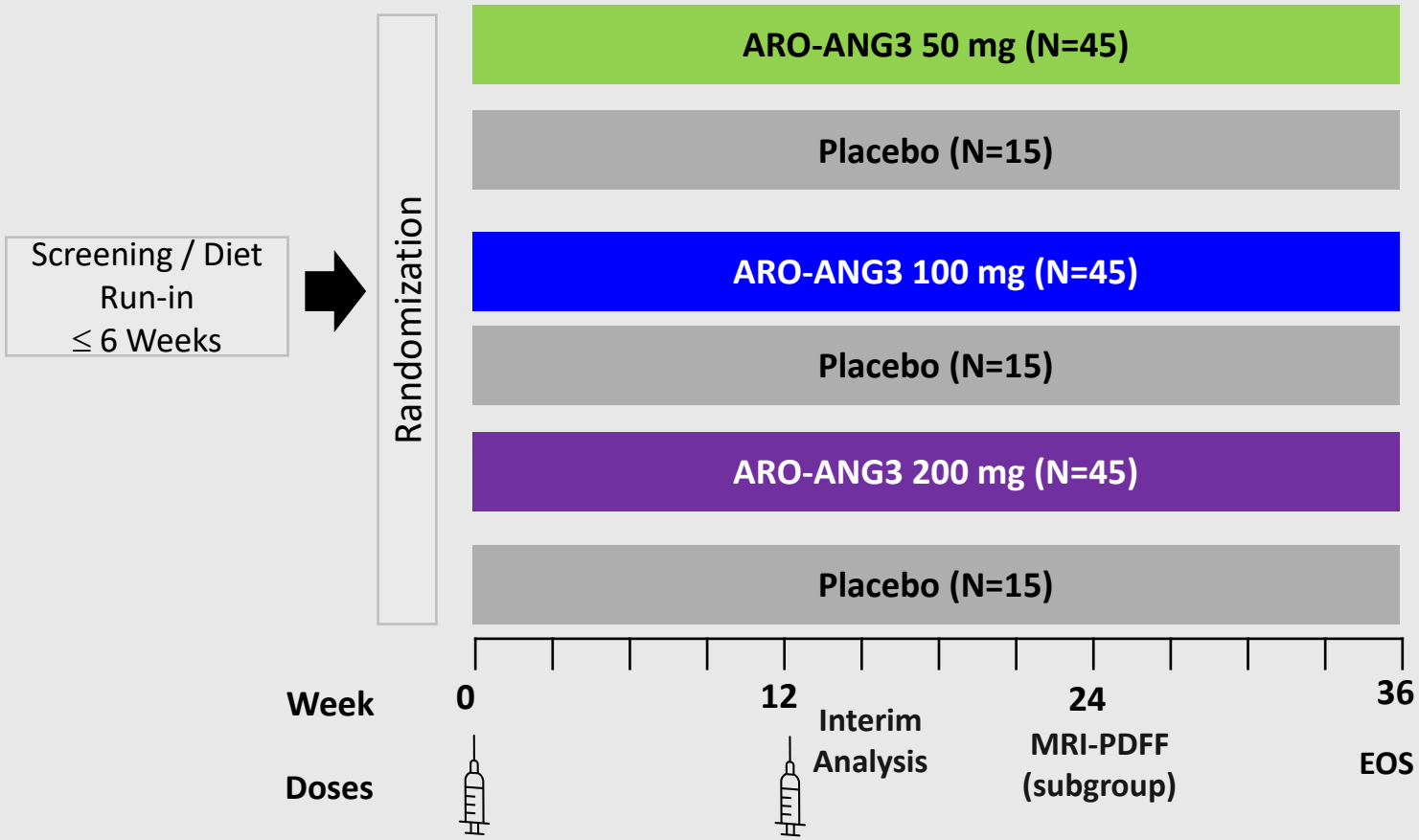
Angiopoietin-like protein 3 (ANGPTL3) as a Target to Treat Dyslipidemia

- Dyslipidemia is a major risk factor for cardiovascular disease (CVD) and residual lipoprotein risk of CVD persists even with current standard of care (including PCSK9 inhibitors)
- ANGPTL3 is a key regulator of lipid and lipoprotein metabolism with multiple potential modes of action, including inhibition of lipoprotein lipase (LPL) and endothelial lipase (EL)
- Loss of function mutations in *ANGPTL3* lead to enhanced LPL and EL activity, resulting in:
  - Low Triglycerides (TG), LDL-C, VLDL-C, and HDL-C
  - Reduced risk of Coronary Artery Disease[1,2]
  - No known adverse phenotype associated with genetic deficiency in ANGPTL3
- ARO-ANG3 is an investigational, hepatocyte-targeted RNA interference (RNAi) therapeutic designed to specifically silence *ANGPTL3* mRNA expression and mimic ANGPTL3 deficiency

ARCHES-2 : Data cutoff 06 Jul 2022

[a]Dewey FE et al. 2017 NEJM 377: 211-221, [b]Stitziel NO et al. 2017 JACC 69:2054-2063

ARCHES-2: Ongoing Double-blind, Placebo-controlled, Dose Ranging Study Of ARO-ANG3 In Subjects With Mixed Dyslipidemia



Study Population:

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

Key Endpoints*

- Serum TG
- ANGPTL3
- Non-HDL-C
- ApoB
- LDL-C
- Remnant cholesterol
- HDL-C
- Liver fat fraction by MRI-PDFF (subgroup)
  - 35 subjects with liver fat fraction ≥ 8% at baseline were evaluated again at Week 24

Interim Analysis

- Conducted when all subjects reached Week 12 (Data cutoff 06 Jul 2022), Week 16 data reported

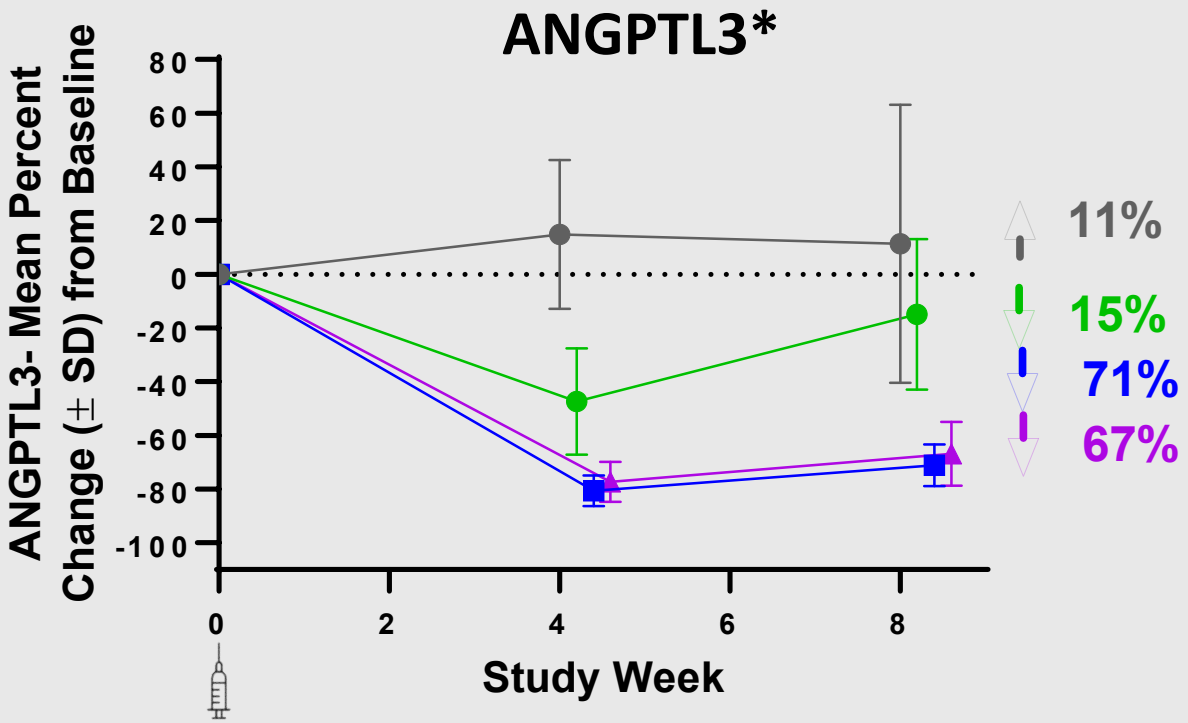
* All samples taken after ≥ 10 hour fast

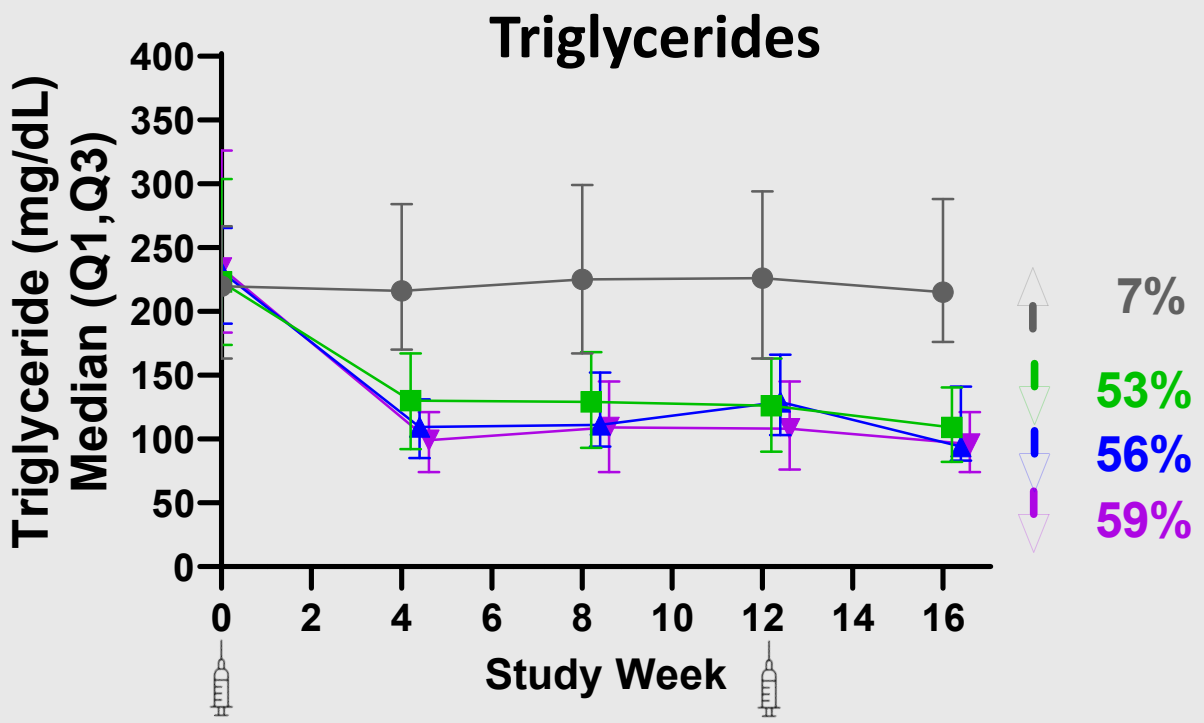
Baseline Characteristics

	Pooled Placebo	ARO-ANG3		
	(N=51)	50 mg (N=51)	100 mg (N=50)	200 mg (N=51)
Mean (SD) age, years	60.2 (11.3)	60.4 (12.7)	60.1 (10.0)	61.5 (12.5)
Female, n (%)	24 (47)	25 (49)	21 (42)	24 (47)
White, n (%)	48 (94)	49 (96)	49 (98)	49 (96)
Mean (SD) BMI, kg/m^2	33.0 (6.8)	33.3 (4.7)	32.6 (5.5)	31.6 (5.5)
Mean (SD) ANGPTL3,[a] µg/L	84.8 (27.7) n=11	74.1 (34.2) n=7	68.9 (10.6) n=5	84.7 (18.1) n=9
Median (Q1, Q3) TG, mg/dL	219.9 (163.2, 266.8)	223.3 (173.8, 303.3)	231.2 (190.5, 265.4)	234.1 (183.5, 326.2)
Mean (SD) LDL-C (Martin Hopkins), mg/dL	102.5 (30.6)	112.8 (29.7)	108.7 (44.8)	105.6 (33.7)
Mean (SD) non-HDL-C, mg/dL	138.6 (41.6)	151.5 (36.0)	149.3 (47.5)	143.3 (39.6)
Mean (SD) ApoB, mg/dL	95.7 (24.1)	106.8 (23.4)	99.6 (26.2)	94.9 (25.0)
Mean (SD) remnant cholesterol,[b] mg/dL	36.1 (31.6)	38.7 (12.1)	40.6 (30.8)	37.6 (14.9)
Mean (SD) HDL-C, mg/dL	41.6 (11.9)	43.2 (13.3)	39.9 (10.6)	42.3 (13.6)

[a] Limited ANGPTL3 results available at the data cutoff date (06 Jul 2022);
[b] Based on calculation: remnant cholesterol = (total cholesterol) - (HDL-C) - (LDL-C (Martin-Hopkins))

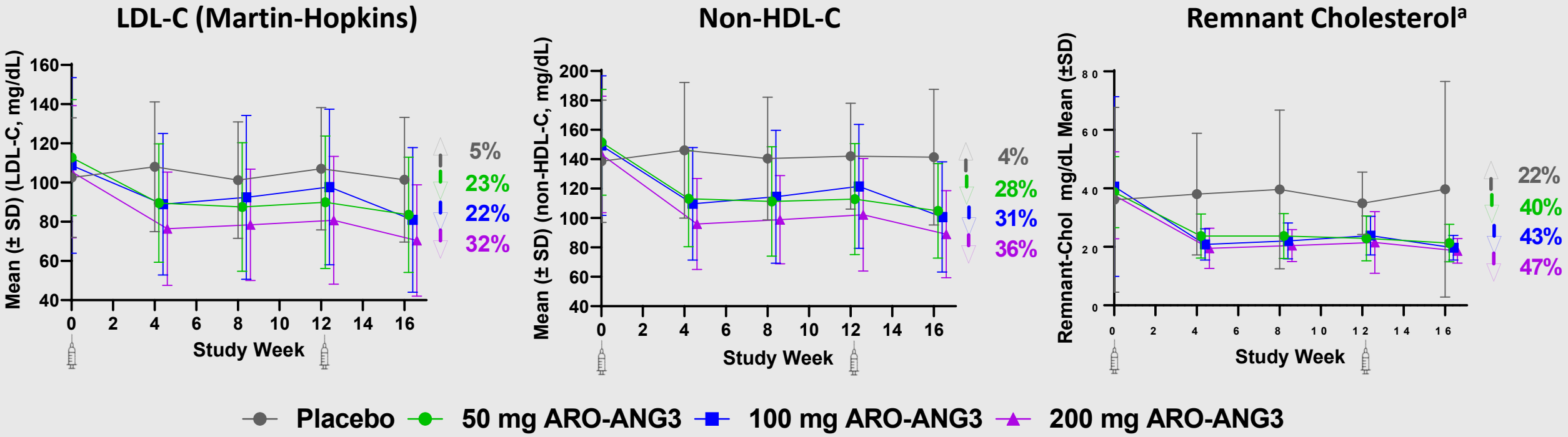
ARO-ANG3 Decreases Serum ANGPTL3 and Triglycerides





Placebo — 50 mg ARO-ANG3 — 100 mg ARO-ANG3 — 200 mg ARO-ANG3

ARO-ANG3 Decreases Serum LDL-C, Non-HDL-C And Remnant Cholesterol

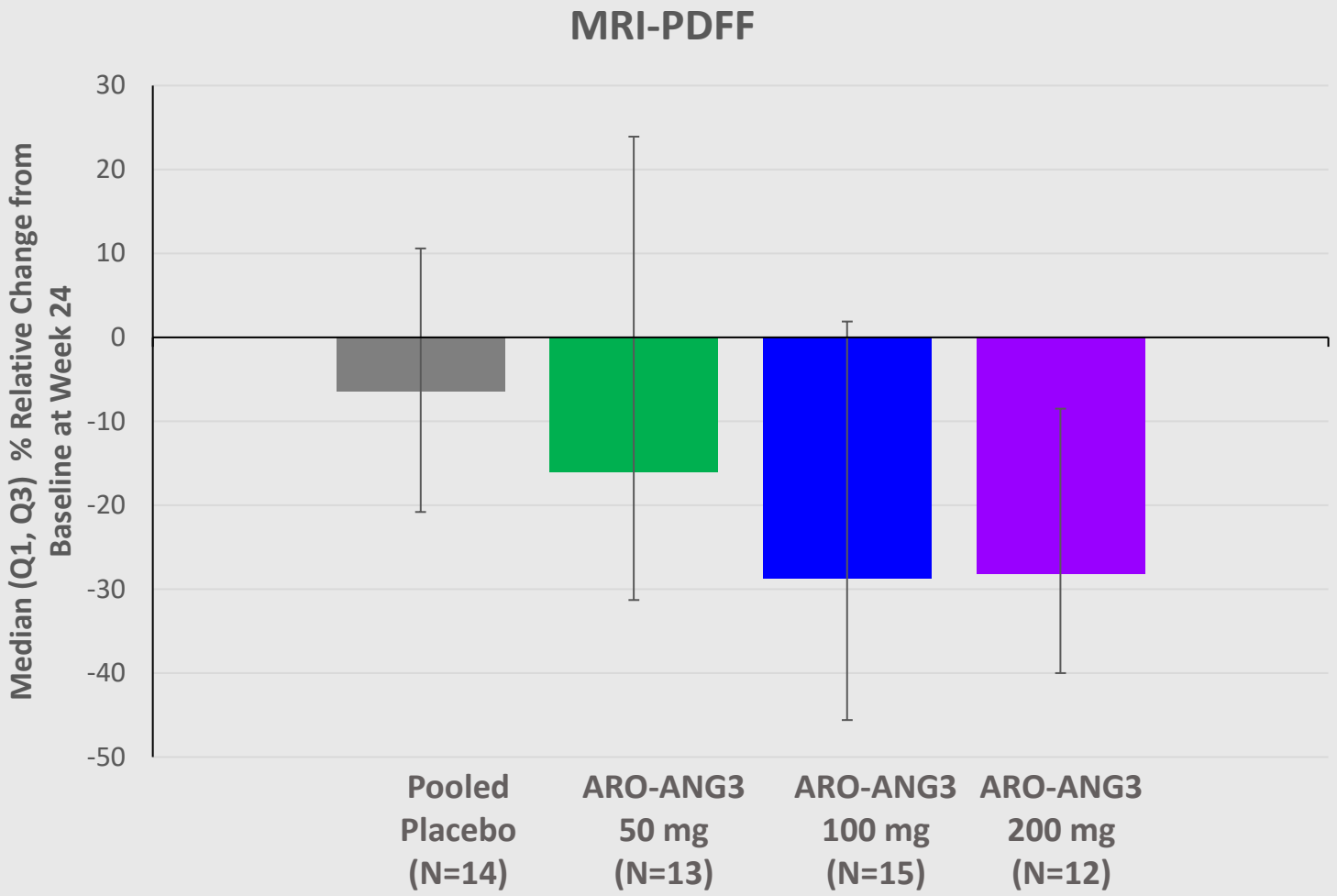


- ARO-ANG3 also reduced ApoB and HDL-C
  - Mean ApoB decreased by 13.2% to 21.8% at Week 16, compared with 0.0% for placebo
  - Mean HDL-C decreased by 17.3% to 30.6% at Week 16, compared with 2.1 % increase for placebo

ARCHES-2 : Data cutoff 06 Jul 2022

[a] Based on calculation: remnant cholesterol = (total cholesterol) - (HDL-C) - (LDL-C (Martin-Hopkins))

Data To Date Suggest ARO-ANG3 is Associated with Reduced Liver Fat Fraction



- Subgroup of 35 Subjects with liver fat fraction of >8% at baseline were selected for additional MRI-PDFF at Week 24

- One subject (<1%) had a transient elevation of ALT (>3x upper limit of normal (no elevated total bilirubin))

Liver Safety With ANGPTL3 Inhibitors Has Been Disparate and Compound Specific

Mechanism	Compound	Study Population	Hepatic Enzymes	Hepatic Fat Fraction
ANGPTL3 mAb[a]	Evinacumab	Severe HTG	No change	No change from baseline to 24 weeks with interquartile range of -23% to +39%.
ANGPTL3 ASO[b]	Vupanorsen	Mixed Hyperlipidemia	Dose dependent increase in AST/ALT >3x ULN up to 33.3 and 44.4% respectively	Dose-dependent increase in hepatic fat fraction up to 76%
ANGPTL3 siRNA	ARO-ANG3	Mixed Hyperlipidemia	No increases in transaminases	Dose-dependent decrease in hepatic fat fraction up to 30%

[a] Rosenson RS, et al. Evinacumab in severe hypertriglyceridemia with or without lipoprotein lipase pathway mutations: a phase 2 randomized trial. Nat Med 2022 (accepted).
[b] Bergmark BA, et al. Effect of vupanorsen on non-HDL lipoprotein cholesterol levels in statin-treated patients with elevated cholesterol: TRANSLATE-TIMI 70. Circulation 2022;45:1377-1386

Aggregated Summary Of Adverse Events

# of Subjects Reporting ≥ 1 Treatment Emergent Adverse Event* (TEAE) N (%)	131/203 (65%)
TEAEs occurring in ≥ 5 subjects	N (%)
COVID-19	22 (11%)
Urinary tract infection	16 (8%)
Upper respiratory infection	13 (6%)
Headache	12 (6%)
Injection site pain	11 (5%)
Diabetes (Diabetes mellitus, Type 2 diabetes mellitus, glycosylated hemoglobin increase)	9 (4%)
Nausea	8 (4%)
Back pain	7 (3%)
Diarrhea	5 (2%)
Dizziness	5 (2%)
Hypertension	5 (2%)
Injection site erythema	5 (2%)
Osteoarthritis	5 (2%)
Treatment-related TEAEs	39 (19%)
Serious TEAEs	9 (4%)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	1 (<1%)
TEAEs causing deaths	1 (<1%)

- TEAEs reported to date are consistent with those expected in this patient population and with associated underlying comorbidities
- Mean change from baseline in HbA1c at Week 16 across cohorts was 0.16% to 0.25% in subjects receiving ARO-ANG3 and -0.05% in subjects receiving placebo, driven by patients with baseline diabetes
- 1 death due to myocardial infarction in subject with multiple recent history of cardiovascular events (eg, CAD, STEMI, PCI, PAD, CHF)
  - Event occurred ~10 weeks after dosing of blinded investigational product and was considered unrelated to study drug.

*To maintain data blind, all TEAEs were pooled regardless of treatment assignment

ARCHES-2 : Data cutoff 06 Jul 2022

Interim Analysis of ARCHES-2 Study of ARO-ANG3 Suggests Favorable Changes in Lipoproteins in Subjects With Mixed Dyslipidemia

- In subjects with mixed dyslipidemia who had baseline median TGs of 220 mg to 234 mg/dL, treatment with ARO-ANG3 at doses of 50 mg, 100 mg or 200 mg ARO-ANG3 resulted in substantial reductions of:
  - ANGPTL3 up to 71% at Week 8
  - TGs up to 59% at Week 16
  - LDL-C up to 32% at Week 16
- ARO-ANG3 is associated with relative reduction in liver fat fraction at Week 24, with no AEs related to LFT changes reported to date
- TEAEs reported to date are consistent with those expected in this patient population and with associated underlying comorbidities
- The favorable changes in serum lipids and lipoproteins support the potential value of ARO-ANG3 for the treatment of mixed dyslipidemia in patients at risk of atherosclerotic cardiovascular disease

American Heart Association Encore

Christie Ballantyne, MD
Baylor College of Medicine, Houston, Texas

#AHA22

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ARO-APOC3, an Investigational RNAi Therapeutic, Decreases Serum Apolipoprotein C3, Triglyceride, and Non-HDL-C Concentrations While Increasing HDL-C in Patients With Severe Hypertriglyceridemia

Christie M Ballantyne, MD
Baylor College of Medicine
on behalf of the SHASTA-2 Study Team

American Heart Association.

Financial Disclosure

Presenter

CM Ballantyne reports grants and/or honoraria from Abbott Diagnostic, Akcea, Althera, Amarin, Amgen, Arrowhead, AstraZeneca, Denka Seiken, Esperion, Genentech, Gilead, Illumina, Ionis, Matinas BioPharma Inc, Merck, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic, and Sanofi-Synthelabo.

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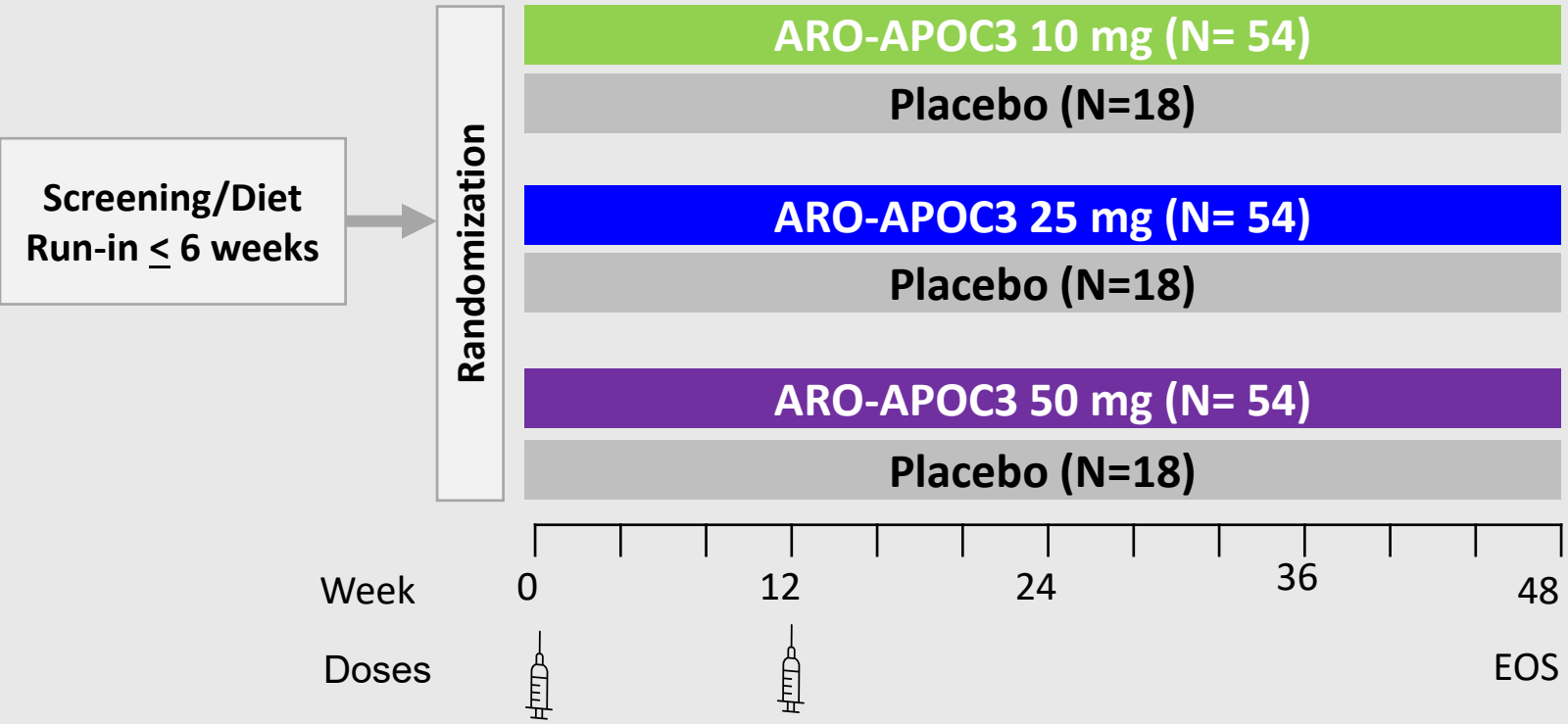
Role of Apolipoprotein C3-Targeted Therapies in Severe Hypertriglyceridemia

- Severe hypertriglyceridemia (SHTG) significantly increases risk of acute pancreatitis.
- Currently, there are limited effective therapies to treat SHTG
- Apolipoprotein C3 (APOC3) regulates circulating levels of triglycerides (TGs) and lipoprotein metabolism by inhibiting lipoprotein lipase-dependent and –independent pathways.
- Loss of function mutations in *APOC3* are associated with:
  - Low TG, chylomicrons, VLDL-C, remnant cholesterol and increased levels of HDL-C
  - Reduced risk of cardiovascular disease (CVD)
  - No known adverse phenotype associated with genetic deficiency in *APOC3*
- ARO-APOC3 is an investigational, hepatocyte-targeted RNA interference (RNAi) therapeutic designed to specifically silence hepatic *APOC3* mRNA expression and reduce circulating APOC3 and TGs.
- Phase 1 studies of ARO-APOC3 in subjects with hypertriglyceridemia resulted in robust and sustained reductions in TGs and non-HDL-C, increases in HDL-C, and with a safety profile supportive of later stage clinical development

SHASTA 2: An Ongoing Double-blind, Placebo-controlled, Dose Ranging Study of ARO-APOC3 in Subjects With SHTG



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 in

- TG
- APOC3
- non-HDL-C
- LDL-C
- HDL-C

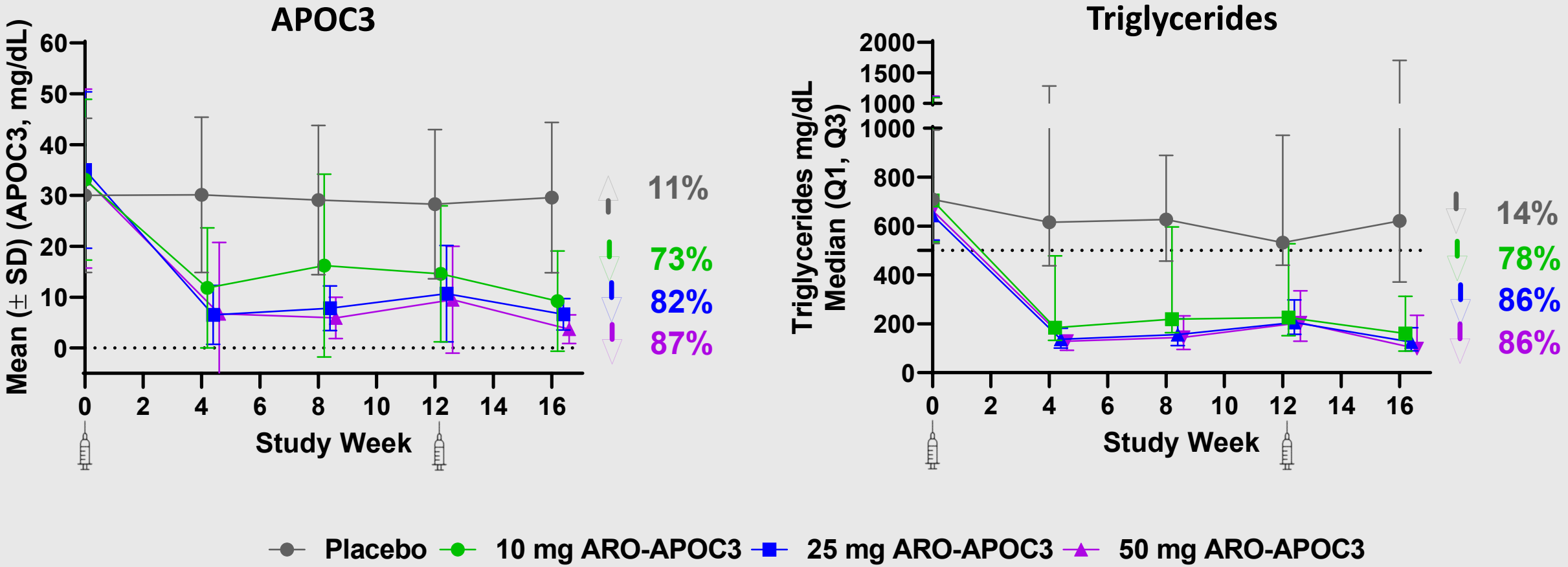
Data Analysis: Ongoing Phase 2 study data evaluated when ≥50% of subjects had reached Week 12 and received both doses. 177 subjects had entered the study at the time of the data cutoff (25 Jul 2022). Data available to the Week 16 visit are presented.

* All samples taken after ≥ 10 hour fast

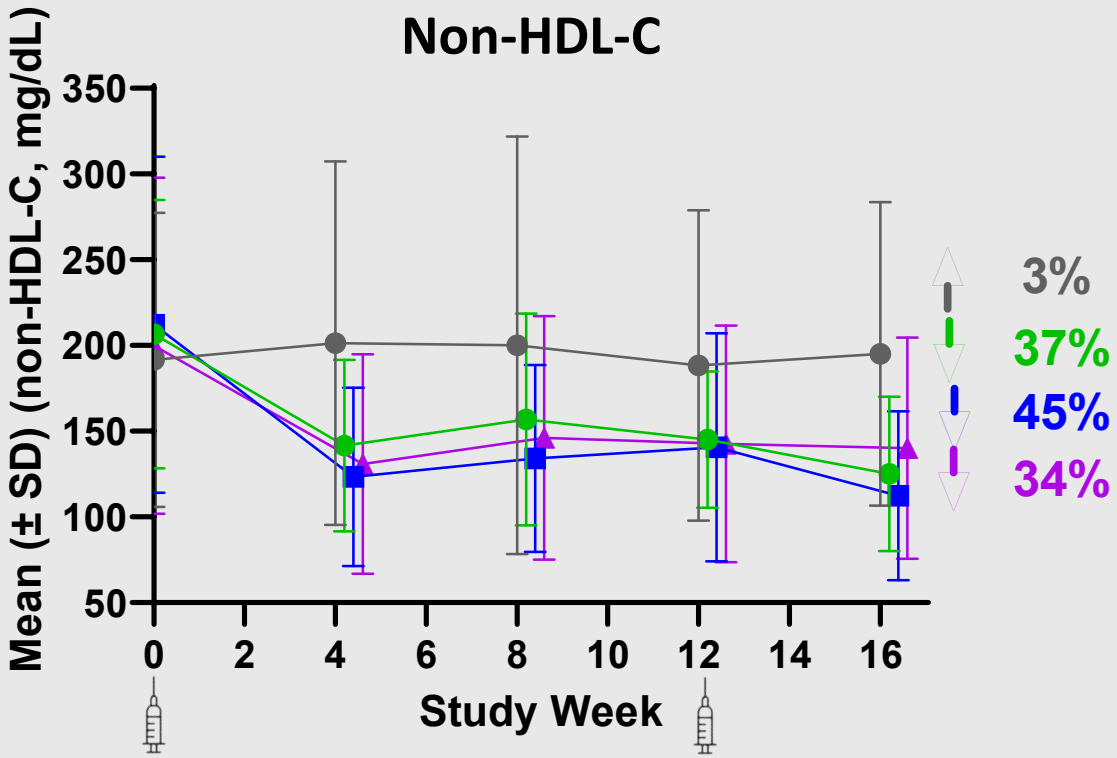
Baseline Characteristics

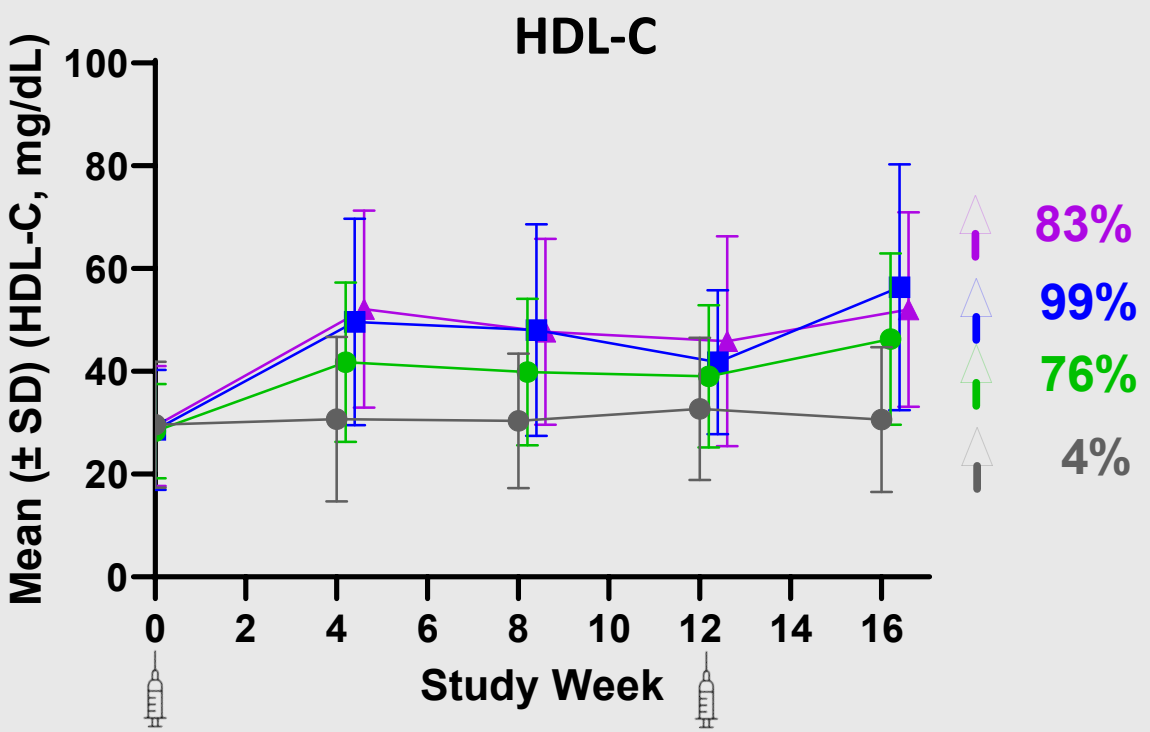
	Pooled Placebo	ARO-APOC3		
	(N=46)	10 mg (N=43)	25 mg (N=43)	50 mg (N=45)
Mean (SD) age, years	56.3 (11.17)	53.9 (9.29)	56.0 (11.70)	54.8 (10.52)
Female, n (%)	11 (24)	4 (9)	12 (28)	13 (29)
White, n (%)	42 (91)	37 (86)	37 (86)	41 (91)
Mean (SD) BMI, kg/m^2	30.4 (3.8)	32.9 (5.1)	31.4 (5.0)	31.3 (5.3)
Mean (SD) APOC3 µg/L	31.3 (17.4)	33.1 (15.8)	35.0 (15.4)	32.6 (17.5)
Median (Q1, Q3) TG, mg/dL	708.5 (528.5, 993.0)	704.4 (535.8, 1097.7)	643.9 (542.7, 1099.2)	663.1 (527.4, 1134.9)
Mean (SD) LDL-C (ultracentrifugation), mg/dL	68.7 (43.0)	75.5 (42.9)	73.81 (42.0)	70.1 (45.6)
Mean (SD) non-HDL-C, mg/dL	191.7 (85.8)	206.6 (78.4)	212.1 (98.1)	199.9 (88.1)
Mean (SD) HDL-C, mg/dL	29.6 (12.3)	28.4 (9.2)	28.6 (11.8)	29.4 (11.7)
Mean (SD) remnant cholesterol,* mg/dL	124.7 (90.5)	130.4 (88.3)	138.3 (103.9)	130.3 (93.7)

ARO-APOC3 Demonstrates Durable Decreases in Serum APOC3 and Triglycerides at All Doses Studied



ARO-APOC3 Decreases Serum Non-HDL-C and Increases HDL-C at All Doses Studied





Placebo — 10 mg ARO-APOC3 — 25 mg ARO-APOC3 — 50 mg ARO-APOC3

Changes In LDL-C and non-HDL-C at Week 16

	Pooled Placebo	ARO-APOC3		
		10 mg	25 mg	50 mg
LDL-C (Ultracentrifugation) (mg/dL)*				
Baseline median (Q1,Q3)	54.0 (31.0, 88.0)	62.0 (29.0, 100.0)	62.5 (44.0, 92.0)	60.0 (30.0, 106.0)
Median (Q1,Q3) at Week 16	72.5 (18.0, 90.0)	69.0 (38.0, 120.0)	64.5 (50.0, 126.0)	83.0 (63.0, 122.0)
Median % change at Week 16 (Q1, Q3)	**-6.6** (-32.8, 34.3)	**22.2** (-20.8, 86.8)	**13.3** (-15.2, 72.4)	**11.6** (0.0, 135.5)
N	(n=26)	(n=23)	(n=26)	(n=21)
Non-HDL Cholesterol(mg/dL)				
Baseline mean (SD)	198.8 (98.1)	213.2 (89.3)	224.6 (111.6)	225.1 (104.0)
Mean (SD) at Week 16	195.0 (88.6)	125.0 (45.1)	112.3 (49.3)	140.1 (64.5)
Mean % change at Week 16 (SD)	**2.8** (34.8)	**-36.5** (26.8)	**-45.0** (21.4)	**-33.5** (25.9)
N	(n=28)	(n=24)	(n=27)	(n=23)

*Median percent change reported due to non-normal distribution

Aggregated Summary of Adverse Events

# of Subjects Reporting ≥ 1 Treatment Emergent Adverse Event (TEAE) N (%)	77/177(44%)
TEAEs occurring in ≥ 4 subjects	N (%)
COVID-19	17 (10%)
Headache	12 (7%)
Urinary tract infection	7 (4%)
Diarrhea	5 (3%)
Hypertension	5 (3%)
Glycosylated hemoglobin increased	5 (3%)
Abdominal pain upper	4 (2%)
Non-Cardiac chest pain	4 (2%)
Type 2 diabetes mellitus	4 (2%)
Treatment-related TEAEs	16 (9%)
Serious TEAEs	10 (6%)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	0 (0%)
TEAEs causing deaths	0 (0%)

- TEAEs reported to date reflect the underlying comorbidities and conditions of the population under study
- All TEAEs were pooled regardless of treatment assignment
- Mean change from baseline in HbA1c at Week 16 across cohorts was 0.24% to 0.43% in subjects receiving ARO-APOC3, and 0.11% in subjects receiving placebo, driven by patients with baseline diabetes
- To date, 2 cases of pancreatitis have been reported (blinded)

Interim Analysis of SHASTA-2 Study Suggests Favorable Changes in Triglycerides and Non-HDL Cholesterol in Subjects With SHTG

- Analysis was performed in SHASTA-2 once 50% of subjects reached their Week 12 visit
- Interim results to date demonstrate that ARO-APOC3 durably decreases serum APOC3, TGs, and non-HDL-C while increasing HDL-C at all dose levels:
  - APOC3 up to -87% at Week 16
  - Triglycerides up to -86% at Week 16
  - Non-HDL-C up to -45% at Week 16
  - HDL-C up to +99% at Week 16
- ARO-APOC3 has been well tolerated in this ongoing Phase 2 study
- Based on these results, RNAi-mediated silencing of hepatic APOC3 expression via ARO-APOC3 appears to be a promising treatment for patients with SHTG

FCS, SHTG, and Pancreatitis

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Severe hypertriglyceridemia and apoCIII

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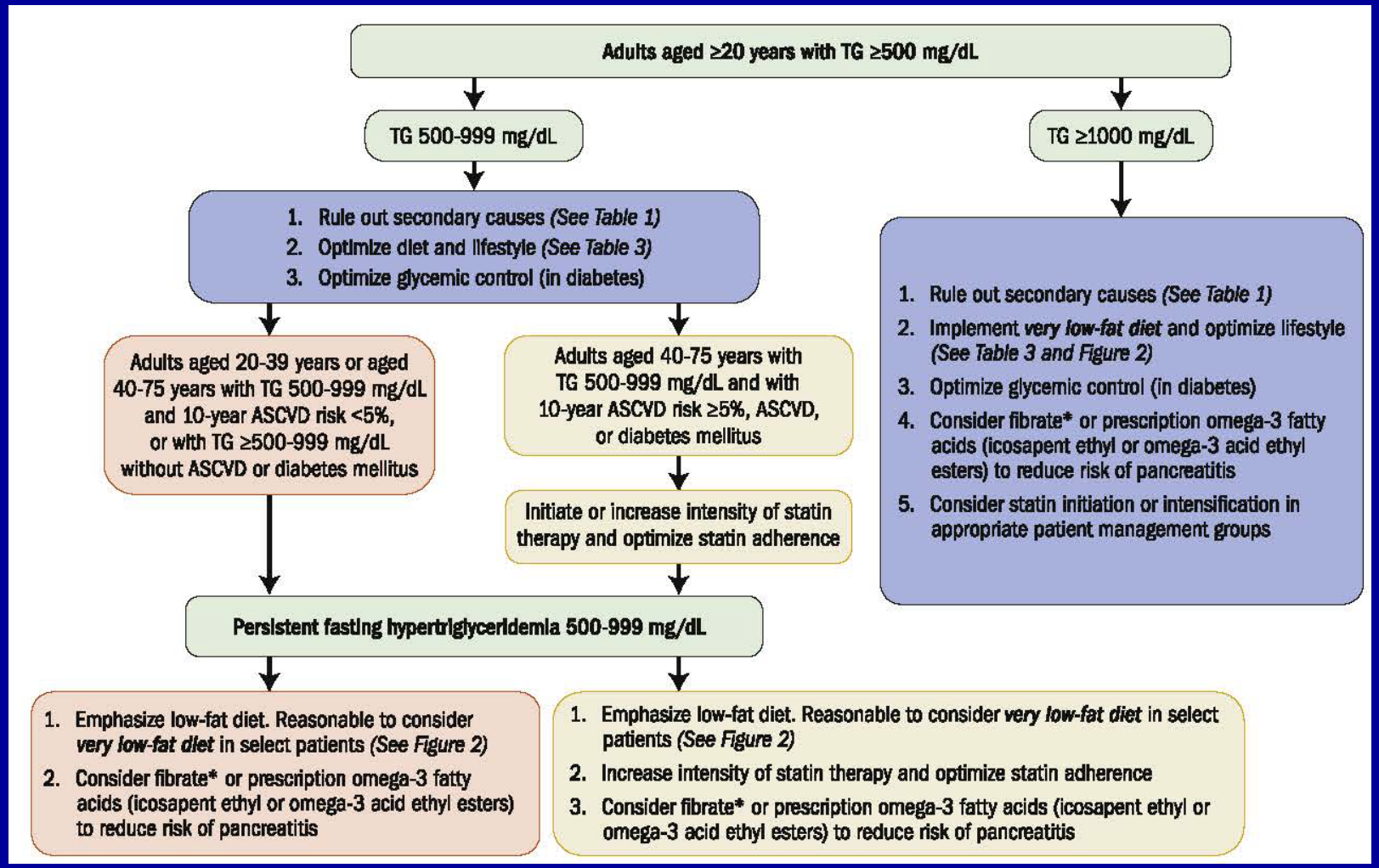
Financial Disclosure

- **Grant/Research Support:** Abbott Diagnostic, Akcea, Amgen, Arrowhead, Esperion, Ionis, Merck, New Amsterdam, Novartis, Novo Nordisk, Regeneron, Roche Diagnostic, NIH, AHA, ADA (all paid to institution, not individual)
- **Consultant:** 89Bio, Abbott Diagnostics, Alnylam Pharmaceuticals, Althera, Amarin, Amgen, Arrowhead, Astra Zeneca, Denka Seiken, Esperion, Genentech, Gilead, Illumina, Ionis, Matinas BioPharma Inc, Merck, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic

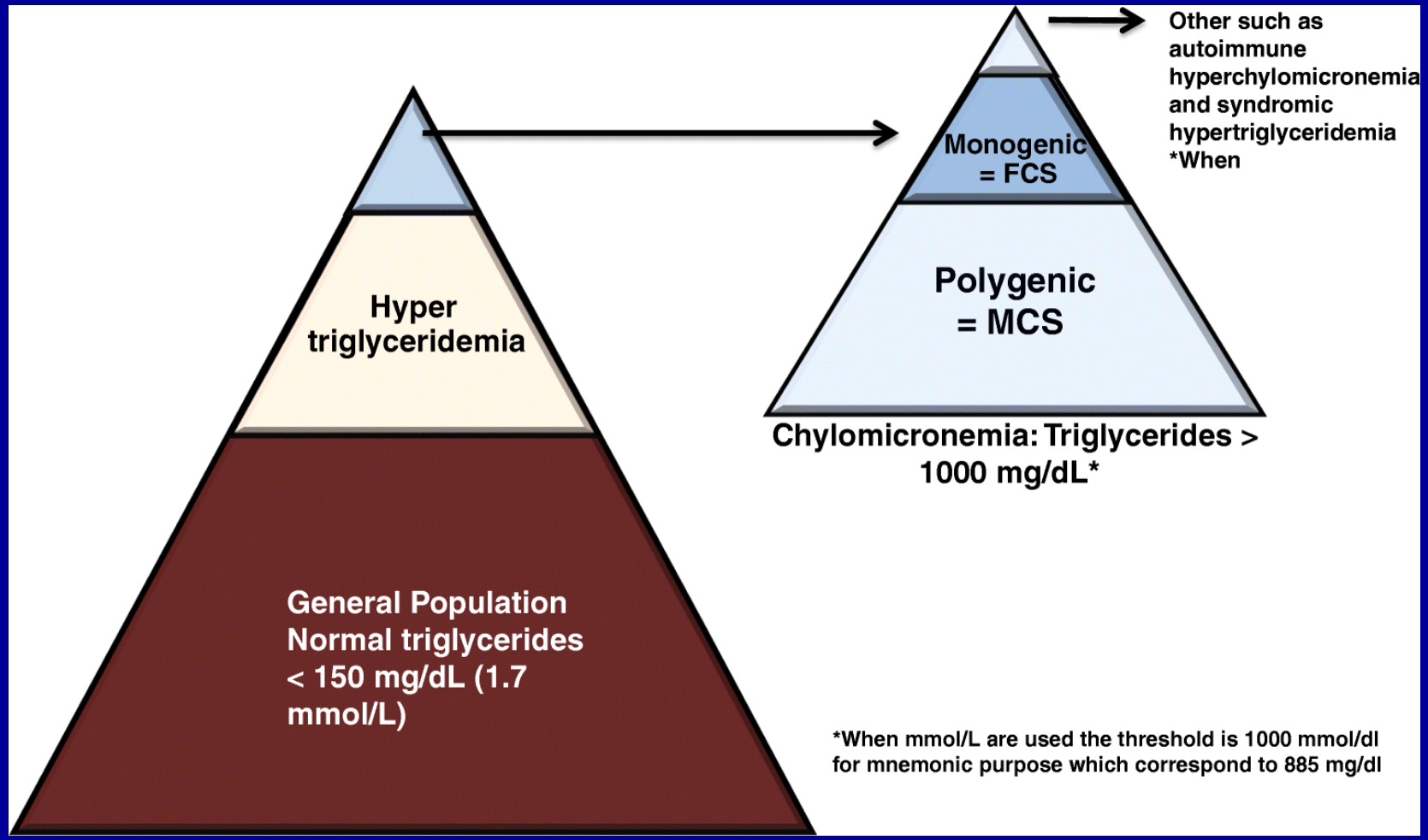
Severe Hypertriglyceridemia (TGs ≥500 mg/dL)



* Fenofibrate preferred

Virani SS et al. *J Am Coll Cardiol* 2021;78:960-993.

FCS and MCS (multi factorial chylomicronemia) among the spectrum of primary hypertriglyceridemia



Gallo A et al. *Curr Atheroscler Rep* 2020;22:63.

Genetic Factors Contribute to Elevated Levels of TG-Rich Lipoproteins

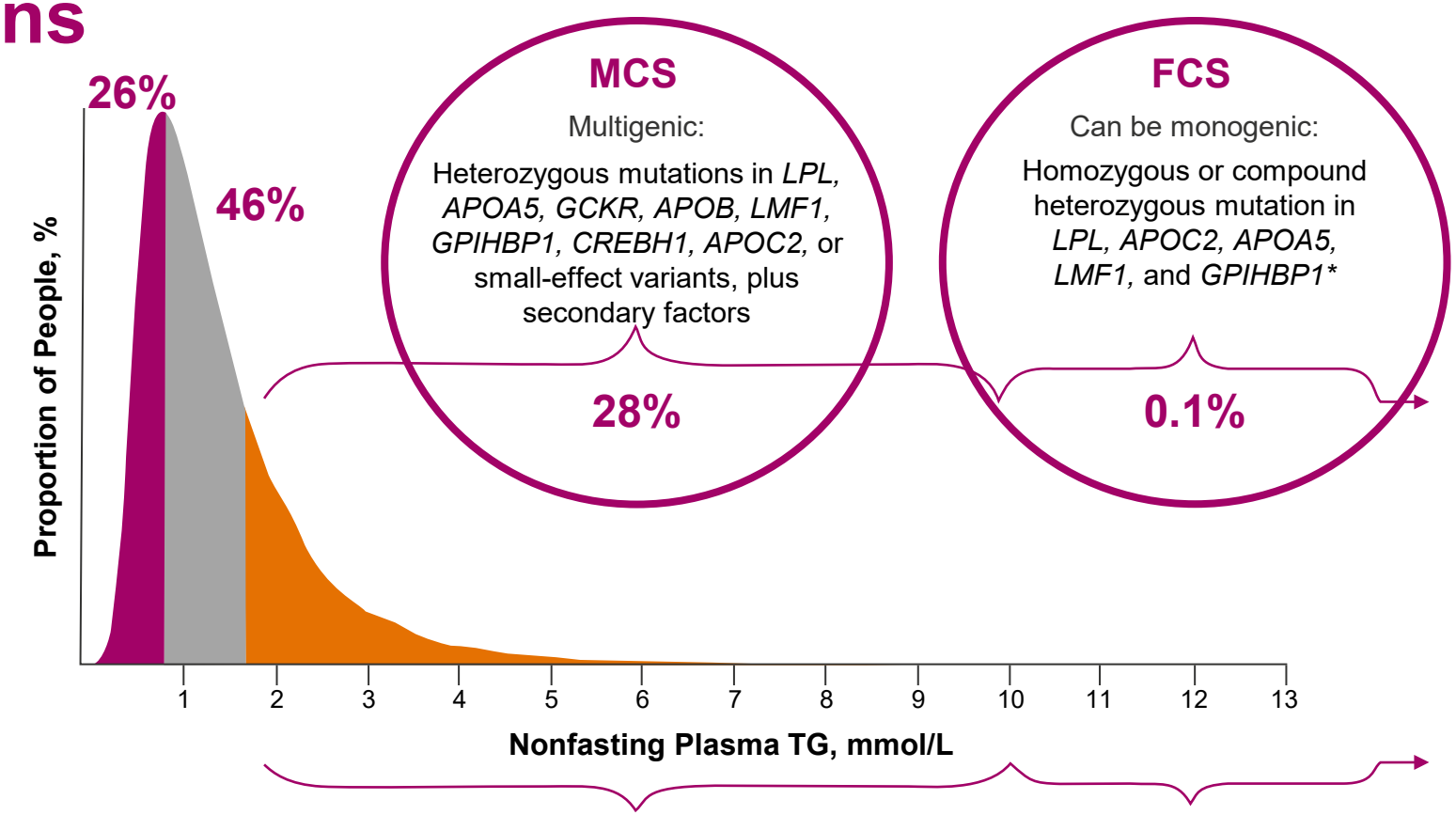
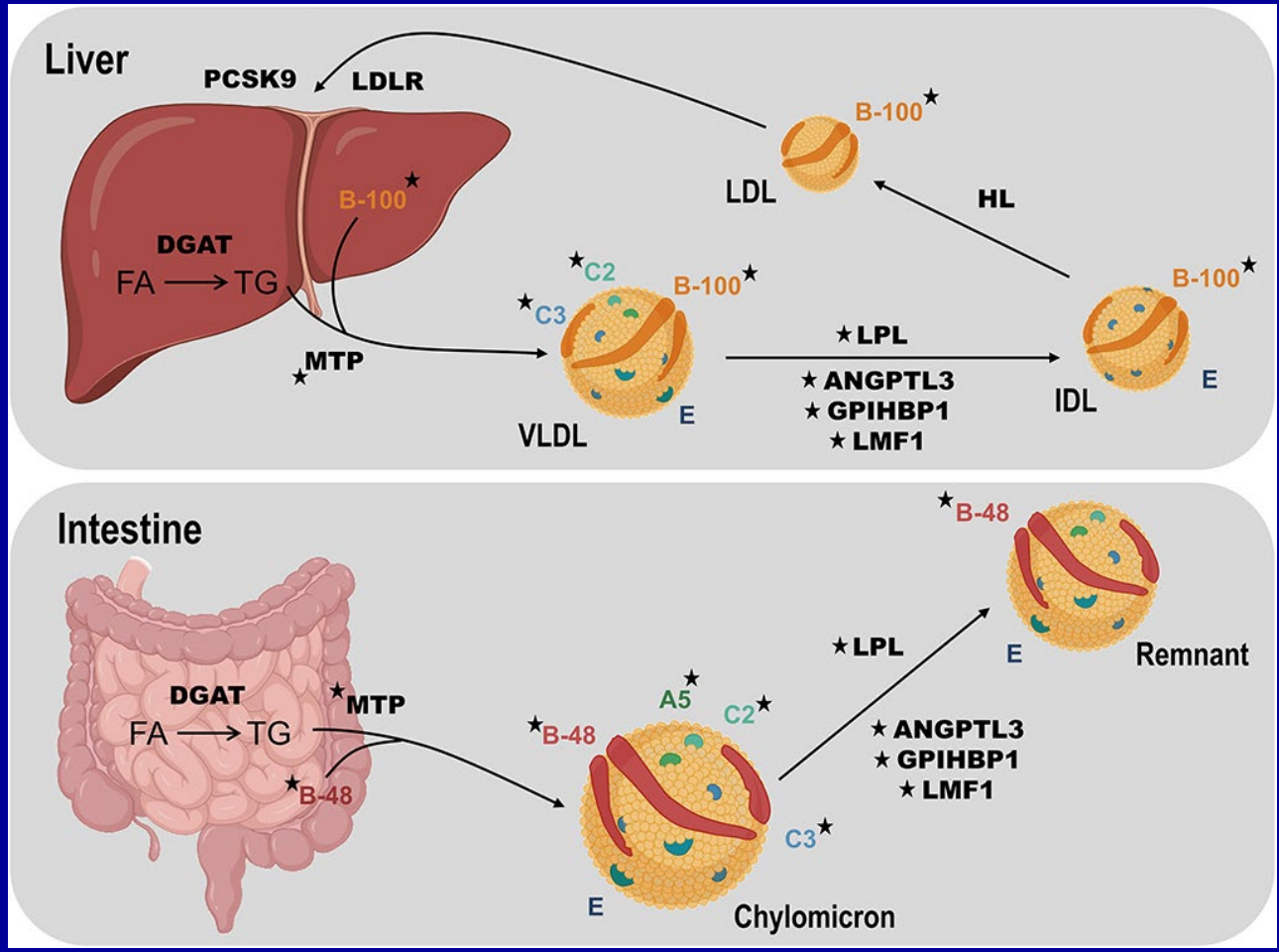


Figure adapted from: Hegele RA, et al. *Lancet Diabetes Endocrinol.* 2014;2:655-666.
1. Moulin P, et al. *Atherosclerosis.* 2018;275:265-272.

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.

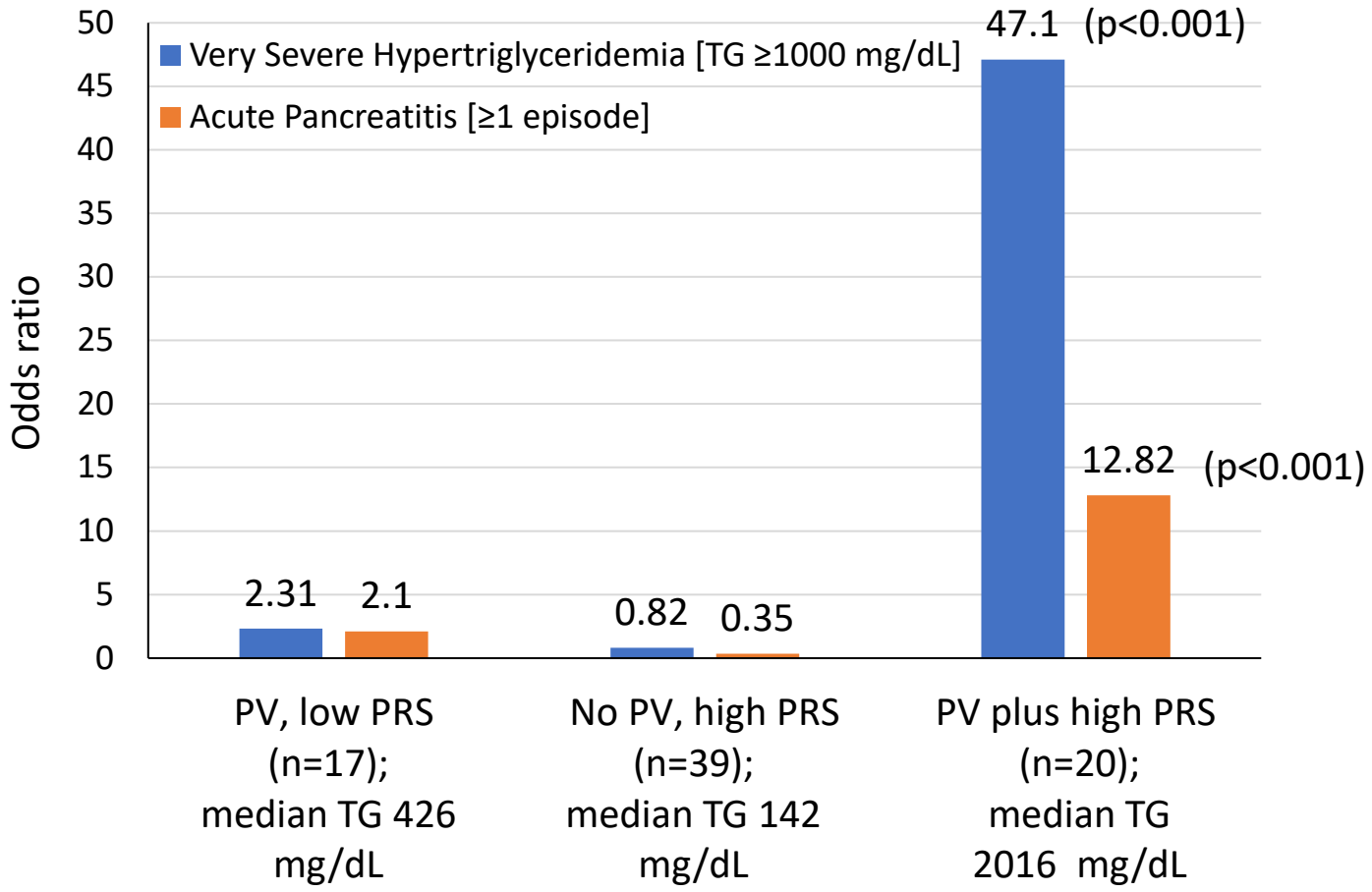
*Additional genes are likely to be identified in future, since in more than one-third of patients with a phenotype similar to FCS, no deleterious mutations in these genes can be identified.[1]

Overview of TG metabolism focusing on human disease genes



Dron JS, Hegele RA. *Front Endocrinol (Lausanne)* 2020;11:455.

Risk for severe HTG and acute pancreatitis in patients with heterozygous pathogenic variant, high polygenic risk score, or both compared with patients with neither genetic risk factor



PRS ≥90th percentile in the general population categorized as high;
PRS <90th percentile categorized as low

Model adjusted for age, sex, race, BMI, DM

Odds ratio compared with reference category with no PV, low PRS (n=287); median TG 192 (116, 337) mg/dL

PRS = polygenic risk score
PV = pathogenic variant

Deshotels MR et al. *ATVB* in press.

Differentiating sHTG Subtypes[1-4]

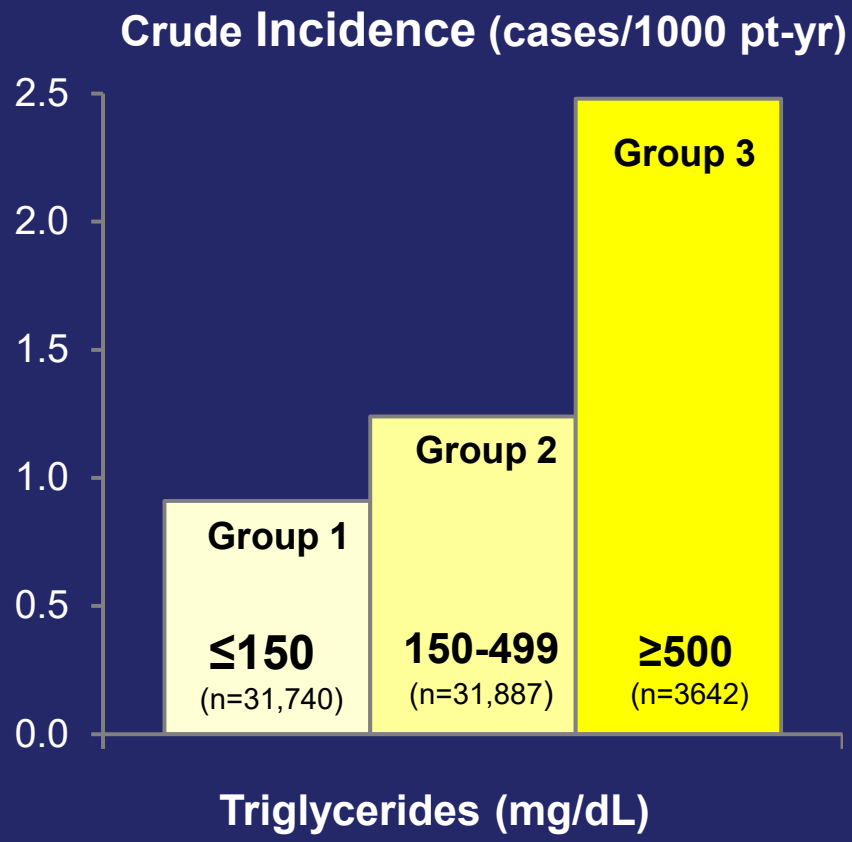
	Familial Chylomicronemia Syndrome	Multifactorial Chylomicronemia
Population frequency	1–10:1,000,000	1:600 to 1:250
TG, mg/dL (mmol/L)	≥885 (≥10)	≥885 (≥10)
Primarily disturbed lipoprotein fractions	Elevations of chylomicrons	Elevations of chylomicrons and remnants Elevations of VLDL and IDL
Genetic basis	Monogenic	Polygenic
Relevant genetic determinants	Causative bi-allelic 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.

Increasing TG Levels Increase Risk of Pancreatitis

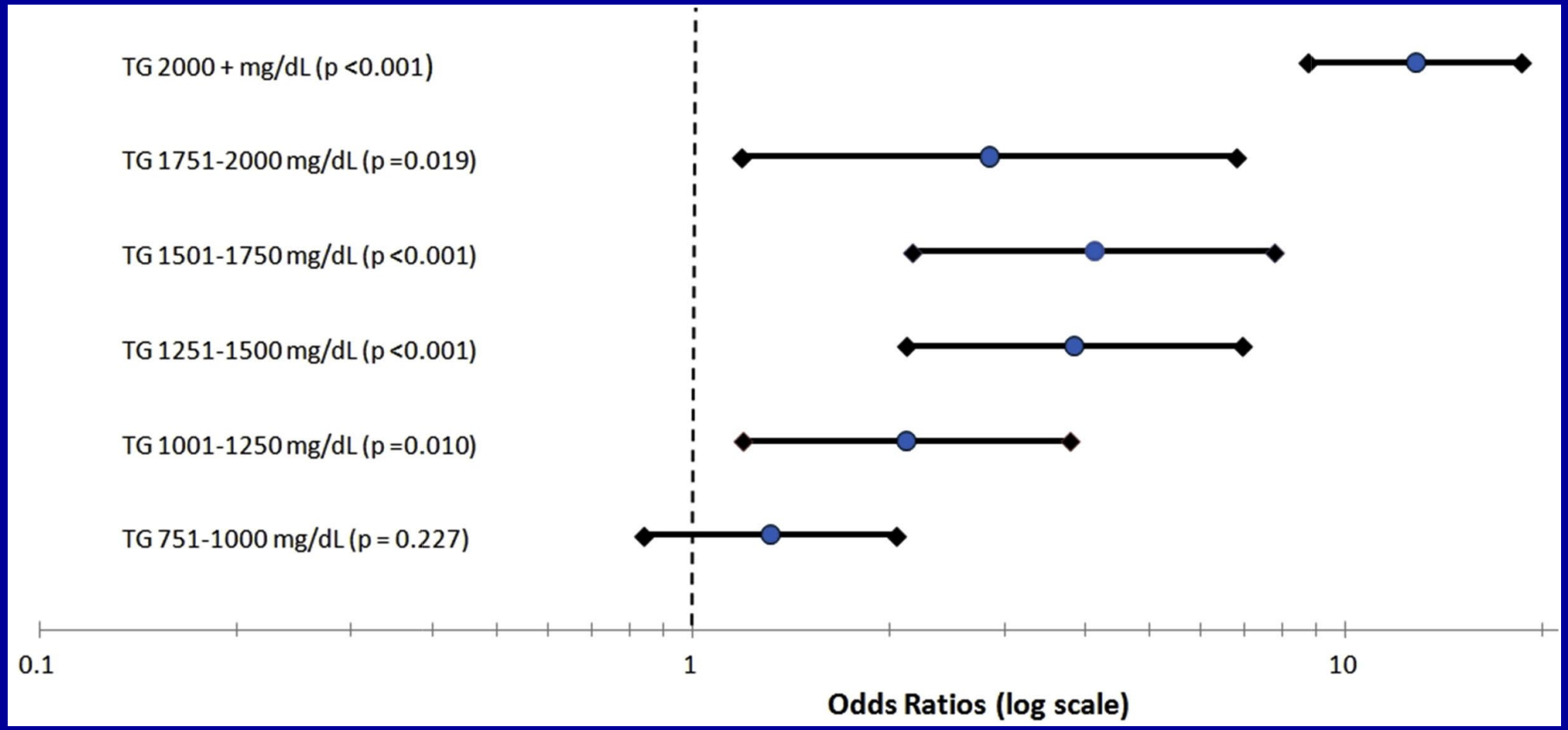
- Dose-response of TG vs pancreatitis (adjusted HR, 1.04 [95% CI, 1.02-1.05])
- Pancreatitis increases 4% for every 100 mg/dL increase in TG above 500 mg/dL*



*After adjustment for covariates and removal of patients hospitalized for gallstones, chronic pancreatitis, alcohol-related morbidities, renal failure, and other biliary disease

Murphy MJ et al. *JAMA Intern Med*. 2013;173:162-4.

Association between baseline TG level and risk of acute pancreatitis over 12-month follow-up in 26,896 US adults with TG >500 mg/dL

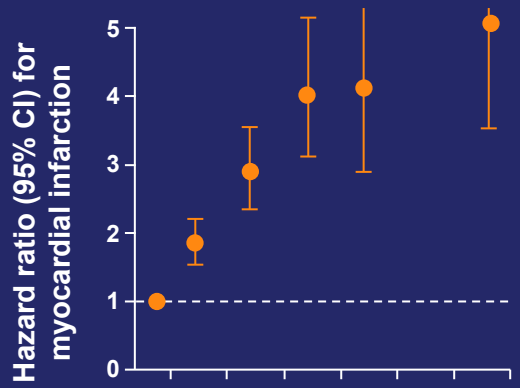


Toth PP et al. *Atherosclerosis* 2014;237:790-797.

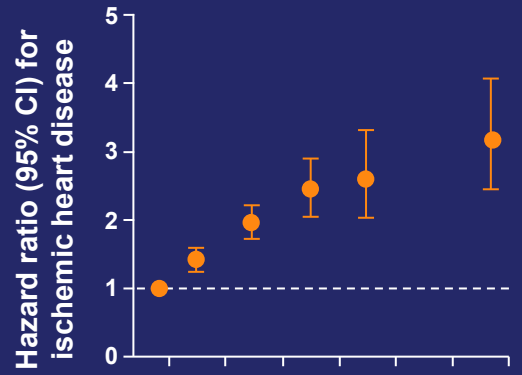
Increasing TG Levels Increases CVD and All-cause Mortality

Copenhagen City Heart Study and Copenhagen General Population Study

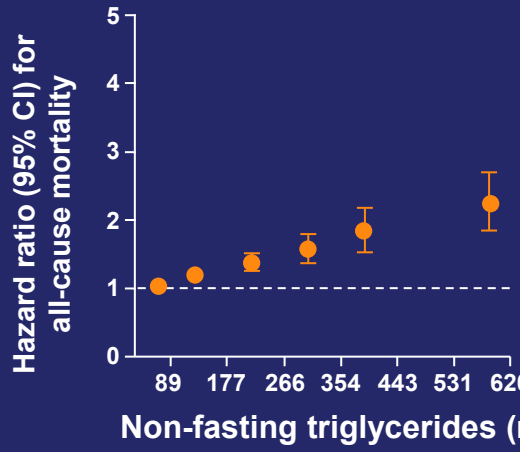
Myocardial Infarction
N=96,394 (events=3287); Median follow-up 6 years



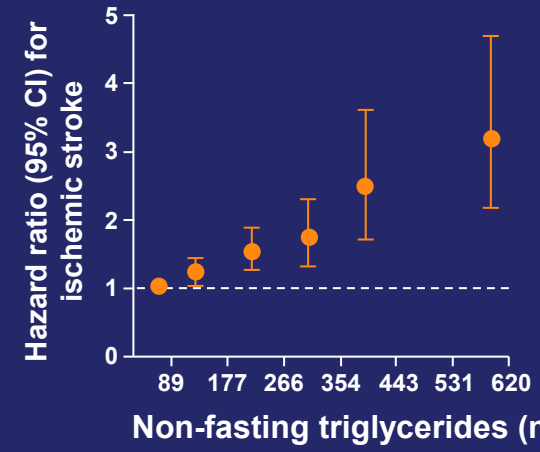
Ischemic heart disease
N=93,410 (events=7183); Median follow-up 6 years



All-cause mortality
N=98,515 (events=14,547); Median follow-up 6 years



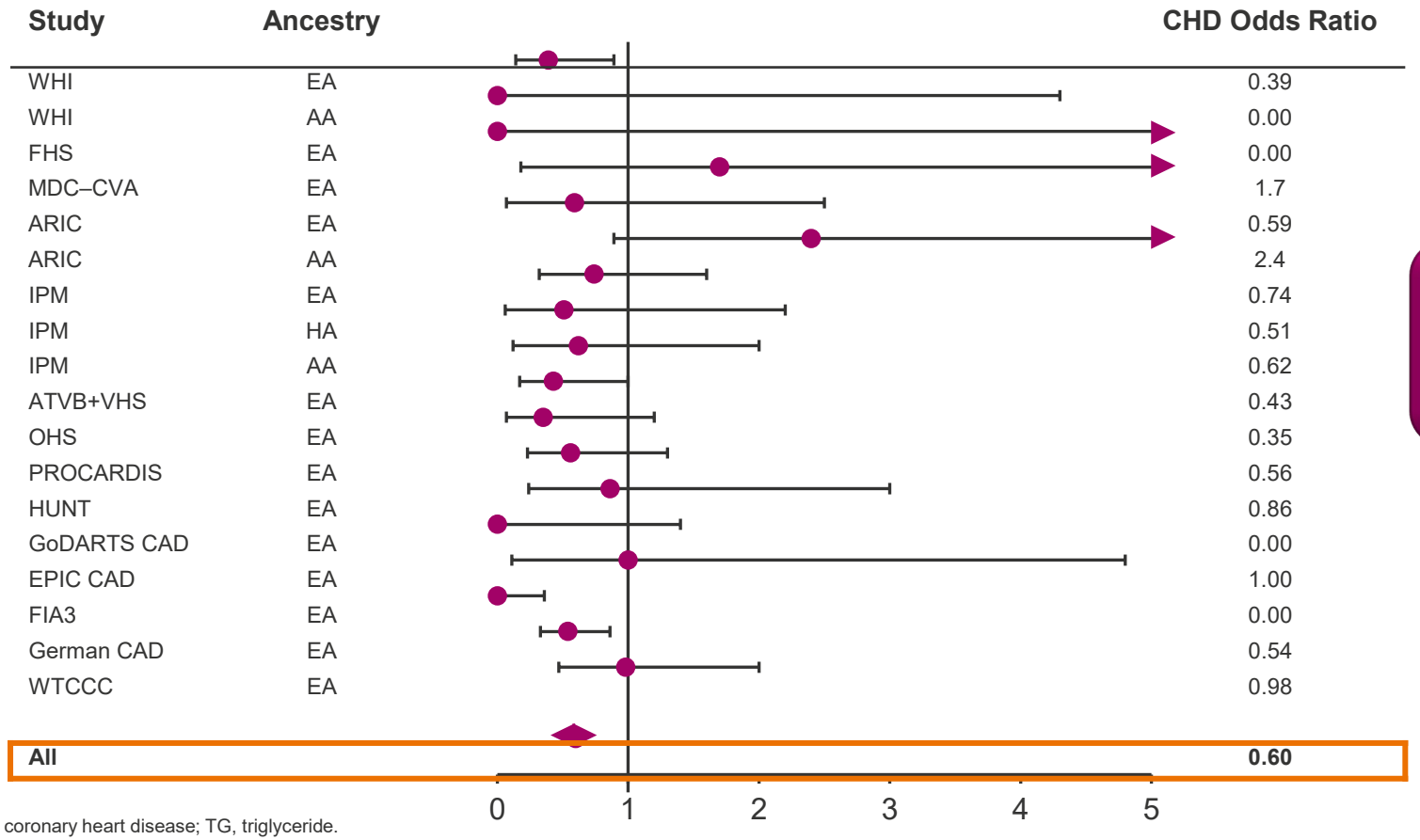
Ischemic stroke
N=97,442 (events=2994); Median follow-up 6 years



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.

Loss of function of apoC-III is cardioprotective

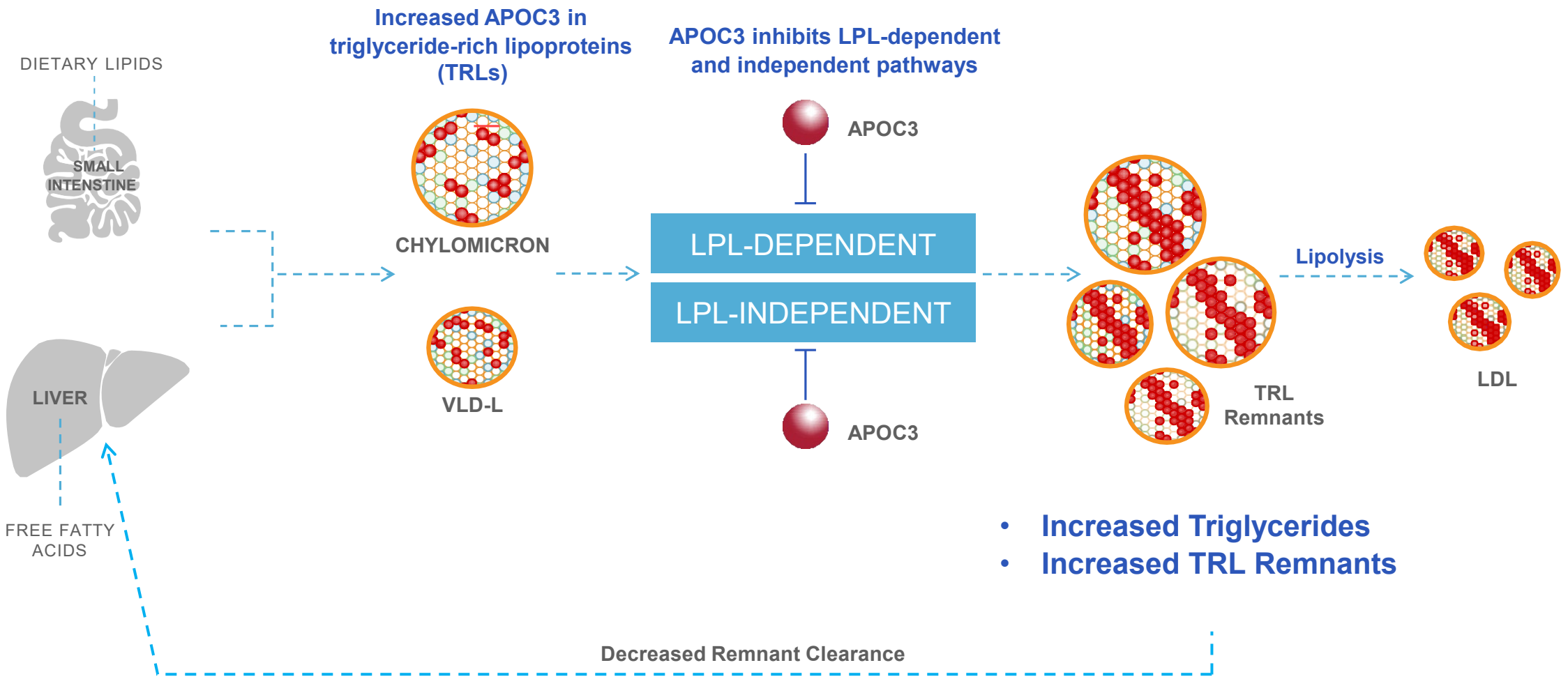
Odds Ratio for CHD of Subjects With Any of 4 ApoC-III Loss-of-Function Mutations Among 110,970 Participants (34,002 patients with CHD; 76,968 controls) in 14 Studies



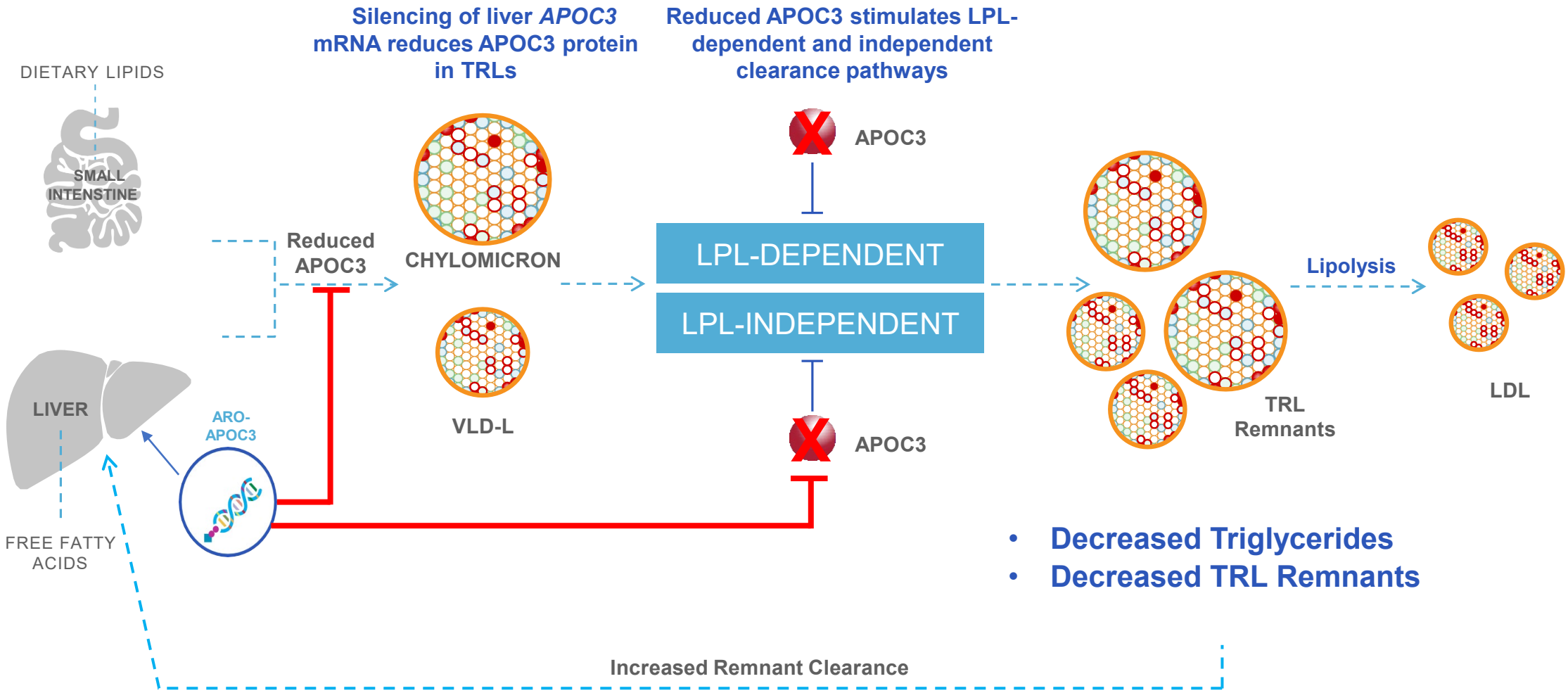
Loss-of-function mutations reduced TG levels by 39%

ApoC-III, apolipoprotein C-III; CHD, coronary heart disease; TG, triglyceride.
Full study names: ARIC, Atherosclerosis Risk in Communities; ATVB, Italian Atherosclerosis, Thrombosis, and Vascular Biology Study; EPIC, European Prospective Study Into Cancer and Nutrition; FHS, Framingham Heart Study; FIA3, First Myocardial Infarction in AC County 3; GoDARTS, Genetics of Diabetes Audit and Research Tayside Study; HUNT, Nord–Trøndelag Health Study; IPM, Mt. Sinai Institute for Personalized Medicine Biobank; MDC–CVA, Malmö Diet and Cancer Study Cardiovascular Cohort; OHS, Ottawa Heart Study; PROCARDIS, Precocious Coronary Artery Disease Study; VHS, Verona Heart Study; WHI, Women's Health Initiative; WTCCC, Wellcome Trust Case Control Consortium.
The TG and HDL Working Group of the Exome Sequencing Project, NHLBI. *N Engl J Med.* 2014;371:22-31.

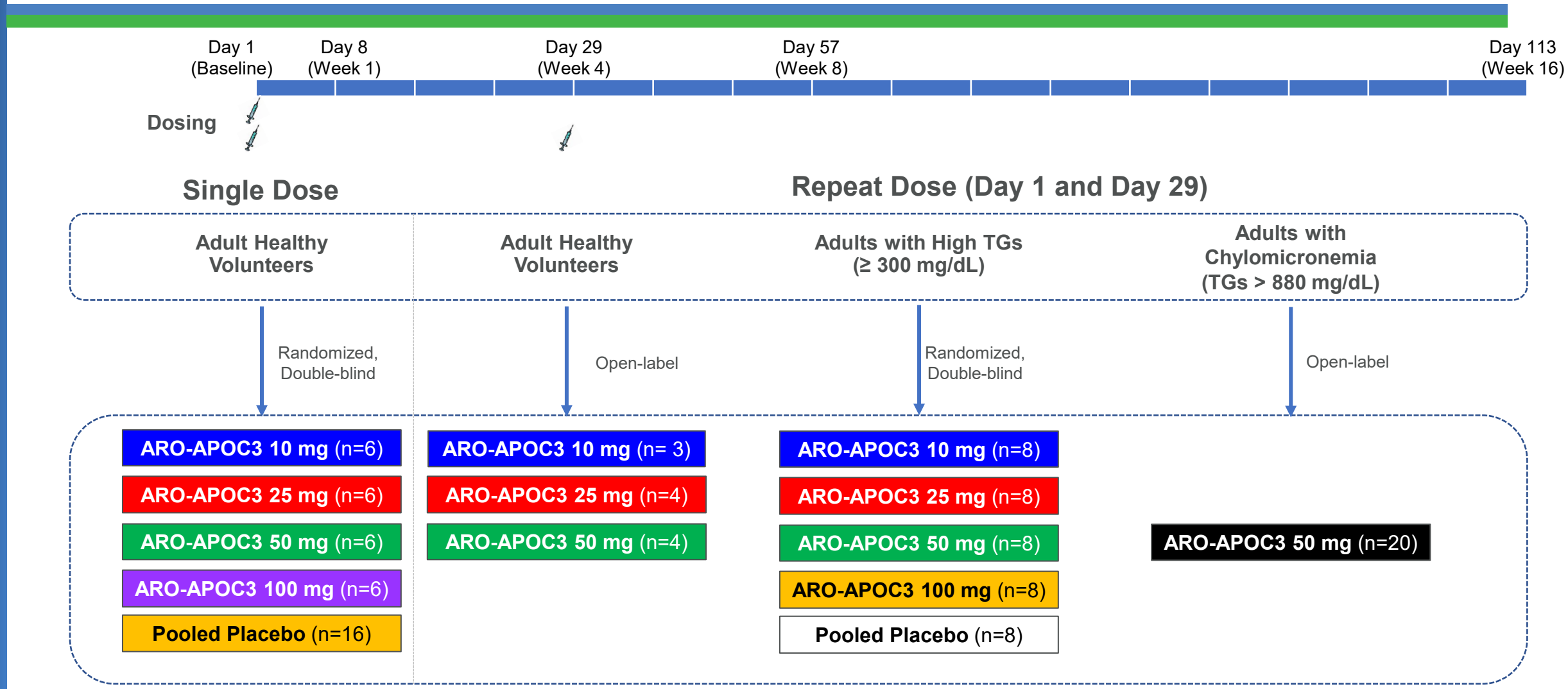
APOC3 Is a Key Regulator of Triglycerides and TRLs Through Inhibition of Lipoprotein Lipase-Dependent and Independent Pathways



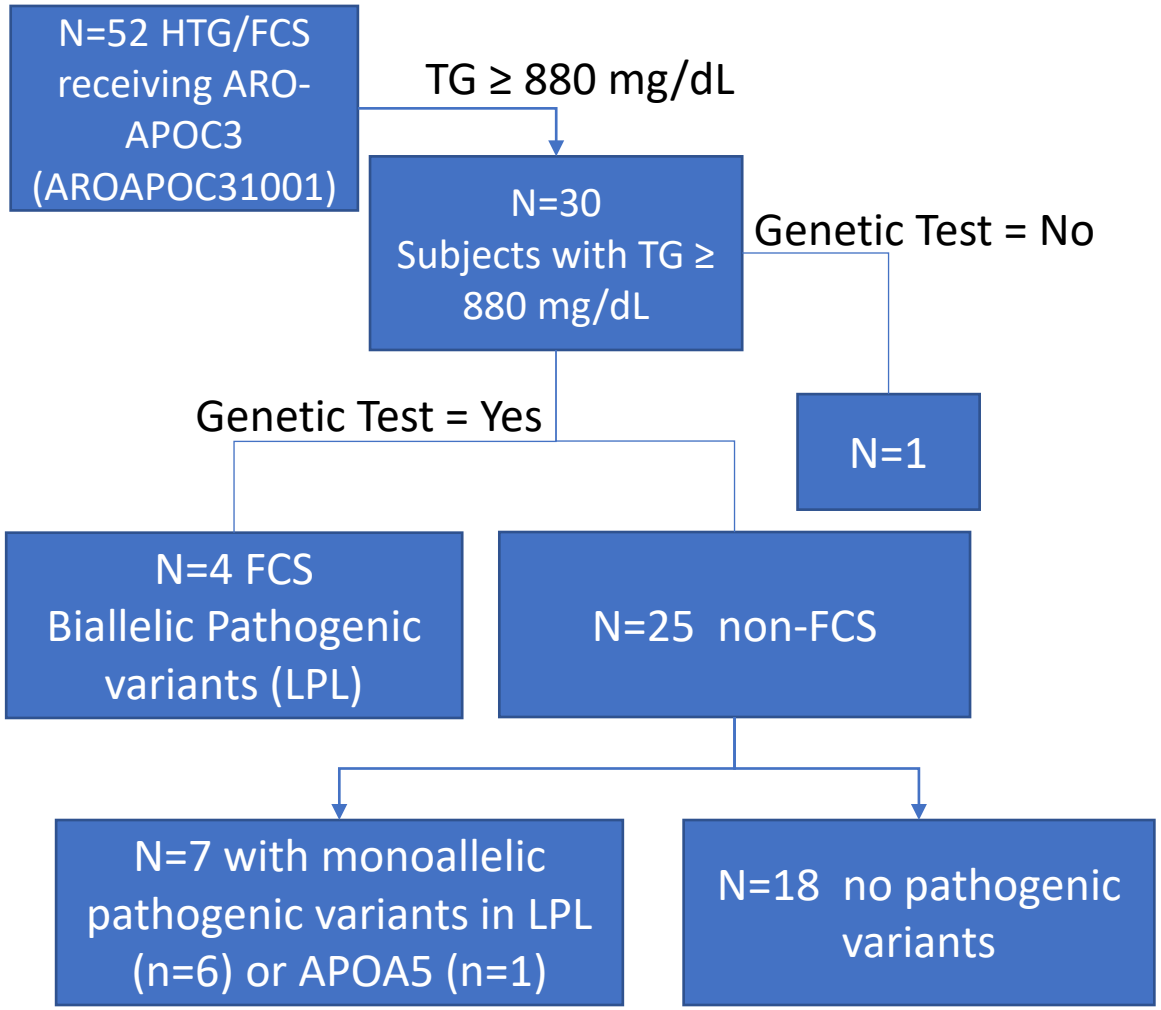
Increased APOC3 Levels Result in Inhibition of Lipoprotein Lipase-Dependent and Independent Pathways Leading to Increased Triglycerides and TRL Remnants



AROAPOC31001 First-in-Human Study Design



Participant Disposition and Baseline Characteristics



Parameter (SD)	FCS n=4	Non-FCS n=25
Age (years)	44.0 (13.5)	46.8 (13.2)
Male (%)	50	60
White (%)	75	76
Asian (%)	25	16
BMI (kg/m^2)**	22.1 (0.8)	30.7 (4.6)
APOC3 (mg/dL)	48.1 (18.0)	47.3 (22.6)
TG (mg/dL)	1650 (1387, 4791)*	1381 (324-5577)*
HDL-C** (mg/dL)	12.5 (1.0)	22.1 (7.6)
Non-HDL-C (mg/dL)	319 (178)	338 (209)

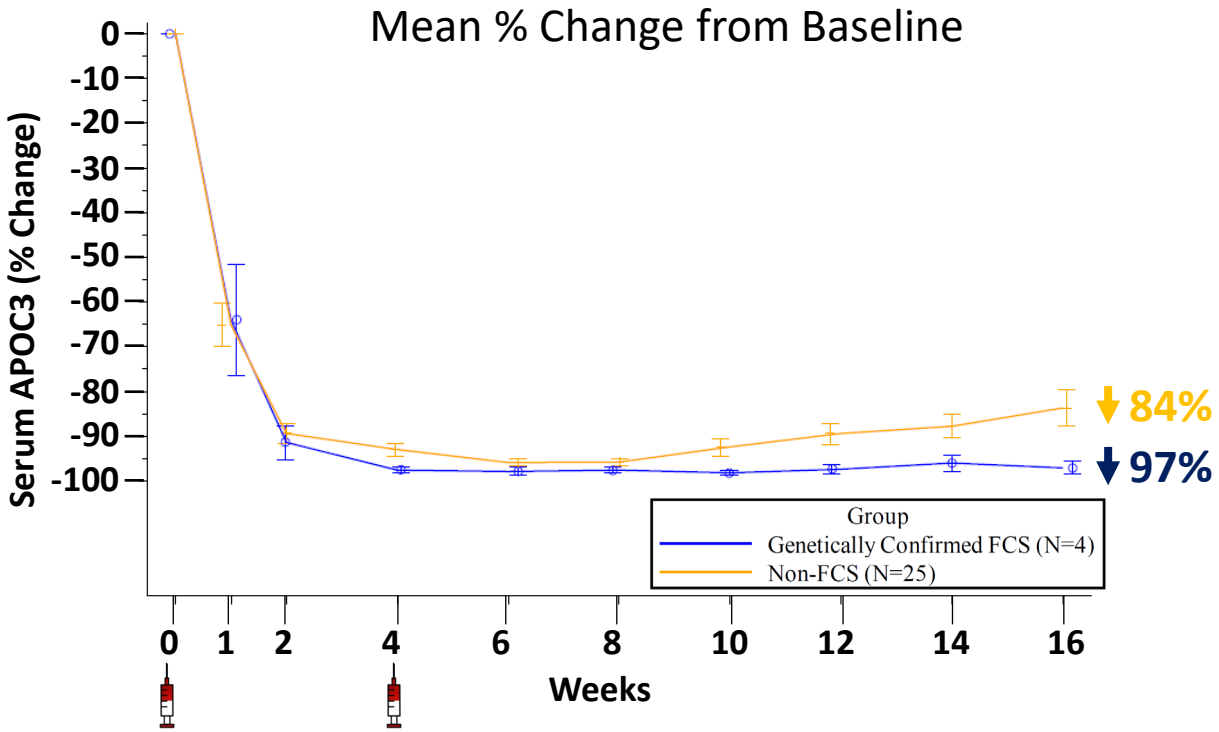
* TG values reported as median (min, max)

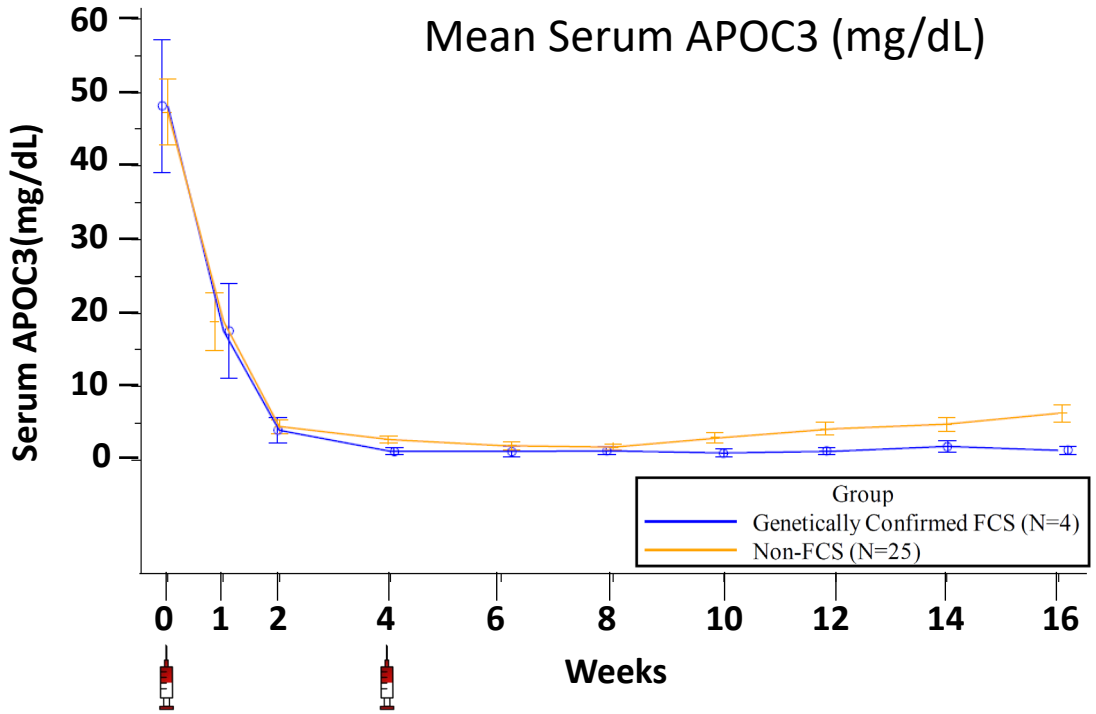
** p<0.001

Clinical Cutoff = 29 Mar 2021 (DBL)

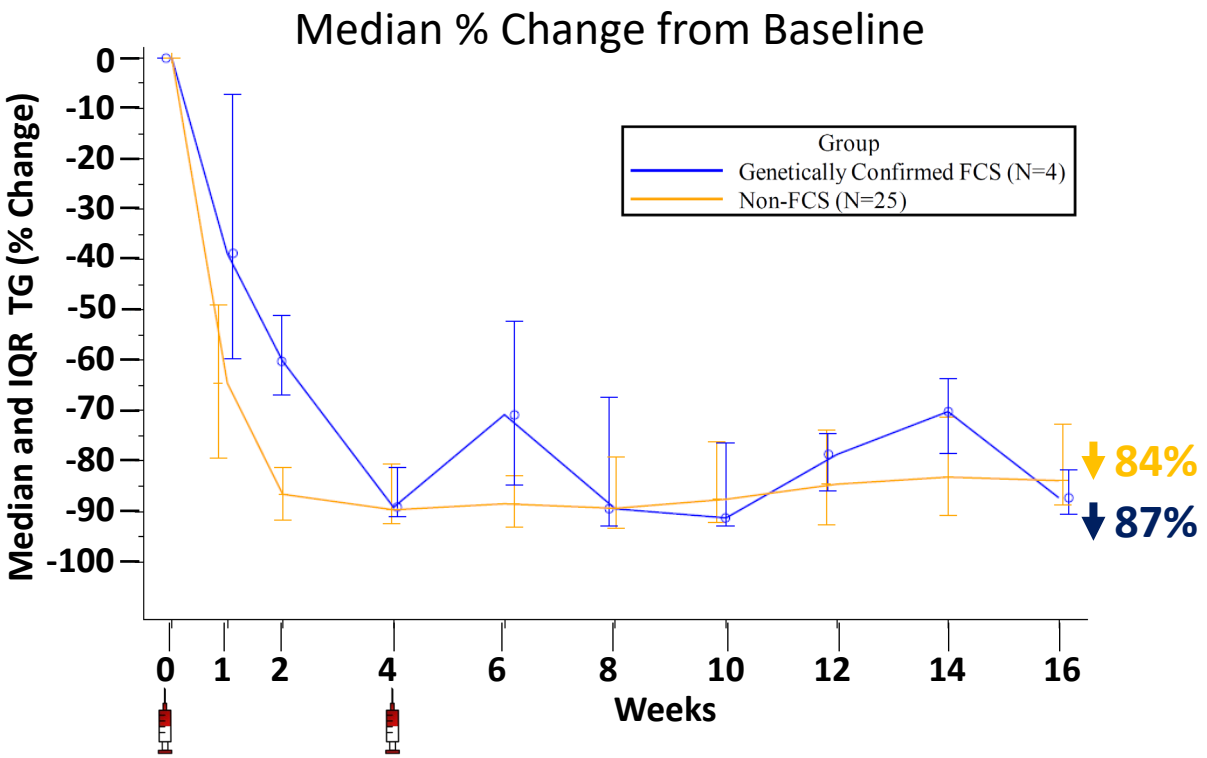
Given similar pharmacodynamic activity, all ARO-APOC3 doses were pooled in non-FCS group

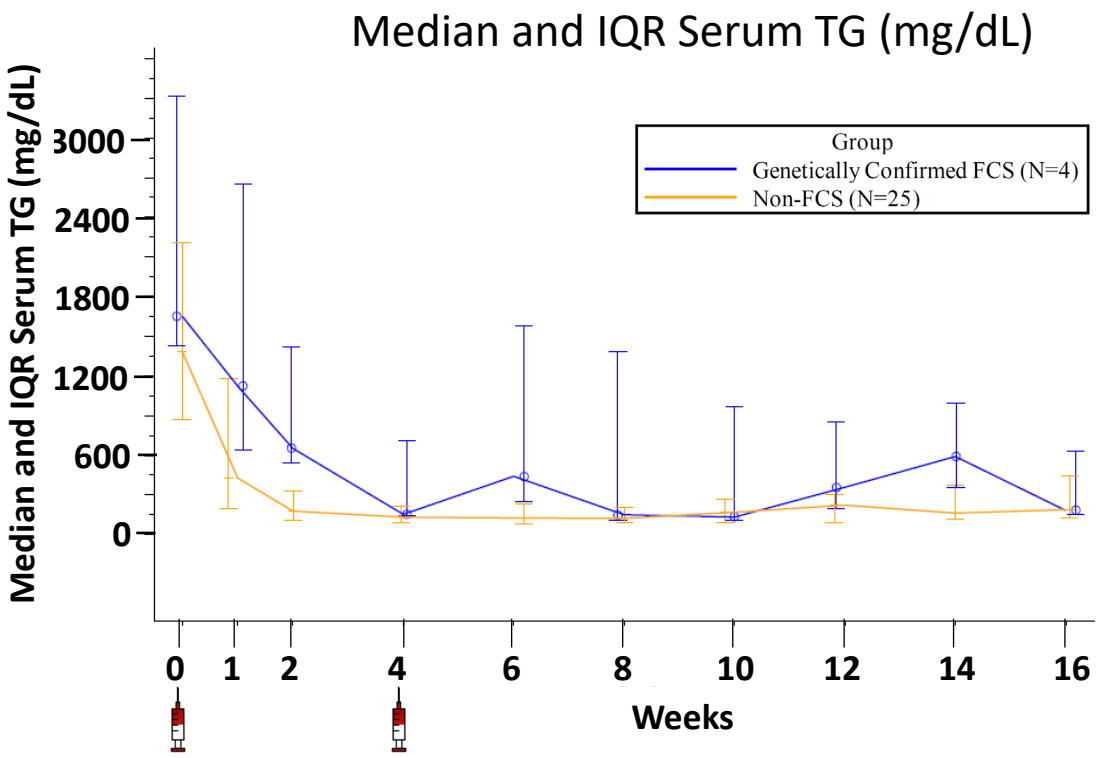
ARO-APOC3 results in similar, sustained reduction in baseline serum APOC3 in FCS and non-FCS participants





ARO-APOC3 results in similar sustained reduction of triglycerides in FCS and non-FCS participants





Summary

- In patients with FCS compared with non-FCS, ARO-APOC3 SC achieves similar levels of reduction of APOC3 and changes in key lipid parameters
- In patients with FCS compared with non-FCS, safety parameters were similar and comparable
- In patients with severe HTG (TG>880 mg/dL), ARO-APOC3 was well tolerated, and consistently decreased APOC3, TG, and non-HDL-C, and increased HDL-C, independent of underlying genetic cause of HTG.
- ARO-APOC3 may represent a promising RNAi therapeutic for the treatment of severe HTG with infrequent dosing (Q3M or greater)

Cardiometabolic/ Lipid Treatment Landscape and Residual Risk

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Marie-Josee and Henry R. Kravis Center for Cardiovascular Health,
Mount Sinai Icahn School of Medicine, New York, New York, USA

ASCVD Residual Risk Associated With TRLs

Robert S. Rosenson, M.D.

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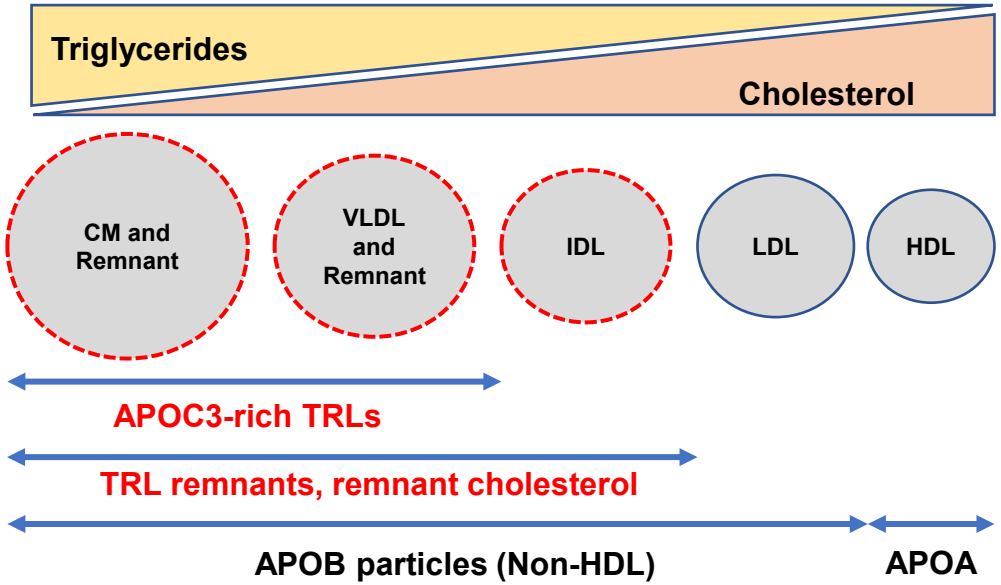
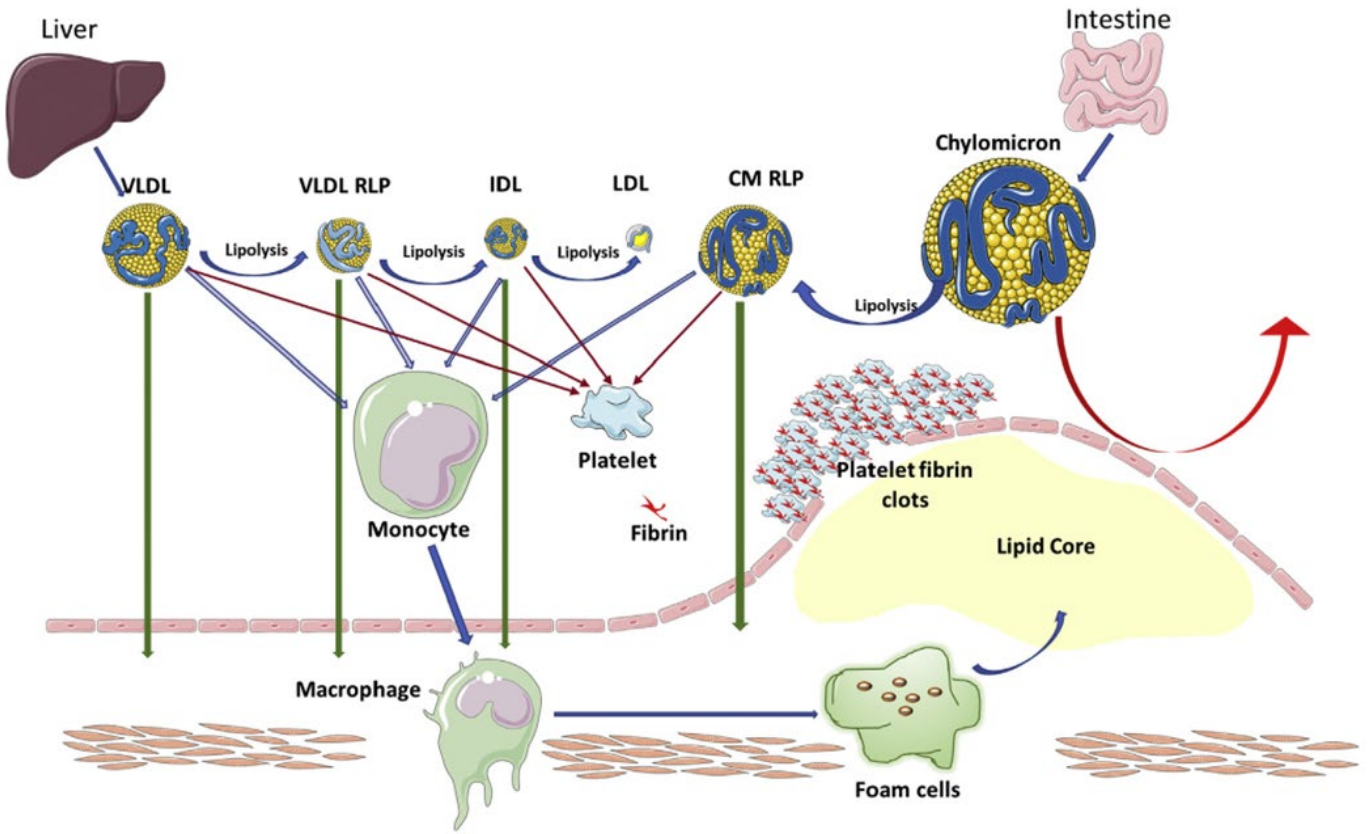
Dyslipidemia is a major risk factor for cardiovascular disease

- ASCVD is the leading cause of mortality worldwide [1]
- Low-density lipoprotein cholesterol (LDL-C) is the primary lipid target to prevent ASCVD (e.g., statins and PCSK9 inhibitors) [2,3,4,5]
- Approximately 20%-25% of patients with ASCVD may have elevated Triglycerides (TGs) and controlled LDL-C [6,7]
- Despite adequate LDL-C control, considerable residual cardiovascular risk remains partly due to increases in circulating levels of: [8,9,10,11]
  - TG-rich lipoprotein (TRL) remnants and associated cholesterol
  - Discordantly high Apolipoprotein B (ApoB) relative to LDL-C or non-HDL-C
  - Apolipoprotein C3 (APOC3)



[1]World Health Organization Cardiovascular diseases (who.int) Accessed May 2022; [2]AHA/ACC. J Am Coll Cardiol 2019;73:e285-350; [3]ACC Expert Consensus. JACC 2021;78:960-93; [4]ESC/EAS. Eur Heart J 2020;41:111-88; [5]Japan Atherosclerosis Society. J Atheroscler Thromb 2018;25:846-984; [6]Lawler PR. Eur Heart J 2020;41:86-94; [7]Fan W. Diabetes Care 2019;42:2307-14 [8]Jorgensen AB. N Engl J Med 2014;371:32-41; [9]Parhofer KG. E Heart J Supplements 2020;22:Suppl J:J21-33; [10]Langsted A. J Intern Med 2020;288:116-27; [11]Kim CW. Circ J 2021;85:900-907.

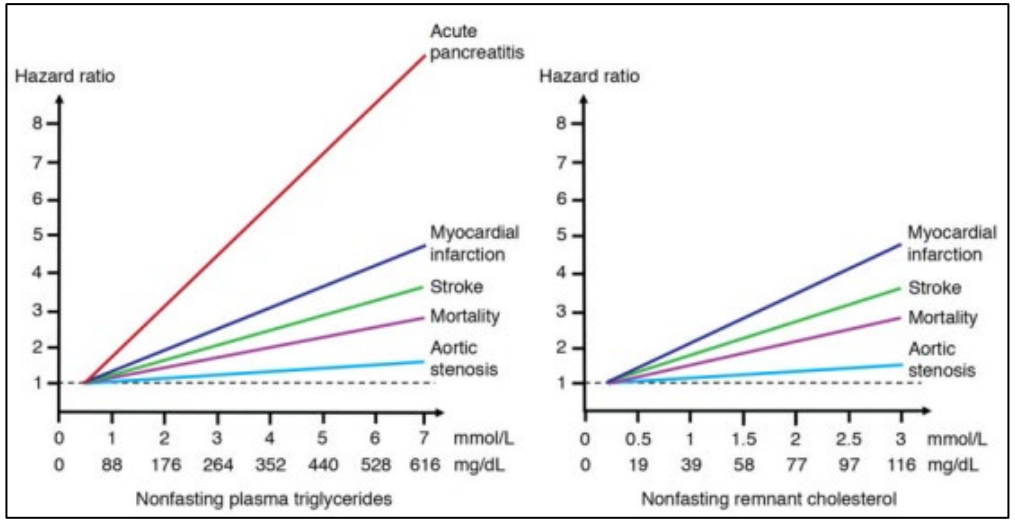
TRL Remnants Increase Atherogenicity

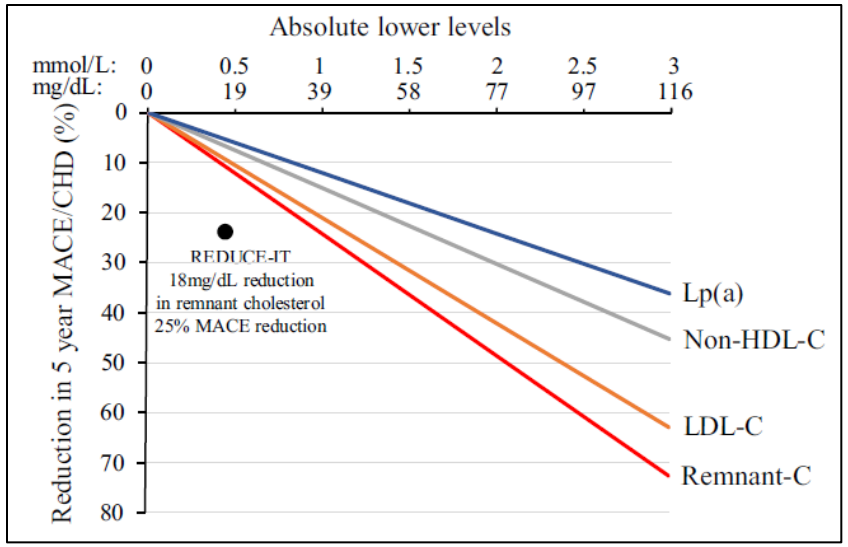


- Multiple pathways of TRL atherogenicity:
  - Receptor binding and uptake by macrophages results in Foam Cells in atherosclerotic lesions
  - Activation of inflammation
  - Facilitate thrombosis

Rosenson RS, Shaik A, Song W. New Therapies for Lowering Triglyceride-Rich Lipoproteins: JACC Focus Seminar 3/4. J Am Coll Cardiol. 2021 Nov 2;78(18):1817-1830.

TRLs in ASCVD: Epidemiologic Evidence



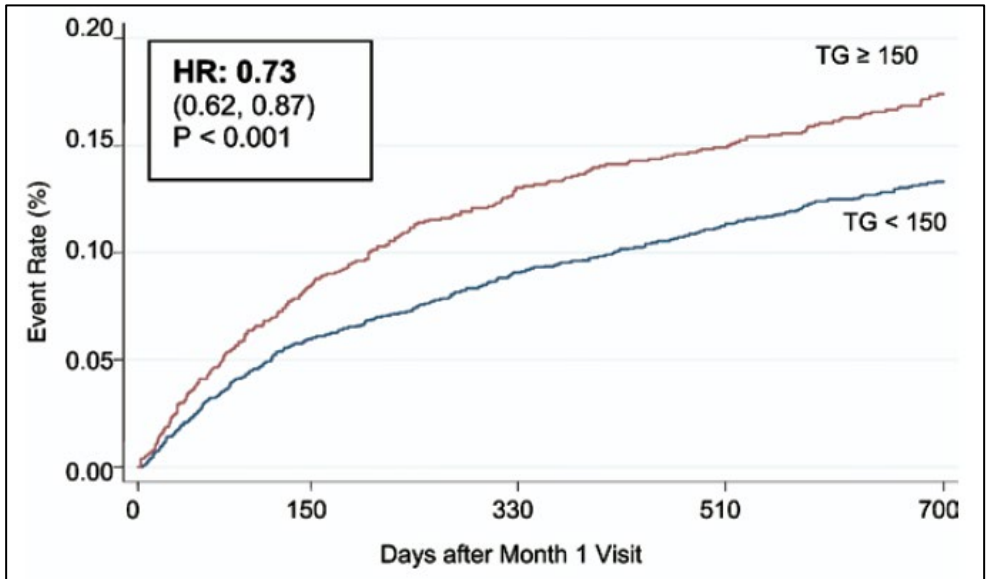


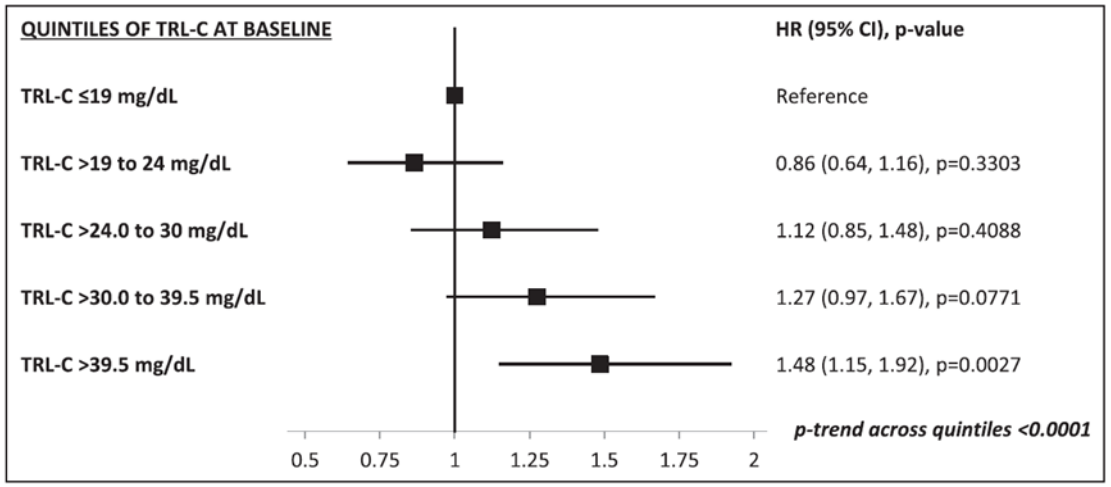
- Increased TG and remnant cholesterol are associated with increased risk of ASCVD events[1]

- A lower remnant cholesterol of 30mg/dL is associated with a 20% decreased risk of recurrent MACE[2]

Copenhagen General Population Study and Copenhagen City Heart Study.
1 Parhofer KG. E Heart J Supplements 2020;22
2 Langsted A. J Intern Med 2020;288:116-27

TRLs in ASCVD: Evidence from Clinical Trials





- Lower TGs are associated with reduced risk of CHD in statin-treated patients[1]
- Higher TRL-C (remnant-C) is associated with higher 5-year MACE rates in statin-treated patients[2]

1 Prove IT-TIMI 22 Trial. Miller M. JACC 2008;51:724-30
2 TNT Trial. Vallejo-Vaz AJ et al. Circulation 2018;138:770-81

Genetic Evidence for ANGPTL3 as a Target in ASCVD

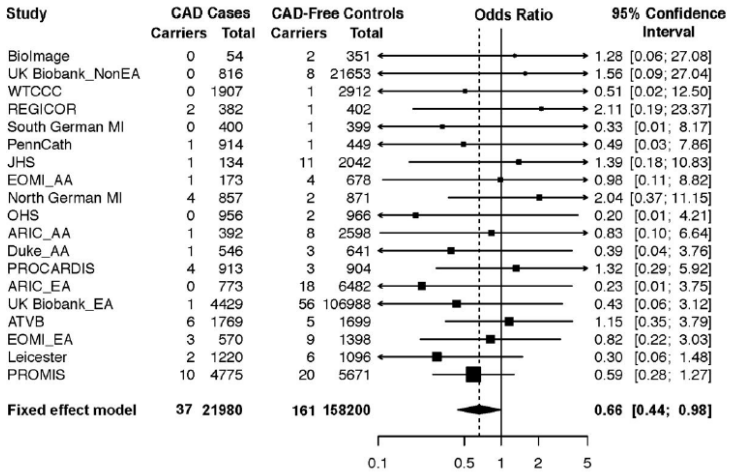


Table 1. Associations between *ANGPTL3* Predicted Loss-of-Function Variants and Lipid Levels in DiscovEHR Study Participants.*

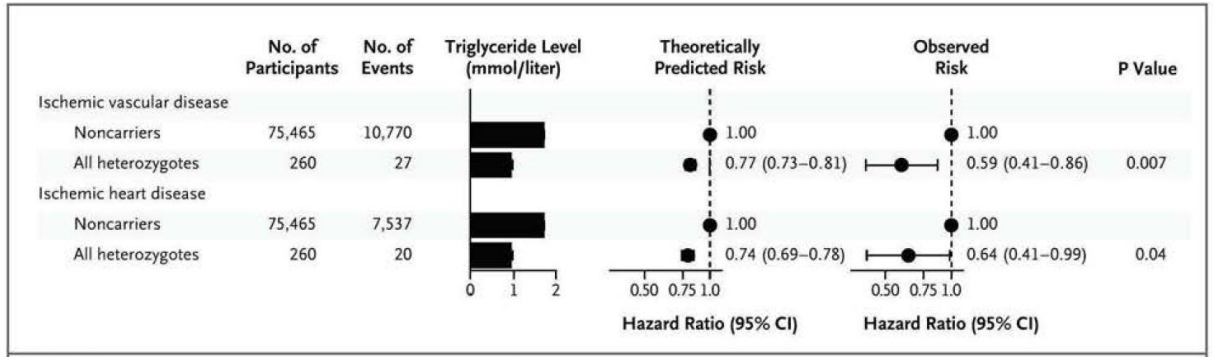
Trait	Noncarriers		Carriers of *ANGPTL3* Loss-of-Function Variants		P Value†
	No. of Participants	Median Level (IQR)	No. of Participants	Median Level (IQR)	
		mg/dl		*mg/dl*	
Triglycerides	45,015	130 (94–179)	191	94 (75–125)	2.5×10^{-21}
HDL cholesterol	45,036	49 (40–59)	190	46 (38–56)	0.02
LDL cholesterol	44,629	121 (100–146)	190	112 (90–136)	2.8×10^{-5}
Total cholesterol	44,877	204 (179–232)	191	179 (160–203)	1.7×10^{-17}

- Heterozygous ANGPTL3 LOF carriers had 17% lower TG levels and a 34% lower odds of coronary artery disease[1]

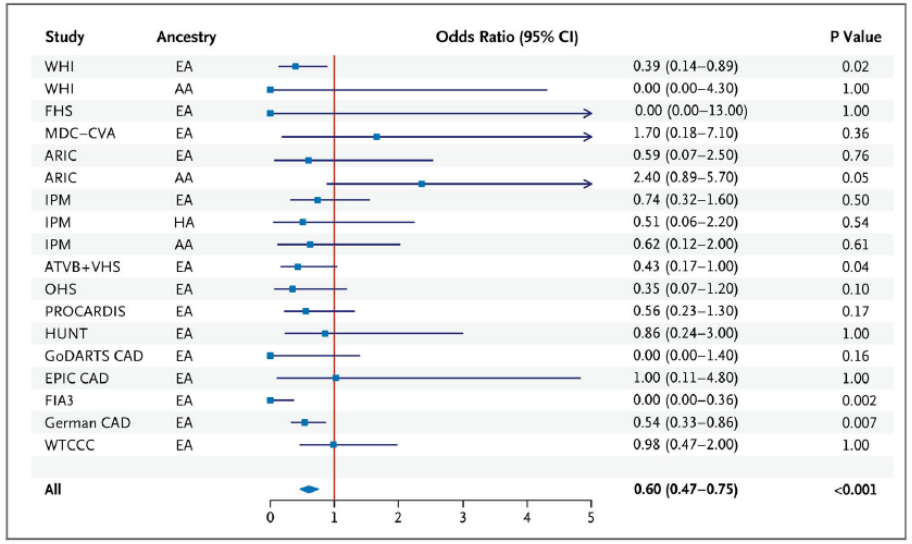
- Heterozygous ANGPTL3 LOF carriers had 27% lower TG levels and a 41% lower odds of coronary artery disease[2]

1 Stitziel NO. J Am Coll Cardiol 2017;69:2054-2063.
2 DiscovEHR Study. Dewey, FE. N Engl J Med 2017;377:211-21

Genetic Evidence for APOC-III as a Target in ASCVD



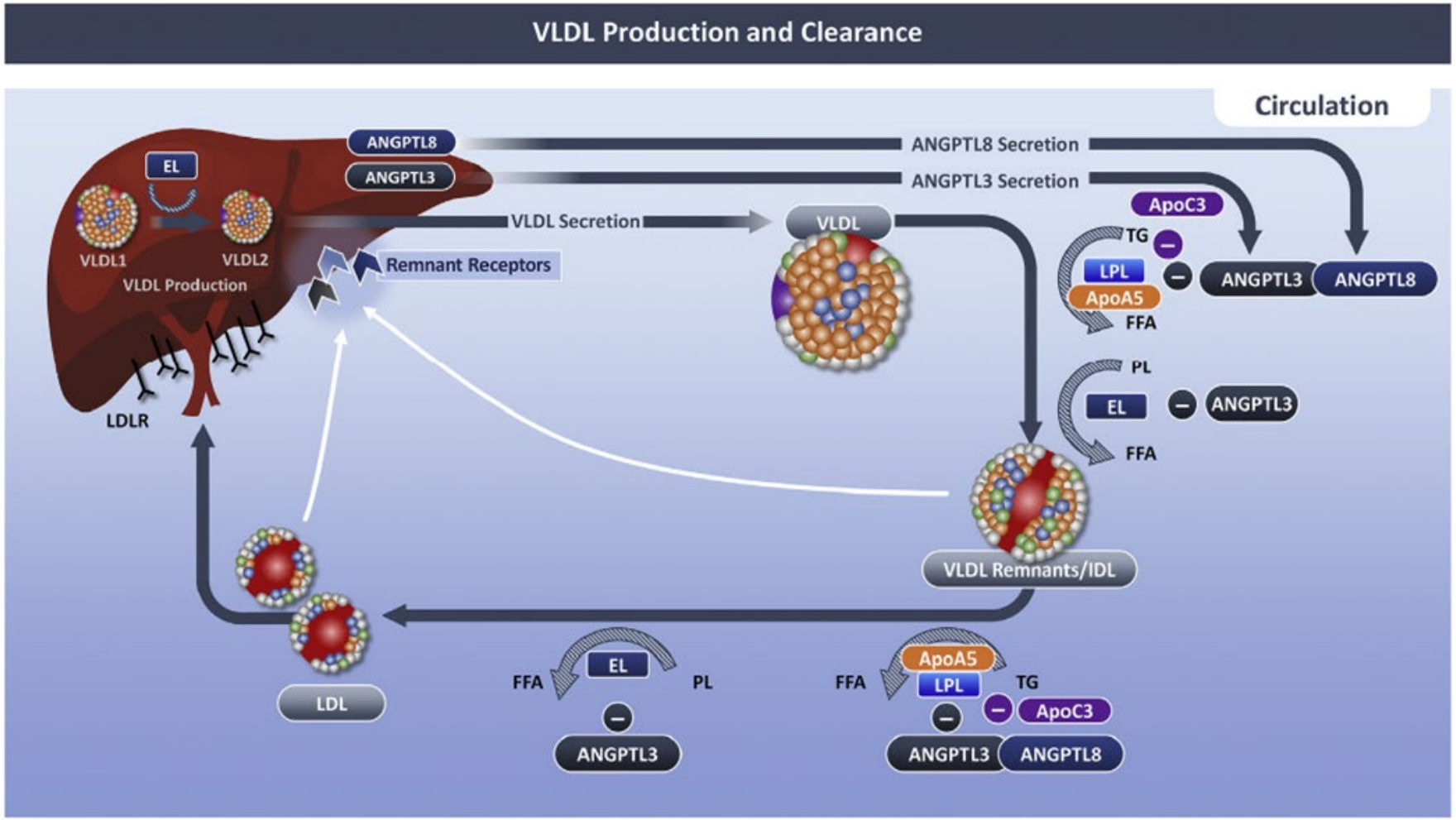
- Heterozygous carriers of APOC-III LOF carriers had 44% lower TG levels and 41% lower risk of ischemic vascular disease[1]



- Heterozygous APOC-III LOF carriers had 39% lower TG levels and a 40% lower odds of coronary heart disease[2]

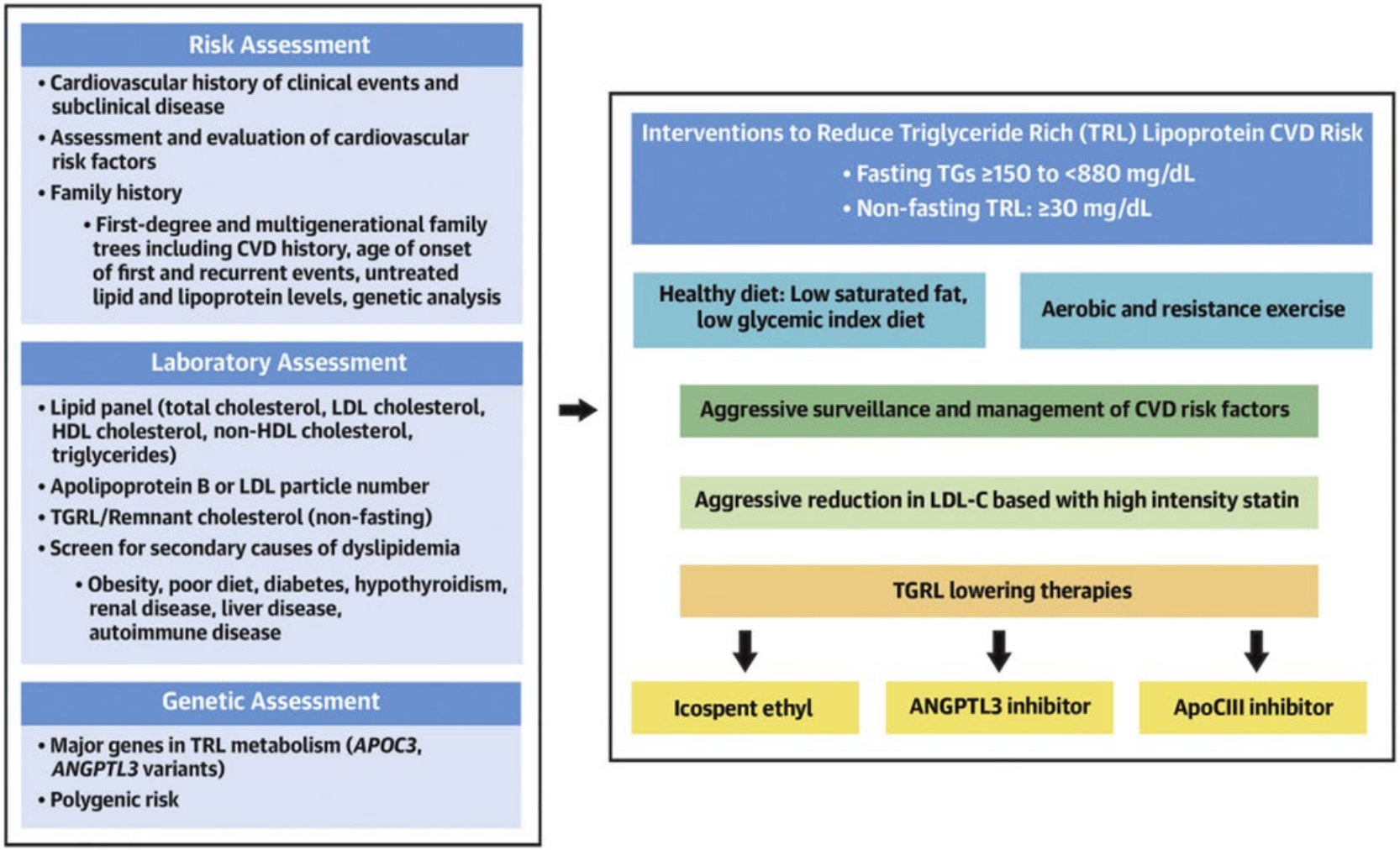
1 Jorgensen AB et al. NEJM 2014;371(1):32-41
2 TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. N Engl J Med. 2014;371:22-31

ANGPTL3 and ApoC-III are Important Regulators of VLDL Production and Clearance



Rosenson RS, Shaik A, Song W. New Therapies for Lowering Triglyceride-Rich Lipoproteins: JACC Focus Seminar 3/4. J Am Coll Cardiol. 2021 Nov 2;78(18):1817-1830.

Clinical Algorithm for Treatment of High TRL



Rosenson RS, Shaik A, Song W. New Therapies for Lowering Triglyceride-Rich Lipoproteins: JACC Focus Seminar 3/4. J Am Coll Cardiol. 2021 Nov 2;78(18):1817-1830.

Summary

- Emerging evidence suggests that elevated TRLs contribute to the risk of atherosclerotic cardiovascular events.
- LOF mutations in ANGPTL3 and APOC-III are associated with lower TRLs and lower risk of ASCVD.
- Clinical trials are warranted to establish the efficacy of inhibiting ANGPTL3 and APOC-III.

Arrowhead Cardiometabolic Pipeline: Journey From Early Development to Registration Path

Javier San Martin, MD
Chief Medical Officer,
Arrowhead Pharmaceuticals

Status of Cardiometabolic Programs

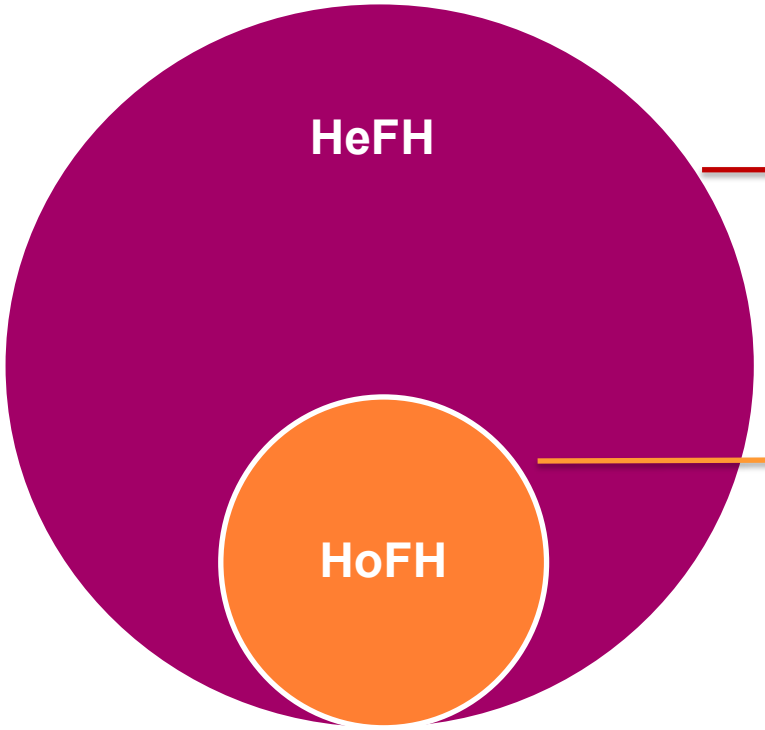
- Robust Clinical & Regulatory Milestones in 2023
  - Three Phase 2 study completion and dose selection
  - One Phase 3 study fully enrolled
  - Three end-of-Phase 2 regulatory meetings
- Interim Analyses of Phase 2 Studies Required to Make Informed Decisions on:
  - Pivotal Phase 3 studies
    - patient populations,
    - indications,
    - study designs, and
    - study execution
  - Registrational path

ANGPTL3: Key Regulator of Lipid and Lipoprotein Metabolism

- ANGPTL3 is a key regulator of lipid and lipoprotein metabolism that inhibits Lipoprotein Lipase (LPL) and Endothelial Lipase (EL)
- ARO-ANG3 has a unique mechanism of action to address hypercholesterolemia distinct from other LDL-C-lowering therapies
  - May address unmet need in patients with specific genetic mutations (eg, patients with dysfunctional LDL receptor [LDLR], HoFH and HeFH)
  - May be added to other LDL-C-lowering therapies in patients not at goal

ARO-ANG3 Development Will Follow Biology With More Targeted Therapy for At-Risk Population

Vista Program



Heterozygous Familial Hypercholesterolemia (HeFH

- LDL-C > 190 mg/dL can lead to increased ASCVD risk
- ~1.4 M patients in the US[1]

Homozygous Familial Hypercholesterolemia (HoFH)

- Rare genetic disease
- LDL-C > 400 mg/dL
- ~1,200 patients in the US[2]

[1] Akioyamen LE et al. 2017 BMJ Open. 2017 Sep 1;7(9):e016461.
[2] Company estimate based on Cuchel M et al. 2014 Eur Heart J. 35:2146-2157

ARO-ANG3 Lowers Lipid Parameters Across Broad Range of Patients with Hypercholesterolemia

	Phase 1 Healthy Volunteers Repeat Dose (Day 1, 29)	Phase 1 HeFH Repeat Dose (Day 1, 29)	Phase 2 Mixed Dyslipidemia (Day 1, Week 12)		
	Pooled ARO-ANG3 (100, 200, 300 mg) (N=12)	Pooled ARO-ANG3 (100, 200, 300 mg) (N=17)	ARO-ANG3 50 mg (N=51)	ARO-ANG3 100 mg (N=50)	ARO-ANG3 200 mg (N=51)
Baseline mean (SD) **LDL-C**, mg/dL	131.1 (32.1)	134.1 (32.6)	112.8 (29.7)	108.7 (44.8)	105.6 (33.7)
Mean % Δ (SD) at Wk 16	**-39.8%** (11.5%)	**-24.4%** (21.3%)	**-23.2%** (24.4%)	**-22.1%** (24.3%)	**-31.7%** (23.3%)
Baseline mean (SD) **Non-HDL-C**, mg/dL	170.5 (37.0)	167.4 (42.0)	151.5 (36.0)	149.3 (47.5)	143.3 (39.6)
Mean % Δ (SD) at Wk 16	**-44.5%** (9.0%)	**-26.9%** (18.0%)	**-28.0%** (19.9%)	**-30.8%** (17.0%)	**-36.3%** (17.8%)
Baseline mean (SD) **ApoB**, mg/dL	101.0 (23.0)	113.6 (35.9)	106.8 (23.4)	99.6 (26.2)	94.9 (25.0)
Mean % Δ (SD) at Wk 16	**-32.7%** (9.5%)	**-14.0%** (16.2%)	**-18.8%** (16.3%)	**-13.2%** (17.5%)	**-21.8%** (21.3%)
Baseline median **TGs**, mg/dL*	137.0 (57, 324)	94.0 (38, 441)	223.3 (174, 303)	231.2 (191, 265)	234.1 (184, 326)
Median % Δ at Wk 16	**-68.1%**	**-32.5%**	**-52.9%**	**-56.4%**	**-59.1%**

* Min, Max for Phase Study and Q1, Q3 for Phase 2 study

ARO-ANG3 Established Impact on Dyslipidemia

- Treatment with ARO-ANG3 results in reductions from baseline of:
  - ~20-40% in LDL-C*
  - ~30-45% in Non-HDL-C*
  - ~15-30% in ApoB*
  - ~40-65% in Triglycerides*
  - ~30% relative reduction in liver fat (MRI-PDFF) (at week 24)
- Favorable effects across various lipid parameters may translate into positive changes for patients with familial hypercholesterolemia and/or metabolic syndrome
- ARO-ANG3 Q3M SQ dosing may improve adherence

* at week 16

ARO-ANG3 Planned Clinical Development and Registration Path

Data Readout			H2 2022	H1 2023
ARO-ANG3-2001	Phase 2	Mixed Dyslipidemia	✓	
ARO-ANG3-2003	Phase 2	HoFH		✓

Regulatory Interactions			H1 2023	H2 2023
ARO-ANG3-2001	EoP2	Mixed Dyslipidemia	✓	
ARO-ANG3-2003	EoP2	HoFH	✓	

Pivotal Study Initiation			H1 2023	H2 2023
ARO-ANG3-3001	Phase 3	HeFH		✓
ARO-ANG3-3002	Phase 3	HoFH		✓

EOP2 = end of Phase 2 meeting

ARO-APOC3 Addresses:

Risk of Pancreatitis in Severe Hypertriglyceridemia Syndromes

and

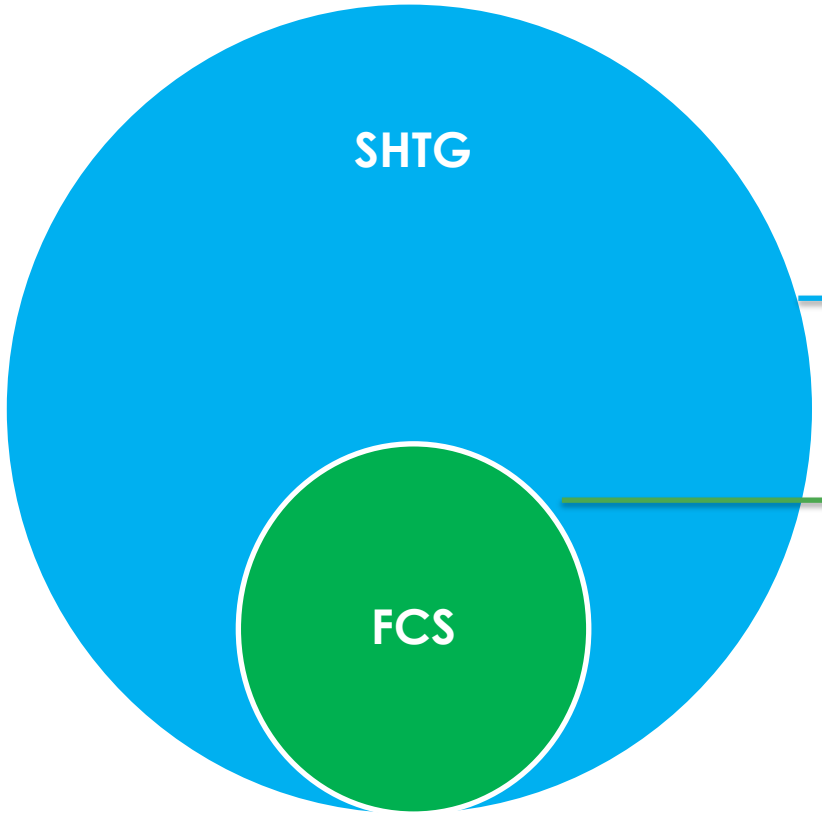
Residual Risk in ASCVD in Mixed Dyslipidemia

APOC3: Key Regulator of Lipid and Lipoprotein Metabolism

- APOC3 is a key regulator of lipid and lipoprotein metabolism that inhibits Lipoprotein Lipase (LPL) and mediates hepatic uptake of remnant particles in an LPL-independent pathway
- ARO-APOC3 improves multiple lipid parameters and may provide clinical benefit in a broad population with dyslipidemias
  - Reduction in TG in patients with SHTG, including FCS, to decrease the risk of acute pancreatitis
  - Reduction in residual cardiovascular risk factors (APOC3, LDL-C, ApoB, remnant cholesterol) in patients at risk of ASCVD

ARO-APOC3 Will Address Unmet Need in Patients With Severely Elevated Triglycerides at Risk for Pancreatitis

SUMMIT PROGRAM



Severe Hypertriglyceridemia (SHTG):

- Reducing risk of pancreatitis in patients with TG ≥ 500 mg/dL
- Prevalence ~4M patients in the US[2]

Familial Chylomicronemia (FCS):

- Reducing risk of pancreatitis and improving QoL in patients with genetic cause of elevated TG
- ~500 patients in US[3]

[1]Fan W: NHANES 2007-2014. Cardiol 9: 207-213
[2]Christian JB 2011 Am J Cardiol 107:P891-897
[3]FCS Foundation

ARO-APOC3 Addresses Severe Hypertriglyceridemia Regardless of Severity and Genetic Background

	Phase 2 SHTG (Day 1, Week 12)			Phase 1 Chylomicronemia Syndrome (MCS) or FCS Repeat Dose (Day 1, 29)	
	ARO-APO3 10 mg (N=24)	ARO-APO3 25 mg (N=27)	ARO-APO3 50 mg (N=23)	MCS ARO-APOC3 50 mg (N=20)	FCS ARO-APOC3 50 mg (N=4)
Baseline median **TGs**, mg/dL*	704.4 (536, 1098)	643.9 (543, 1099)	663.1 (527, 1135)	1715.0 (344, 5577)	1650 (1387, 4791)
Median % Δ at Wk 16	**-77.8%**	**-86.1%**	**-85.6%**	**-85.5%**	**-87.3%**
Baseline mean (SD) **Non-HDL-C**, mg/dL	206.6 (78.4)	212.1 (98.1)	199.9 (88.1)	337.6 (218.7)	319.0 (178.0)
Mean % Δ (SD) at Wk 16	**-36.5%** (26.8%)	**-45.0%** (21.4%)	**-33.5%** (25.9%)	**-47.2%** (25.2%)	**-53.7%** (28.9%)
Baseline mean (SD) **HDL-C**, mg/dL	28.4 (9.2)	28.6 (11.8)	29.4 (11.7)	17.6 (7.0)	12.5 (1.0)
Mean % Δ (SD) at Wk 16	**75.8%** (50.1%)	**99.2%** (65.5%)	**83.0%** (55.2%)	**102.9%** (56.3%)	**130.1%** (59.7%)

* Min, max for Phase 1 study and Q1, Q3 for Phase 2 study

ARO-APOC3 Clinical Development for SHTG and FCS and Registration Path

Data Readout			H1 2023	H2 2023	H1 2024
AROAPOC3-2001	Phase 2	SHTG		✓	
AROAPOC3-3001	Phase 3	FCS			✓

Regulatory Interactions			H1 2023	H2 2023	H1 2024
AROPOC3-2001	EoP2	SHTG			✓
AROAPOC3-3001	NDA	FCS			✓

Pivotal Study Initiation				H2 2023	H1 2024
AROAPOC3-3002	Phase 3	SHTG			✓
AROAPOC3-3003	Phase 3	SHTG			✓

EoP2 = end of Phase 2; NDA = new drug application

ARO-APOC3: Addressing the Residual Risk in ASCVD New Interim Data from Ongoing MUIR Study in Mixed Dyslipidemia

MUIR Study Design: Mixed Dyslipidemia

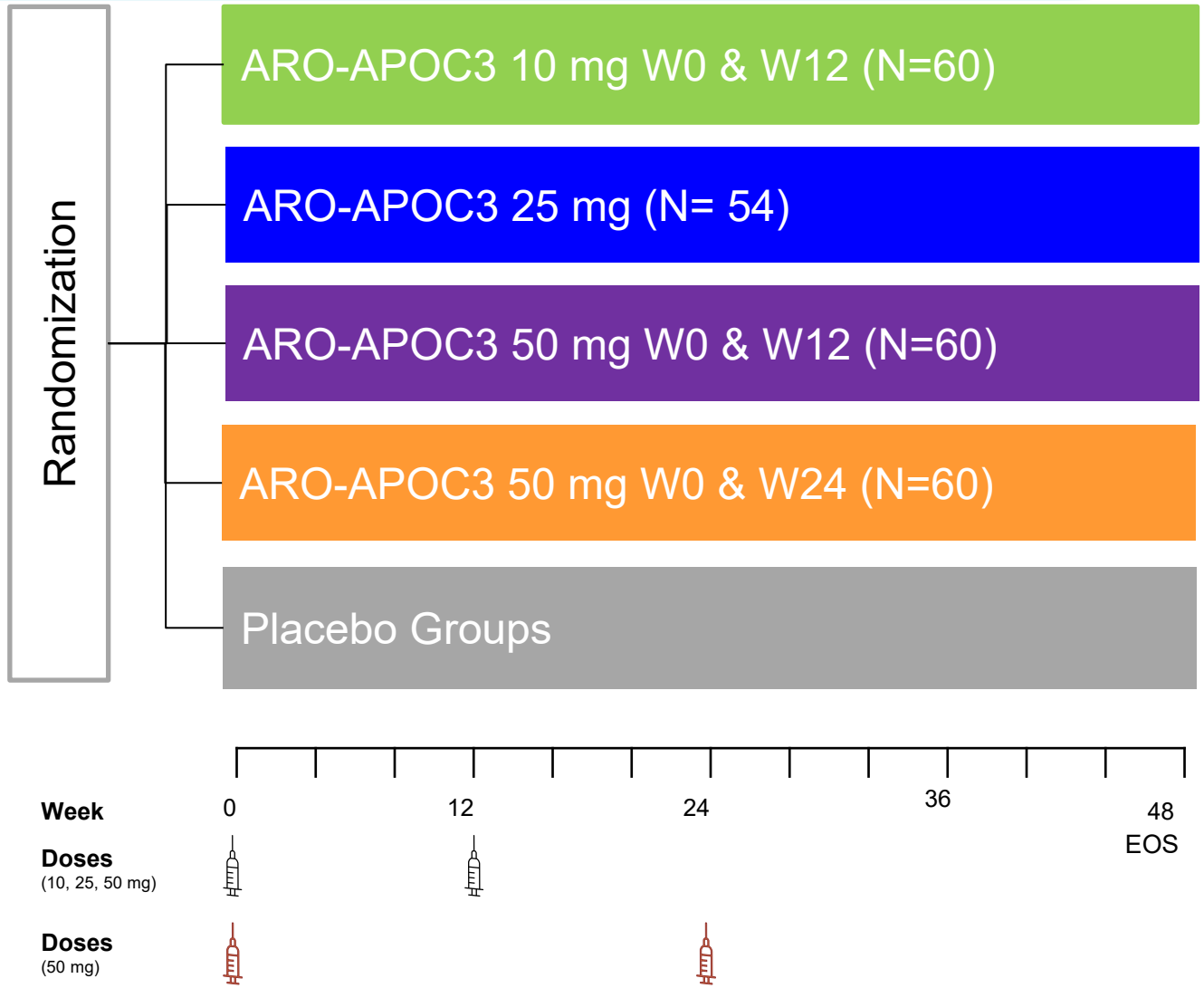
Study Population:
- fasting TG between 150-499 mg/dL and either
  - LDL-C ≥ 70 mg/dL or
  - Non-HDL-C ≥ 100 mg/dL
- Stable optimal statin therapy

Key Endpoints*:
% change from baseline in:

- TG
- APOC3
- non-HDL-C
- ApoB
- LDL-C
- HDL-C
- VLDL-C

Data Analysis:

Ongoing Phase 2 study data evaluated when ≥50% of subjects had reached Week 12 (cutoff date Sept 1, 2022



* All samples taken after ≥ 10 hour fast

MUIR: Baseline Characteristics

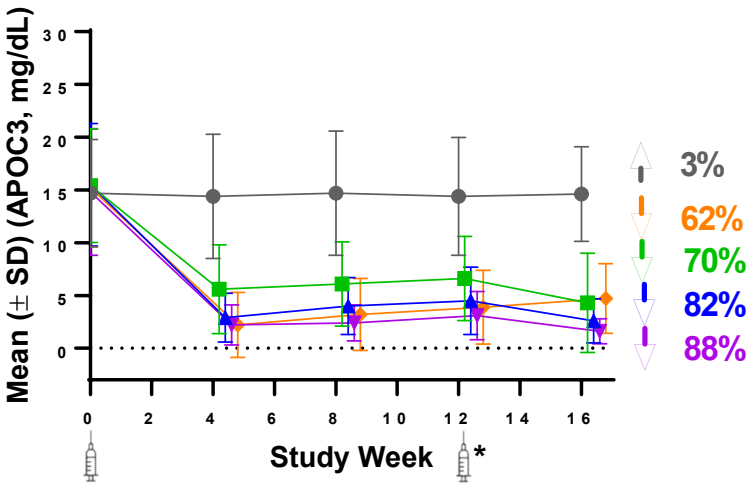
	Pooled Placebo	ARO-APOC3 (W0 and W12)			ARO-APOC3 (W0 and W24)
	(N=84)	10 mg (N=65)	25 mg (N=67)	50 mg (N=66)	50 mg (N=64)
Mean (SD) age, years	58.8 (9.9)	60.5 (11.4)	61.3 (11.3)	62.6 (10.5)	61.2 (11.9)
Female, n (%)	40 (47.6%)	30 (46.2%)	29 (43.3%)	29 (43.9%)	23 (35.9%)
White, n (%)	76 (90.5%)	61 (93.8%)	60 (89.6%)	63 (95.5%)	61 (95.3%)
Mean (SD) BMI, kg/m^2	31.40 (5.357)	30.51 (5.687)	32.13 (6.386)	32.56 (6.530)	31.99 (5.623)
Mean (SD) APOC3, mg/L	14.7 (5.1)	15.4 (5.4)	15.5 (5.8)	14.8 (6.0)	15.1 (5.6)
Median (Q1, Q3) triglyceride, mg/dL	222.90 (181.8, 283.9)	223.70 (195.2, 318.8)	208.40 (174.8, 278.2)	235.85 (185.4, 300.8)	226.20 (187.2, 298.2)
Mean (SD) LDL-C (Hopkins), mg/dL	111.6 (38.8)	116.6 (38.3)	111.7 (44.4)	114.3 (42.8)	116.1 (35.2)
Mean (SD) non-HDL-C, mg/dL	148.6 (43.5)	154.2 (42.3)	147.7 (48.4)	151.8 (49.3)	153.0 (43.0)
Mean (SD) ApoB, mg/dL	102.3 (30.6)	99.7 (24.7)	95.5 (23.7)	93.6 (22.5)	100.1 (22.3)
Mean (SD) remnant cholesterol,[a] mg/dL	45.9 (20.2)	48.7 (20.9)	46.4 (20.6)	48.6 (27.1)	46.0 (23.5)
Mean (SD) HDL-C, mg/dL	42.2 (11.4)	42.4 (11.2)	44.7 (13.6)	42.7 (11.7)	41.0 (12.8)

[a] Based on calculation: Total cholesterol – HDL-C – LDL-C (ultracentrifugation)

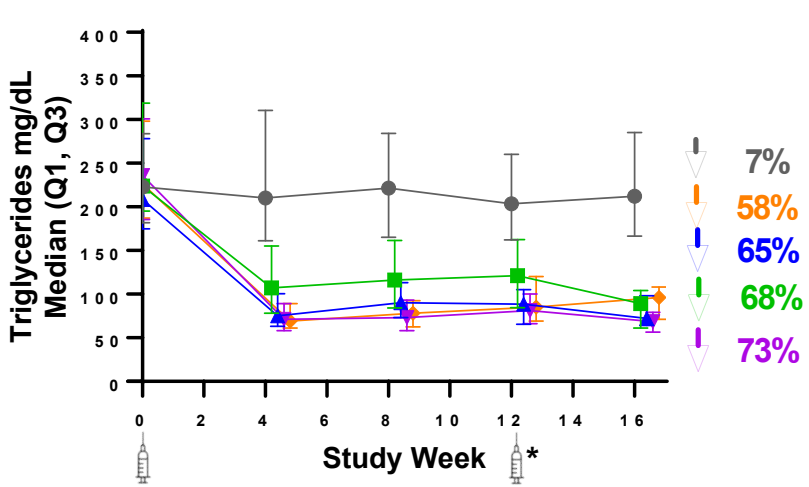
Muir: Data cutoff 01 Sept 2022

MUIR: ARO-APOC3 Results in Durable Decreases in Serum APOC3 and Triglycerides at All Doses Studied

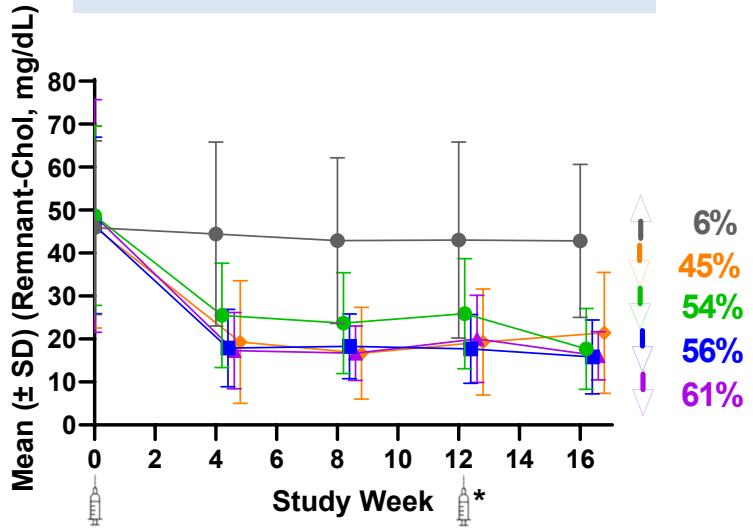
APOC3



Triglycerides



Remnant Cholesterol[a]



Placebo | 10 mg ARO-APOC3 | 25 mg ARO-APOC3 | 50 mg ARO-APOC3 | 50 mg ARO-APOC3 (Q24W)

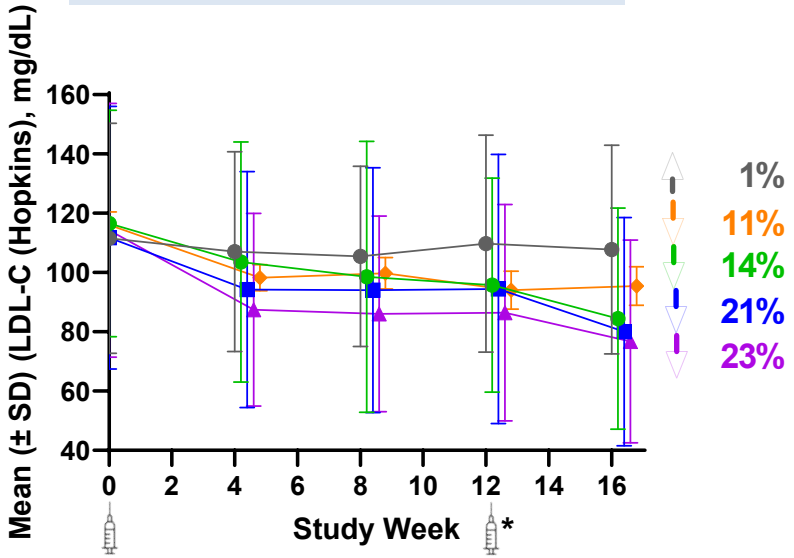
*Dose given only for cohorts receiving Q12W dose

[a] Based on calculation: Total cholesterol – HDL-C – LDL-C (ultracentrifugation)

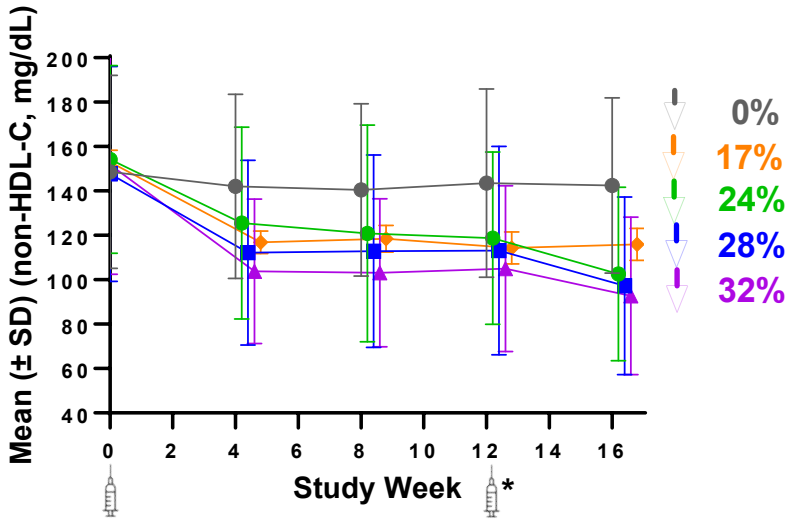
Muir: Data cutoff 01 Sept 2022

MUIR: ARO-APOC3 Decreases Serum LDL-C, Non-HDL-C and Increases HDL-C

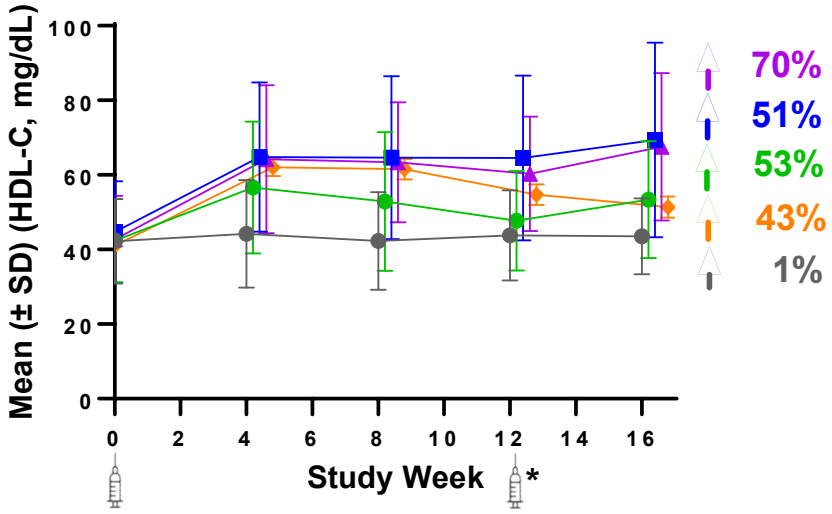
LDL-C (Hopkins)



Non-HDL-C



HDL-C



Placebo | 10 mg ARO-APOC3 | 25 mg ARO-APOC3 | 50 mg ARO-APOC3 | 50 mg ARO-APOC3 (Q24W)

*Dose given only for cohorts receiving Q12W dose

Muir: Data cutoff 01 Sept 2022

MUIR STUDY: Summary of Adverse Events

Total Number of Subjects	348
# of Subjects Reporting > 1 Treatment Emergent Adverse Event (TEAE) N (%)	126/348 (36.2%)
TEAEs occurring in ≥ 5 subjects	
Covid 19	12 (3.4%)
Headache	11 (3.2%)
Cystitis	10 (2.9%)
Diabetes (Type 2 DM, Glycated hemoglobin increased)	10 (2.9%)
Upper Respiratory Tract Infection	7 (2.0%)
Urinary Tract Infection	6 (1.7%)
Back Pain	5 (1.4%)
Lipase increased	5 (1.4%)
Treatment-related TEAEs	22 (6.3%)
Serious TEAEs	8 (2.3%)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	2 (0.6%)
TEAEs causing deaths	1 (0.3%)

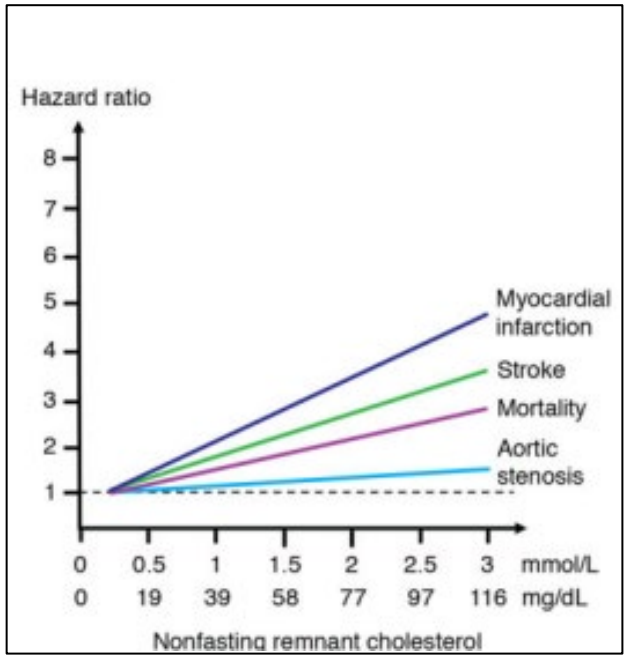
- TEAEs reported to date reflect the underlying comorbidities and conditions of the population under study
- All TEAEs were pooled regardless of treatment assignment
- Mean change from baseline in HbA1c at Week 16 across cohorts was 0.17% to 0.36% in subjects receiving ARO-APOC3, and -0.01% in subjects receiving placebo, driven by patients with baseline diabetes

Muir: Data cutoff 01 Sept 2022

Beyond LDL-C Control: What Drives the Residual Risks in ASCVD?

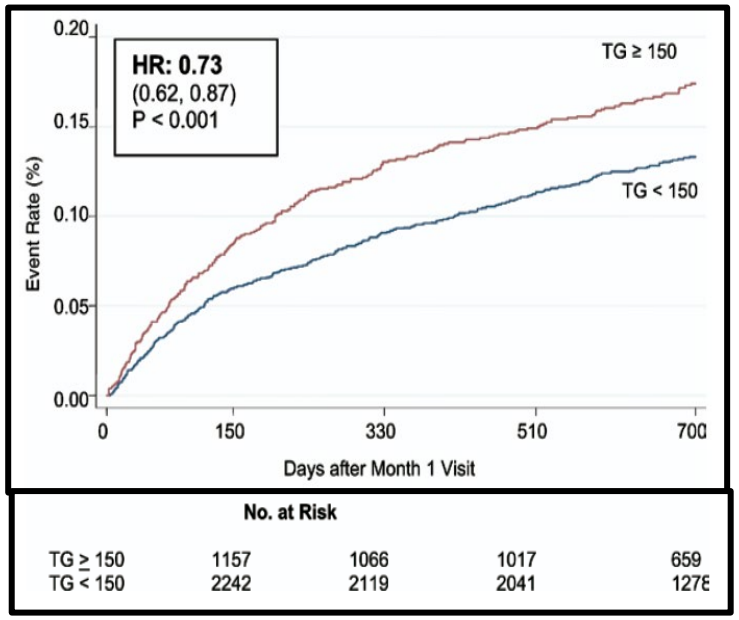
Copenhagen General Population Study and Mendelian Randomization Study

- ↑ **Remnant cholesterol associated with ↑ risk of ASCVD events** [1,2,3]



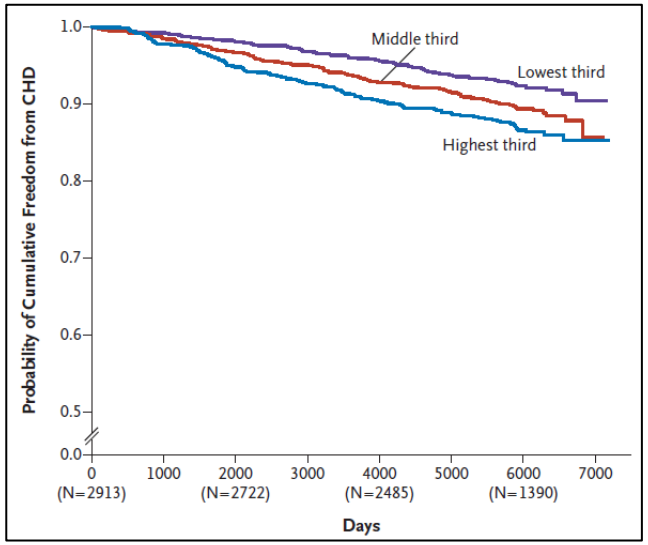
PROVE IT-TIMI 22 [4]

- ↓ **TGs associated with ↓ risk of CHD in statin-treated patients**



TG and HDL Working Group[5]

- ↑ **APOC3 associated with ↓ cumulative probability of freedom from CHD**



Lowest third: APOC3 levels ≤ 14.2 mg/dL
Middle third: APOC3 levels 14.3 – 17.9 mg/dL
Highest third: APOC3 levels ≥ 18.0 mg/dL

[1]Miller M. JACC 2008;51:724-30; [2]Langsted A. J Intern Med 2020;288:116-27; [2]TG and HDL Working Group. N Engl J Med 2014;371:22-31 [4]Miller M. JACC 2008;51:724-30; [5]Kaltoft M. E Heart J 2020;41:2288-99.

Muir: Data cutoff 01 Sept 2022

ARO-APOC3 Addresses Lipid Abnormalities Associated with Increased Cardiovascular Risk

- Elevated atherogenic lipids
  - LDL-C
  - VLDL-C
  - Remnant cholesterol
  - Elevated TG
  - Low HDL-C

- Patients at risk despite maximally tolerated statins ~ 12 M in US[1]

[1]Fan W: NHANES 2007-2014. Cardiol 9: 207-213

ARO-APOC3 Improves Lipid Parameters Across Multiple Dyslipidemia Populations

	Phase 1 Healthy Volunteers Repeat Dose (Day 1, 29)	Phase 2 Mixed Dyslipidemia Repeat Dose (Day 1, Week 12)		
	Pooled Active (n=11)	**ARO-APOC3 10 mg (N=65)**	**ARO-APOC3 25 mg (N=67)**	**ARO-APOC3 50 mg (N=66)**
Baseline mean (SD) **LDL-C (Hopkins)**, mg/dL	154.8 (50.5)*	116.6 (38.3)	111.7 (44.4)	114.3 (42.8)
Mean % Δ (SD) at Wk 16	**-20.1%** (15.9%)	**-14.4%** (31.3%)	**-20.8%** (20.4%)	**-23.2%** (28.8%)
Baseline mean (SD) **Non-HDL-C**, mg/dL	184.2 (52.9)	154.2 (42.3)	147.7 (48.4)	151.8 (49.3)
Mean % Δ (SD) at Wk 16	**-27.7%** (12.2%)	**-24.3%** (26.0%)	**-27.8%** (17.4%)	**-31.7%** (24.5%)
Baseline mean (SD) **ApoB**, mg/dL	116.8 (32.8)	99.7 (24.7)	95.5 (23.7)	93.6 (22.5)
Mean % Δ (SD) at Wk 16	**-25.5%** (10.5%)	**10.0%** (33.3%)	**-20.4%** (10.8%)	**-24.5%** (16.0%)
Baseline median (min, max) **TGs**, mg/dL*	135.0 (101, 198)	223.7 (195, 319)	208.4 (175, 278)	235.9 (185, 301)
Median % Δ at Wk 16	**-66.3%**	**-67.9%**	**-64.6%**	**-73.3%**
Baseline mean (SD) **HDL-C**, mg/dL	45.7 (7.4)	42.4 (11.2)	44.7 (13.6)	42.7 (11.7)
Mean % Δ (SD) at Wk 16	**39.0%** (28.3%)	**53.2%** (50.8%)	**51.0%** (28.8%)	**70.1%** (37.0%)

* LDL-C (direct) reported for Ph1

ARO-APOC3 Reduces Key Residual ASCVD Risk Factors

Average Lipid Profiles in MUIR

	APOC3	TG	Non-HDL-C	LDL-C	ApoB	Remnant Cholesterol	HDL-C
Pre-treatment	15	220	150	110	95	46	42
Post-treatment	**3**	**77**	**108**	**88**	**76**	**18**	**63**
% change	-80%	-65%	-28%	-20%	-20%	-60%	+50%

ARO-APOC3 Planned Clinical Development (ASCVD) and Registration Path

Data Readout			H2 2023	2024
ARO-APOC3-2002	Phase 2	Mixed Dyslipidemia	✓	

Regulatory Interactions			H2 2023	2024
ARO-APOC3-2002	EoP2	Mixed Dyslipidemia	✓	

Pivotal Study Initiation			H2 2023	H1 2024
ARO-APOC3-3004	Phase 3	CVOT		✓

EoP2 = end of Phase 2

ARO-APOC3: Key Considerations for CVOT in Patients with Mix Dyslipidemia

- This Interim Analysis will accelerate study design
  - Patients with residual risk despite LDL-C control
  - Patients with established ASCVD
  - Patients not meeting LDL-C treatment goal
  - Modeling to estimate event rates and effect size
  - Length of study
  - Dose and interval

Cardiometabolic Strategy

- Pursuing 5 indications
  - ARO-APOC3
    - Familial Chylomicronemia Syndrome
    - Severe Hypertriglyceridemia
    - Treatment of mixed dyslipidemia: ASCVD risk reduction
  - ARO-ANG3
    - Homozygous Familial Hypercholesterolemia
    - Heterzygous Familial Hypercholesterolemia

Concluding Remarks

Chris Anzalone, PhD
Chief Executive Officer
Arrowhead Pharmaceuticals

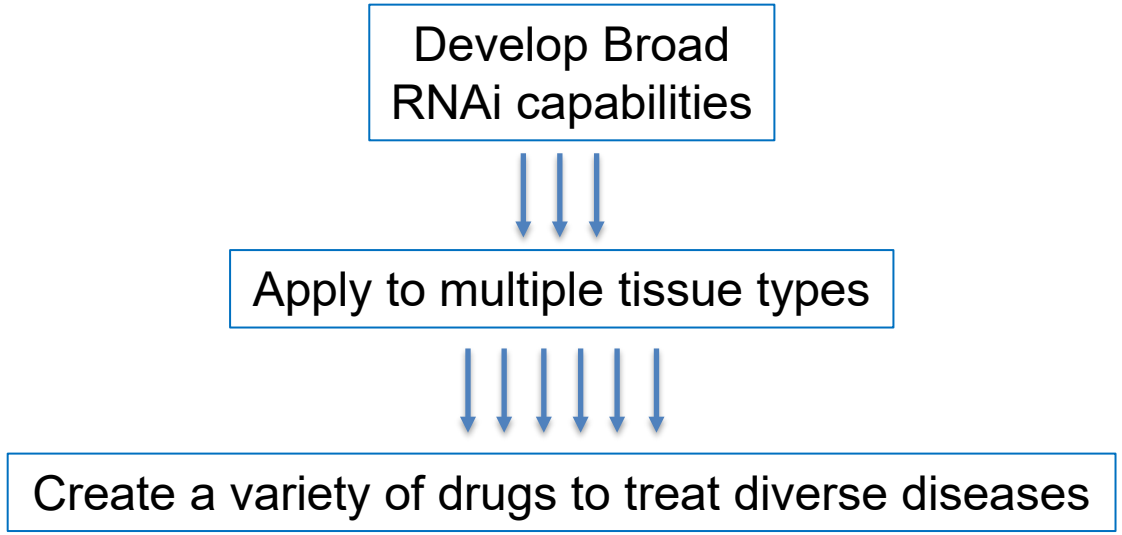
RNAi is on the Cusp of Changing Cardiometabolic Treatment

- Leqvio® could change the PCSK9 market
- Olpasiran could change the way LP(a) is addressed
- ARO-ANG3 could change the way familial hypercholesterolemia is treated
- ARO-APOC3 could change the way triglyceridemia and dyslipidemia are treated

Not very long ago, the only treatments were diet and statins:
So these innovations represent substantial leaps forward

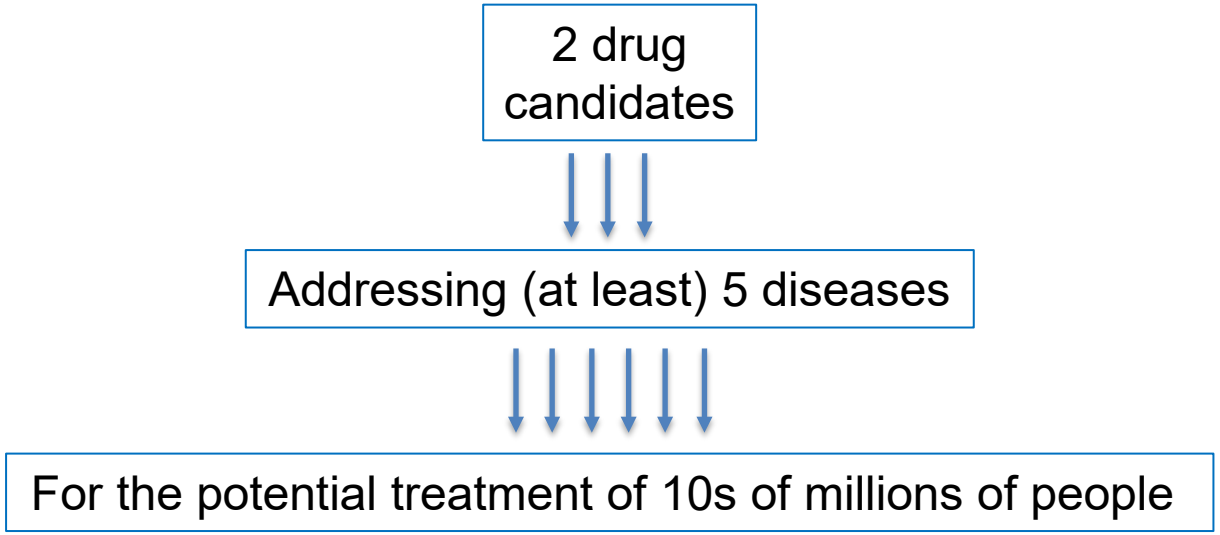
Arrowhead developed 3 of these 4 drug candidates

Our Business Model Relies on Leverage



Designed to maximize ROI and the clinical reach of our technology

Cardiometabolic Franchise is an Example of Leverage



Currently running 1 cardiometabolic Phase 3 and expect 4 additional over next 18 months

Staged Commercial Approach: Small to Large

ARO-ANG3

ARO-APOC3

Enables us to:

- Interact with patients and physicians early
- Learn from the market before addressing larger indications
- Build out commercial infrastructure at a measured pace

Access to Sufficient Capital

- $582m of cash and equivalent reported in last filing on form 10-q
- Currently have 6 partnered programs with 5 different companies
  - Expect to receive milestone payments from each company over next 12 months
- Given our platforms, we expect ~1 new partnership every year
- Sale of potential royalties from Amgen on future Olpasiran sales for $250m up front
  - Eligible for up to $160m in additional payments from Royalty Pharma
  - Eligible for up to $400m in milestone payments from Amgen

Entering the Golden Age of Treating Cardiometabolic Diseases

- Multiple tools to treat multiple risk factors
- Enabling physicians to dial in personalized treatment paradigms
- Providing millions of patients with new hope

Arrowhead is leading the way

Q & A - Panel