ARO-APOC3 KOL Webinar

November 18, 2020

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Welcome and Introductions

Vince Anzalone, CFA

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 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.

Panelists

Baylor College of Medicine

Christie Ballantyne, M.D..
Chief of Cardiology and the Chief of Cardiovascular Research, and the Director of the Lipid Metabolism and Atherosclerosis Clinic Center for Cardiometabolic Disease Prevention at Baylor College of Medicine

Arrowhead Pharmaceuticals

Chris Anzalone, Ph.D
President & Chief Executive Officer

Vince Anzalone, CFA
Vice President, Investor Relations

Javier San Martin, M.D.
Chief Medical Officer

Jim Hassard
Chief Commercial Officer

Agenda

- Welcome and Introductions – Vince Anzalone
- Market Opportunity – Jim Hassard
- APOC3 as a Therapeutic Target in Hypertriglyceridemia – Dr. Christie Ballantyne
- ARO-APOC3 Clinical Development – Dr. Javier San Martin
- Wrap up – Dr. Christopher Anzalone
- Q & A – Panel

Broad Pipeline

THERAPEUTIC AREA		PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	Product Rights
Cardiometabolic	**ARO-APOC3** FCS, sHTG					
	ARO ANG Dyslipidemia					
	AMG 890 CVD					AMGEN
Pulmonary	**ARO-ENAC** Cystic fibrosis					
	ARO-Lung2 COPD					
Liver	**ARO-HSD** NASH					
	ARO-AAT AATD					Takeda
	JNJ 3989 HBV					janssen
Oncology	**ARO-HIF2** RCC					
Undisclosed	**JNJ1**					janssen
	JNJ2					janssen
	JNJ3					janssen

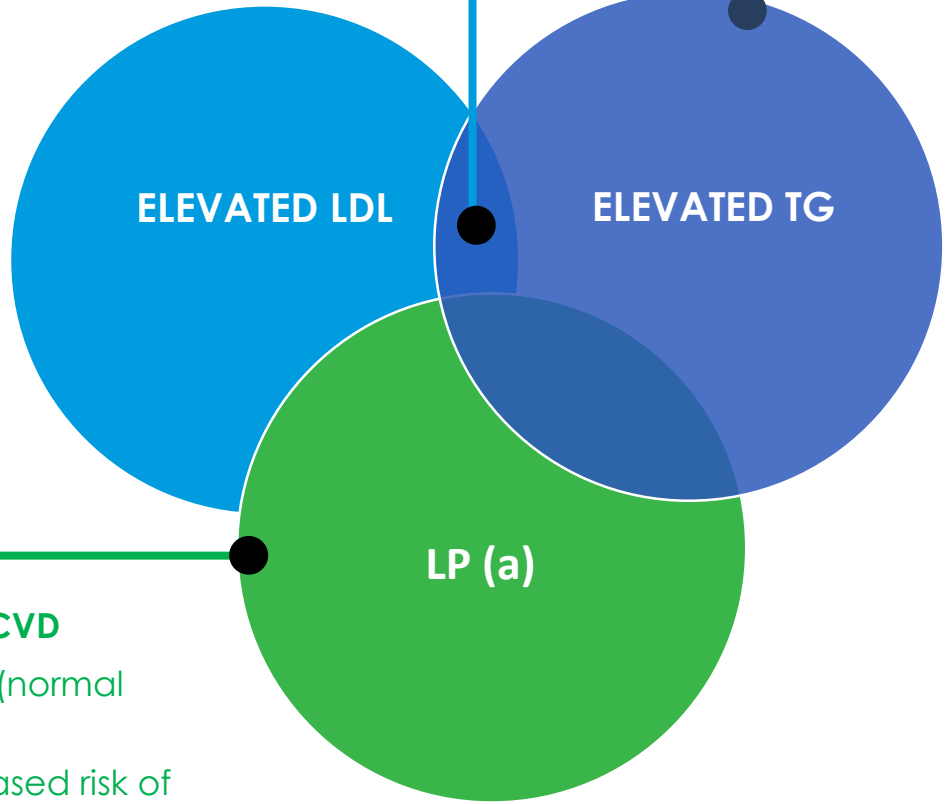
Tissue Targets

Liver Lung Tumor

Our Cardiometabolic Strategy

Mixed dyslipidemia patients have elevated LDL & elevated TG associated with increased risk of CVD

- ~15M[1] patients in the US with elevated LDL and TG
- Current standard of care not providing necessary reductions of LDL and TGs



LP(a) is an independent risk factor for CVD

- ~25% of population has >30 mg/dl (normal levels: 0.1-25mg/dl)
- Higher levels associated with increased risk of CVD

Hypertriglyceridemia (HTG) and Severe HTG (SHTG) are associated with increased risk of CVD

- Affects ~7M and ~4M patients/year respectively.
- HTG (TG>150mg/dl) and SHTG (TG>500 mg/dl) are associated with increased risk of CVD
- Severe HTG may lead to acute pancreatitis

Familial chylomicronemia syndrome (FCS)

- Affects ~500 patients in the US every year
- A rare and severe genetic disorder which causes TG > 880 mg/dL, associated with CVD and may lead to acute pancreatitis
- Currently no approved therapies

1. Fan et al Cardiology Journal (2019) 26(5): 604-606

Market Opportunity

Jim Hassard

Residual CV risk remains despite LDL-lowering drugs

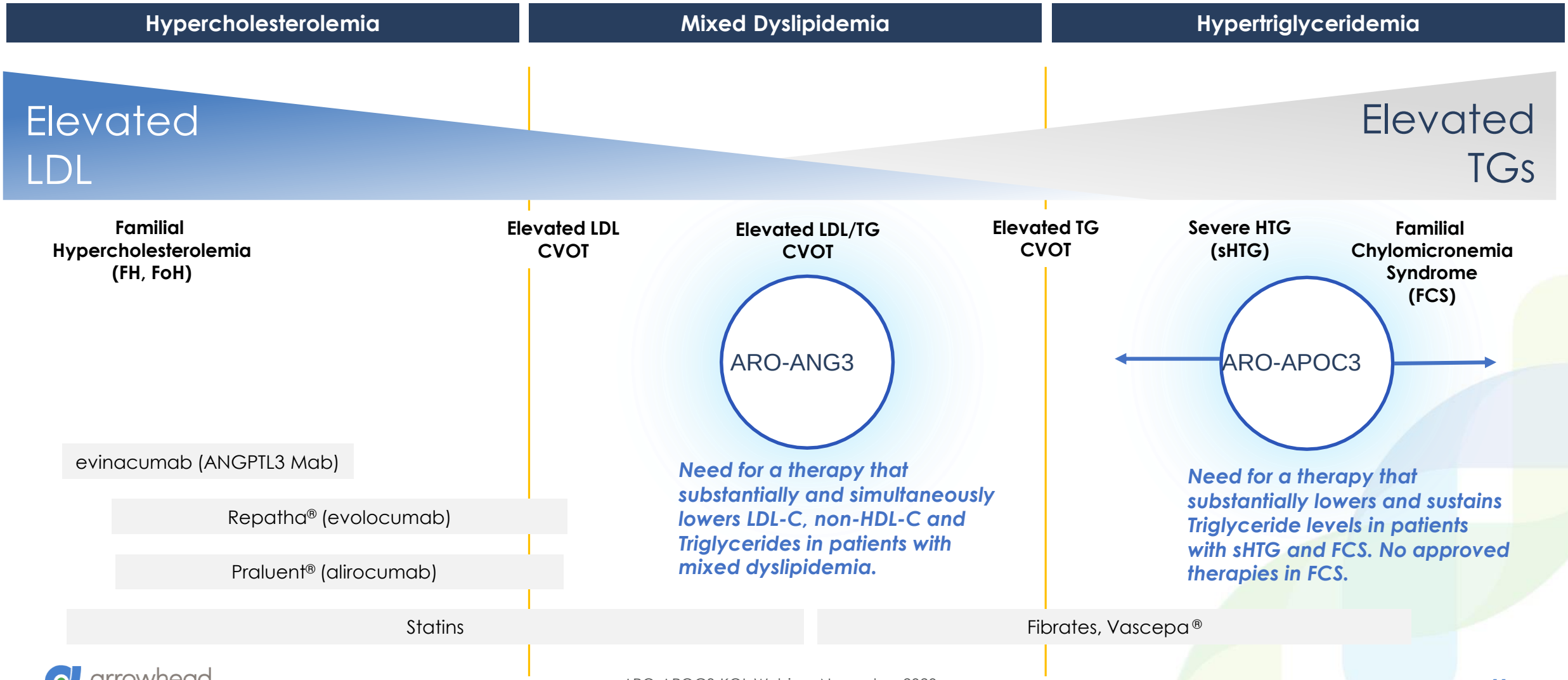
CVD accounts for:	Avg annual cost of CVD in US:	Residual risk despite LDL lowering drugs[3]
1 of every 3 deaths globally[1] **600,000 deaths per year in the US[2]**	**>$350Bn in 2015[3]** **Projected >1.1 Tn in 2035[3]**	**Statins reduce risk of CV death by ~20-40%[4]** **26% ↑ rate of major CVE in patients with CVD on statins if TG ≥150 mg/dL[5]**

1. World Heart Federation. 2. CDC Heart Disease Facts.. 3. AHA Heart Disease and Stroke Statistics-2019 At-a-Glance. 4. Cholesterol Treatment Trialists Collaboration. 2010. 6. Toth 2019.

ARO-APOC3 serves a variety of patient types with elevated TGs

DECREASING PATIENT PREVALENCE (US)		CURRENT TREATMENT OPTIONS	GOAL OF NEW THERAPY
~500 patients	FCS (TG>880)	No FDA approved therapies	TG reduction and prevention of pancreatitis related events
~4M patients	sHTG (TG>500)	Fibrates, Vascepa® Many patients will not achieve their TG targets	TG reduction and prevention of pancreatitis related events and CV risk reduction
~51M patients	HTG (TG>150)	Fibrates, Vascepa® Many patients will not achieve their TG targets	CV Risk reduction

ARO-ANG3 and ARO-APOC3 target unique patient populations



APOC3 as a Therapeutic Target in Hypertriglyceridemia

Christie Ballantyne, M.D.

Rationale for APOC3 as a Therapeutic Target

Plasma APOC3 levels predict coronary heart disease

Genetic *APOC3* loss of function mutations reduce plasma lipoproteins and cardiovascular disease risk by ~40%

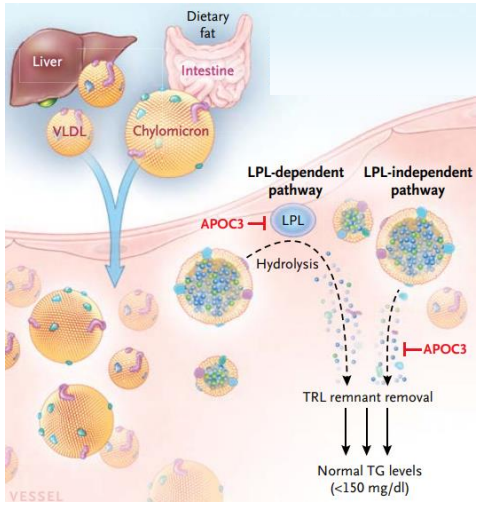
APOC3 increases VLDL secretion and promotes pathogenic processes in cardiovascular disease

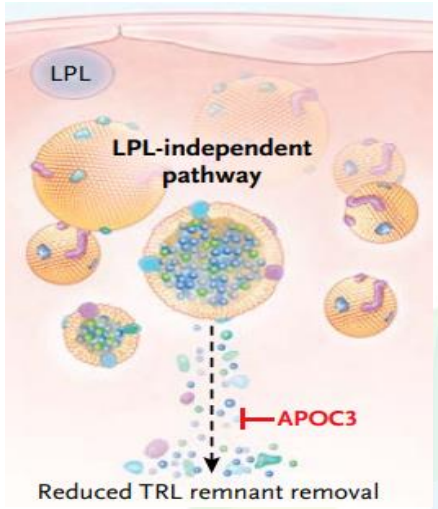
Inhibition of lipolysis

APOC3 enrichment results in accumulation of TRLs by limiting their enzymatic degradation

Antagonism of lipoprotein clearance

APOC3 enrichment limits clearance of TRL remnants by LDL receptor pathways in the liver





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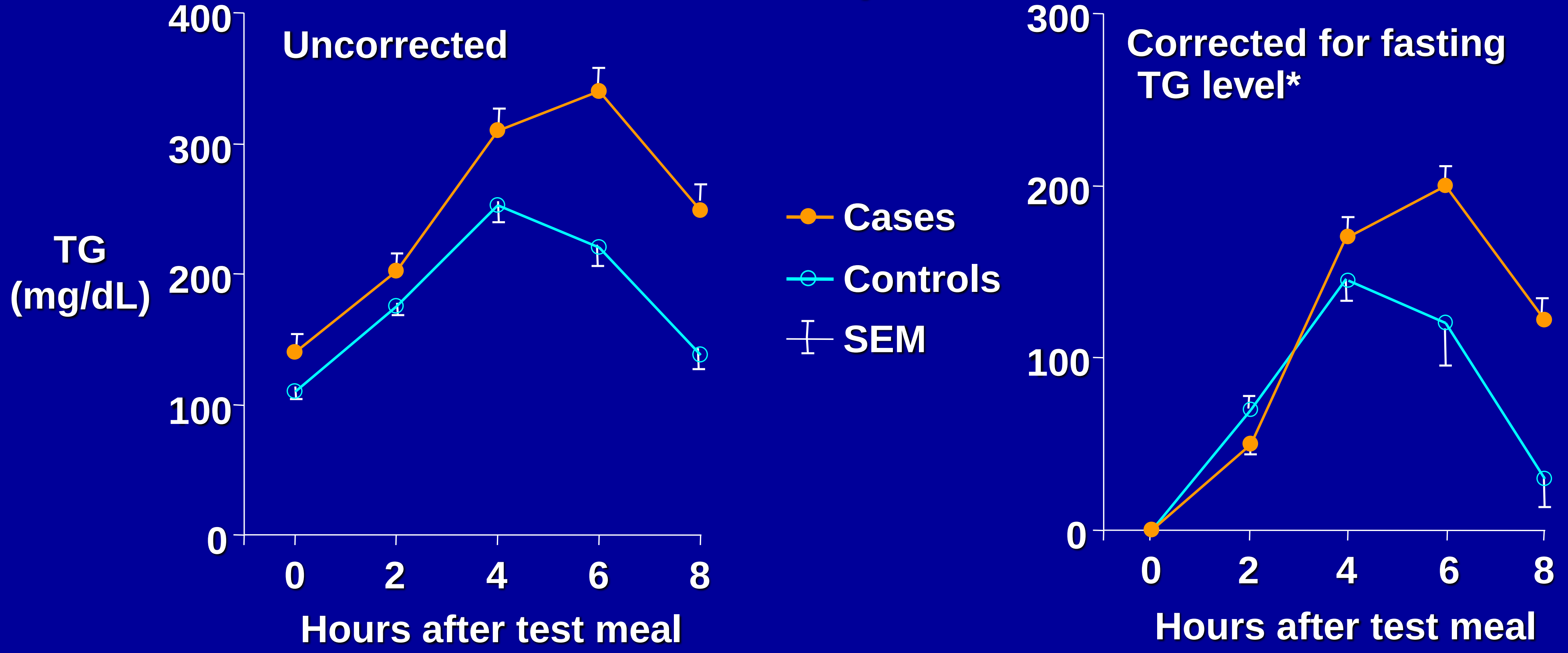
APOC, Apolipoprotein C; APOE, Apolipoprotein E; LDL, Low Density Lipoprotein; SMase, Sphingomyelinases; TRL, Triglyceride-rich Lipoproteins
Boren J.Frontiers in Endocrinology. 2020; HDL working group.N Engl J Med.2014; Jorgensen.N Engl J Med.2014; Sacks. Circulation.2000; Taskinen MR.Curr Atheroscler Rep.2019

TG Metabolism in CHD: Studies in the Postprandial State



Line plots of postprandial TG kinetics in coronary artery disease patients and control subjects.
* TG levels in the course of postprandial lipemia in cases and control subjects.

Patsch JR et al. *Arterioscler Thromb*. 1992;12:1336-1345.

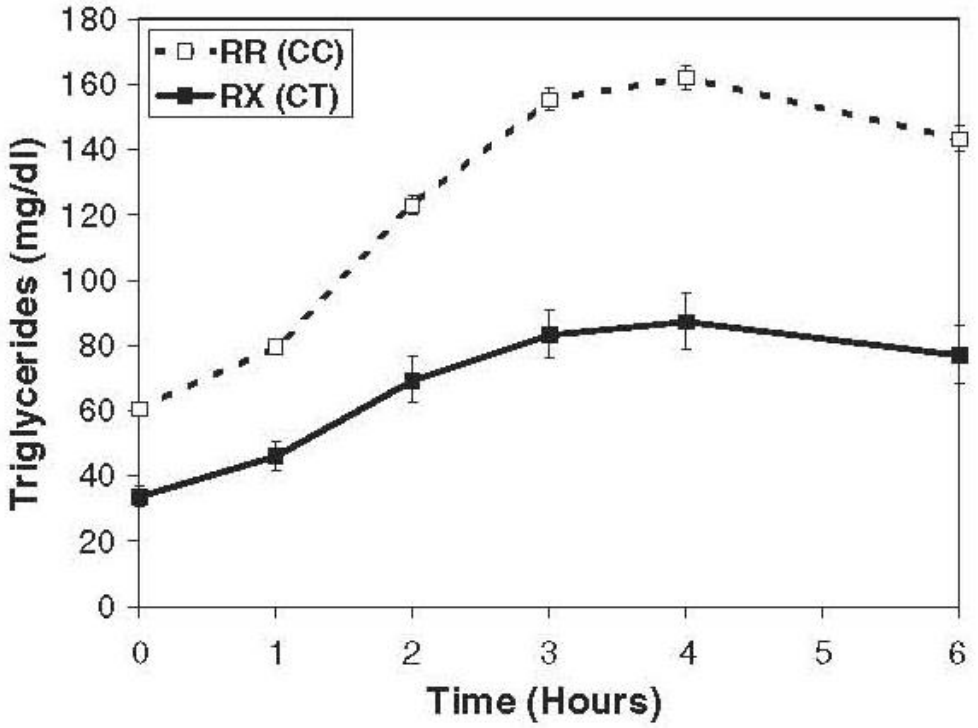
A Null Mutation in Human *APOC3* Confers a Favorable Plasma Lipid Profile and Apparent Cardioprotection

Toni I. Pollin,[1] Coleen M. Damcott,[1] Haiqing Shen,[1] Sandra H. Ott,[1] John Shelton,[1] Richard B. Horenstein,[1] Wendy Post,[2] John C. McLenithan,[1,3] Lawrence F. Bielak,[4] Patricia A. Peyser,[4] Braxton D. Mitchell,[1] Michael Miller,[1] Jeffrey R. O'Connell,[1] Alan R. Shuldiner[1,3]

12 DECEMBER 2008 VOL 322 **SCIENCE**

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

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



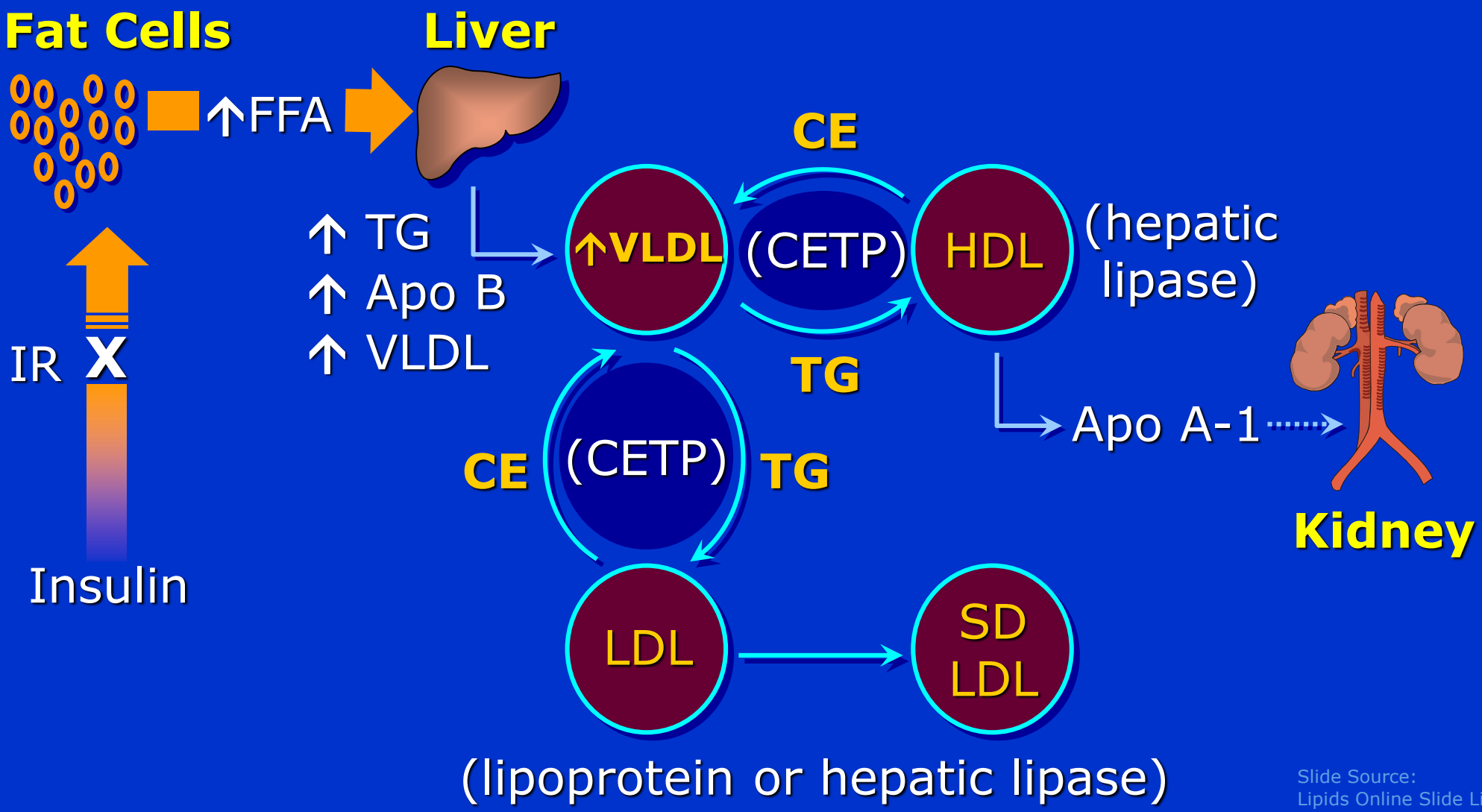
Pollin TI et al. *Science*. 2008;322:1702-1705.

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

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

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

Mechanisms Relating Insulin Resistance and Dyslipidemia



Patients with elevated TGs experience a significant burden in managing their disease

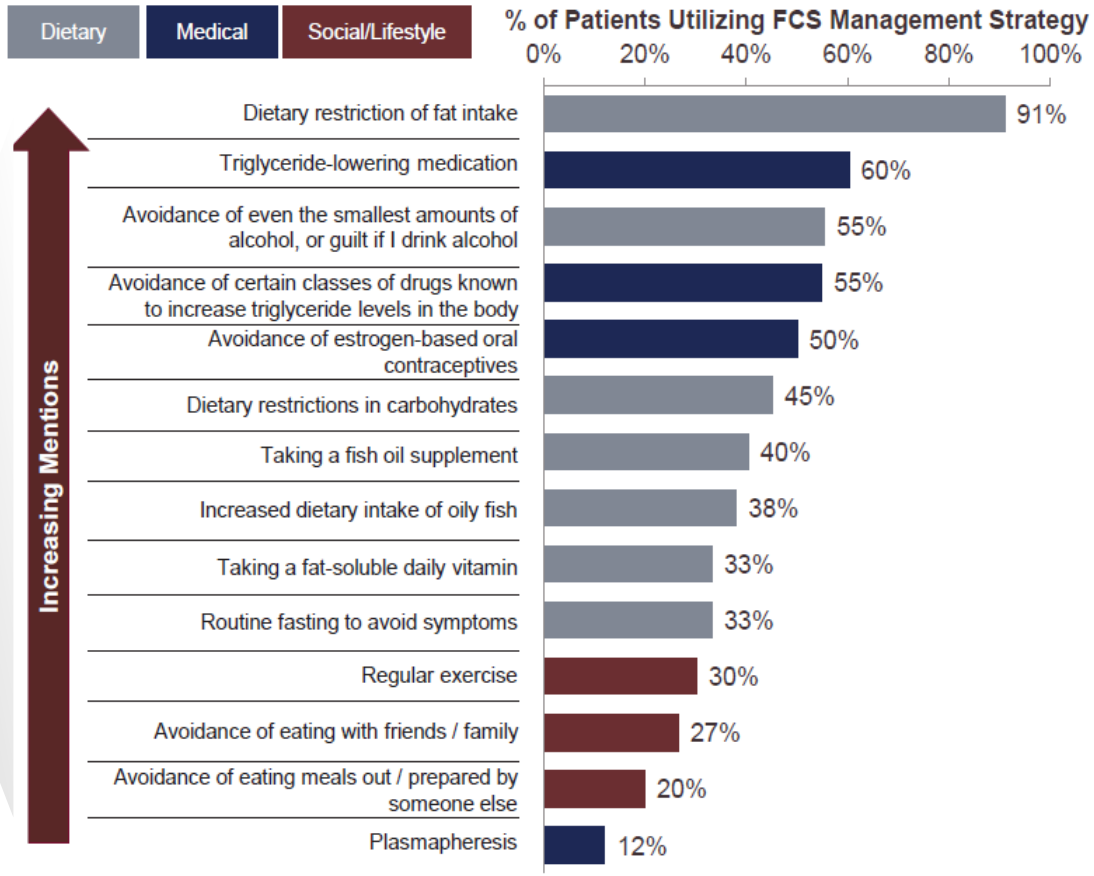
Severe hypertriglyceridemia

- Most cases are the result of polygenic risk and lifestyle (e.g. obesity, diabetes, alcohol consumption, sedentary behaviors)

Familial Chylomicronemia Syndrome

- The result of homozygous or compound heterozygous loss-of-function mutations in gene(s) responsible for lipoprotein lipase dependent triglyceride clearance (*LPL, APOC2, LMF1, APOA5, GPIHBP1*)
- 85% of FCS patients experience pancreatitis in year 1. Pancreatitis is associated with up to 30% mortality[1]
- FCS symptoms such as nausea, xanthoma, fatigue, cognitive impairment occur regularly[1,2]
- There is no effective therapy for FCS[1,2,4]
  - Failure to adhere to severe dietary restrictions is common

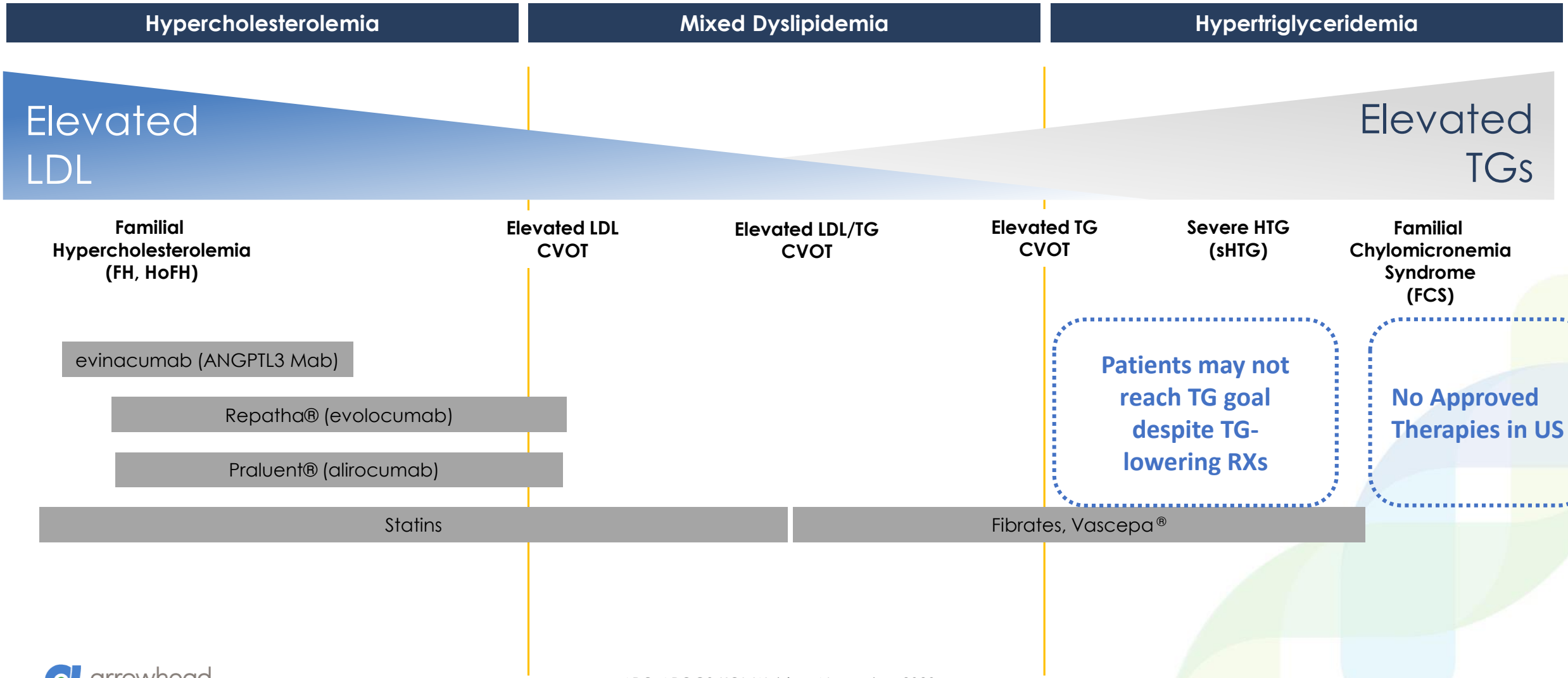
81% of FCS patients report extremely-time consuming symptom management[1]



Dietary restrictions include: limiting total fat intake (<20g/day), reduced intake of simple carbohydrates, no or limited alcohol intake

1. Davidson M.J Clin Lipid. 2018; 2. Esan O.Drug Des, Dev, Ther.2020; 3. Fox R.Exp Rev Card Ther.2020; 4. Gaudet. N Eng J Med.2014;.

Current CV treatment landscape leaves open key unmet needs



ARO-APOC3 Clinical Development

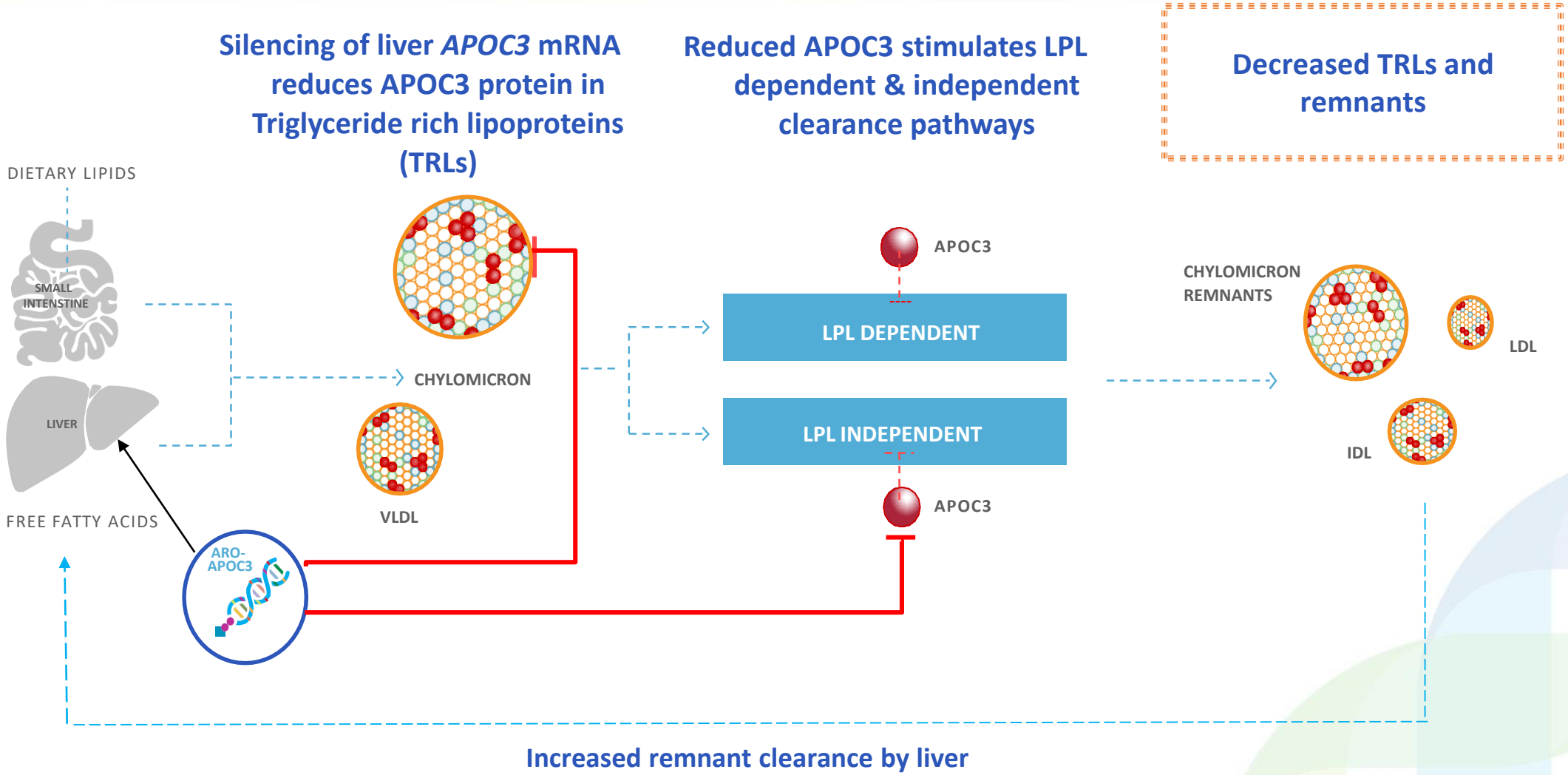
Javier San Martin, M.D.

APOC3 is a key regulator of triglyceride-rich lipoproteins (TRLs) through lipoprotein lipase (LPL)-dependent and -independent pathways

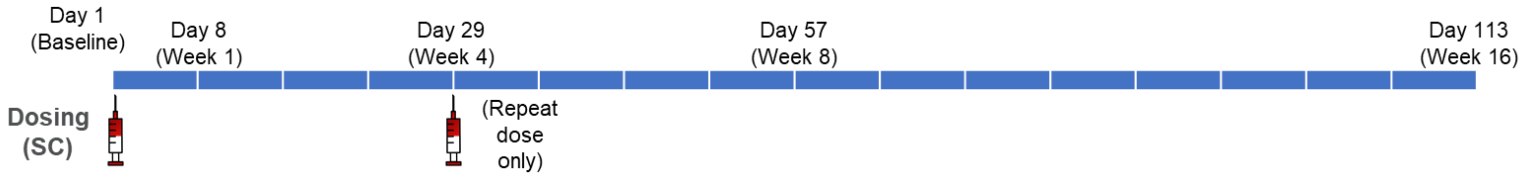
- **Severe hypertriglyceridemia (SHTG) is characterized by triglyceride (TG) levels ≥ 500 mg/dL, which can lead to acute pancreatitis**
  - SHTG may be caused by a combination of genetics (i.e., chylomicronemia), diet, and comorbid conditions (e.g., metabolic syndrome, diabetes)
  - Reduction and maintenance of TG levels below 500 mg/dL can reduce the risk of acute pancreatitis and is a goal of therapy[1]
- **APOC3 is a key regulator of TG metabolism**
  - SHTG is characterized by excess levels of Apolipoprotein C3 (APOC3)-containing particles, such as chylomicrons or VLDL
  - Loss-of-function mutations in *APOC3* are associated with lower TG, lower post-prandial lipemia and decreased incidence of coronary artery disease
- **ARO-APOC3 is designed to specifically target and silence the *APOC3* gene, thereby reducing TG levels**
  - ARO-APOC3 is an investigational synthetic, double-stranded, hepatocyte-targeted RNA interference trigger designed to specifically target *APOC3* mRNA transcripts

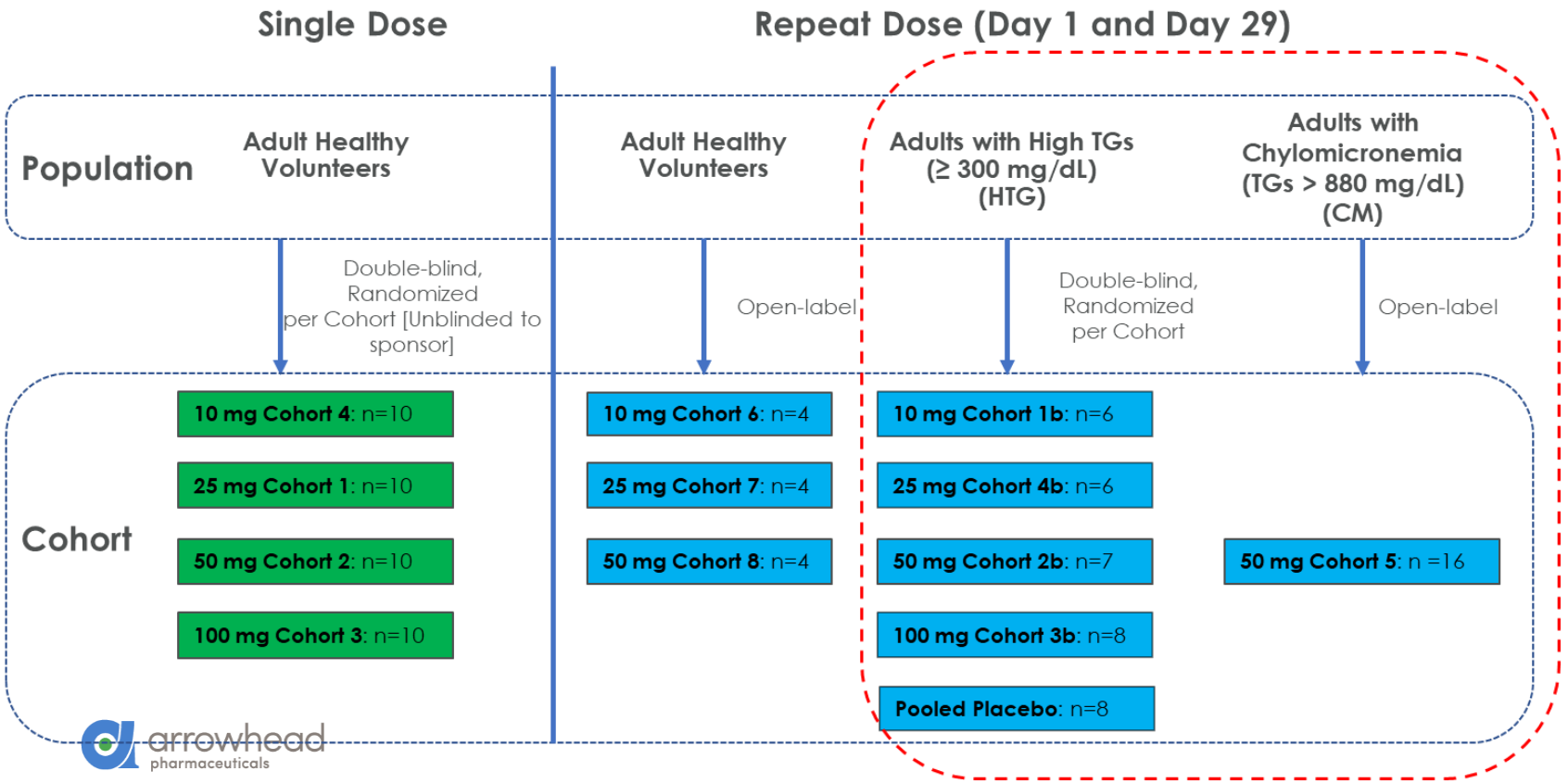
[1]NCEP 2002. Circulation 106:3143-3421

ARO-APOC3 targets and silences the *APOC3* gene, reducing TG levels



Phase 1 study to evaluate the effect of ARO-APOC3 in HTG & Chylomicronemia





Study Endpoints

Safety (Primary):

- Incidence and frequency of adverse events

Key Pharmacodynamics (PD) and Lipid Parameters:

- Change from baseline over time in APOC3
- Change from baseline over time in the following key parameters: Triglyceride, HDL-C, non-HDL-C

Data cut date: 31 Aug 2020

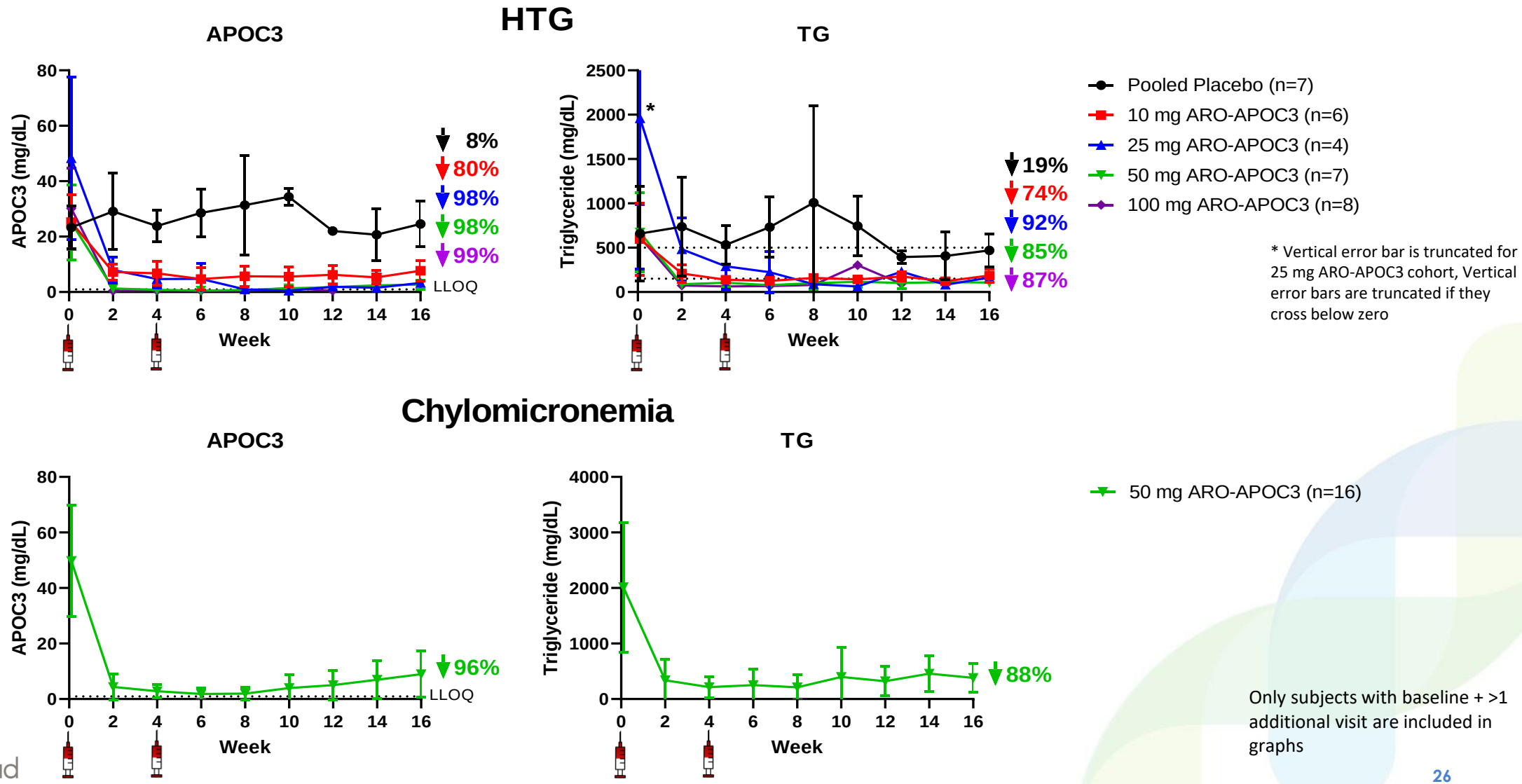
Baseline characteristics of HTG and CM patient cohorts

	HTG (TG≥ 300 mg/dL)					Chylomicronemia
Mean (range) Fasting values	**Pooled Placebo n=8**	**10 mg ARO-APOC3 n = 6**	**25 mg ARO-APOC3 n = 6**	**50 mg ARO-APOC3 n = 7**	**100 mg ARO-APOC3 n = 8**	**50 mg ARO-APOC3 n=16 (all active)**
Age (years)	47.6 (30-68)	50.2 (40-55)	53.8 (36-62)	48.1 (19-64)	55.0 (36-70)	46.8 (20-65)
% Male	75	100	67	43	75	56
BMI (kg/m^2)	30.7 (21.8-39.5)	32.7 (25.3-39.2)	30.5 (25.8-34.7)	30.7 (20.1-40.0)	32.2 (27.3-36.3)	29.6 (20.3-35.3)
APOC3 (mg/dL)	23 (13-34)	25 (15-42)	45 (25-88)	25 (13-49)	30 (18-63)	50 (19-88)
Triglycerides (mg/dL)	618 (262-1746)	596 (318-1381)	1659 (459-3546)	671 (294-1593)	616 (283-1448)	2015 (344-4636)
VLDL-C (mg/dL)*	88 (40-200)	128 (62-372)	321 (94-645)	98 (51-253)	104 (61-162)	259 (58-542)
LDL-C (mg/dL) (direct assay)	80 (15-144)	87 (56-130)	87 (16-150)	76 (23-117)	95 (12-184)	25 (2-77)
HDL-C (mg/dL)	28 (16-38)	28 (12-38)	28 (18-38)	29 (22-44)	33 (18-64)	18 (10-36)
non-HDL-C (mg/dL)	168 (81-231)	213 (110-443)	347 (188-696)	210 (126-332)	204 (139-314)	302 (123-598)

* VLDL-C is not calculated when TG > 400 mg/dL

Data cut date: 31 Aug 2020

ARO-APOC3 results in substantial & sustained reduction of APOC3 and TG

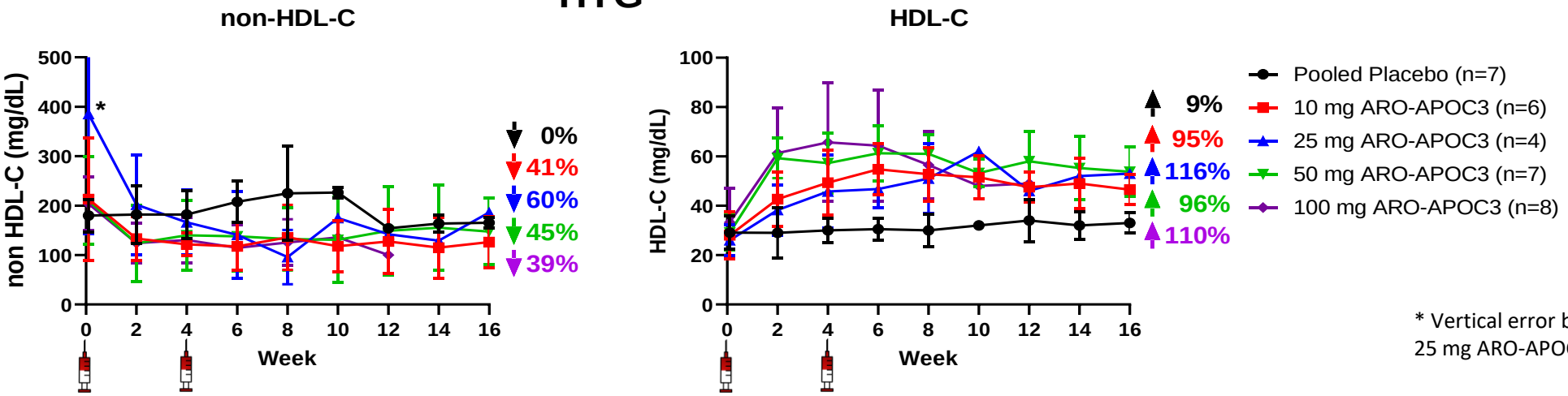


Mean values +/- SD are plotted for each cohort ;% values are maximum mean reductions for each cohort (n>1 subject at a visit date)

Data cut date: 31 Aug 2020

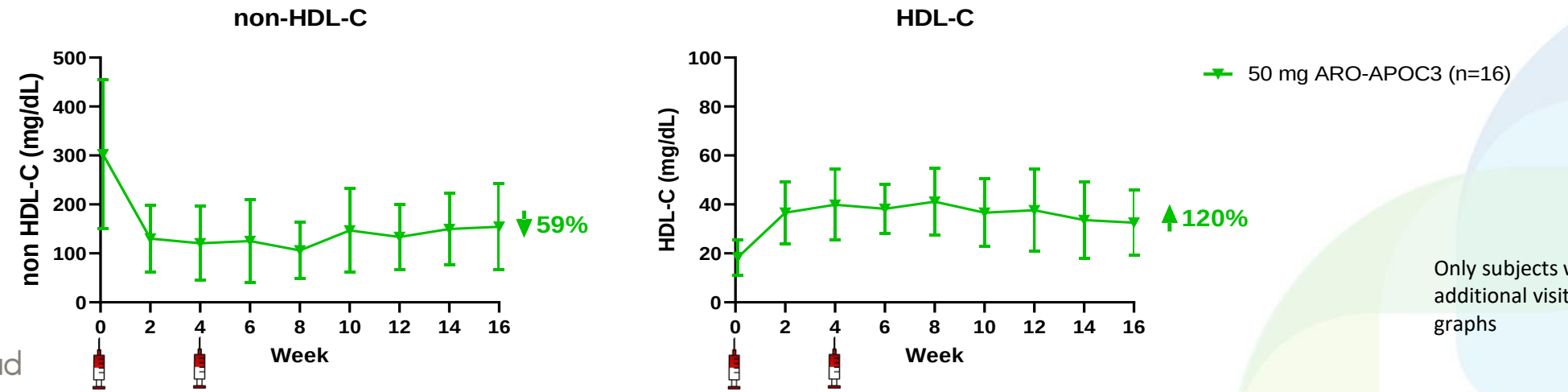
ARO-APOC3 substantially reduces non-HDL-C and increases HDL-C

HTG



* Vertical error bar is truncated for 25 mg ARO-APOC3 cohort

Chylomicronemia



Only subjects with baseline + >1 additional visit are included in graphs

Mean values +/- SD are plotted for each cohort ;% values are maximum mean reductions for each cohort (n>1 subject at a visit date)

Data cut date: 31 Aug 2020

Summary interim safety findings in HTG and CM patients

	HTG Cohorts (TG>300 mg/dL)					CM TG>880mg/dL	
TEAEs Reported in > 1 subject, AE Term (MedDRA Preferred Term)	**10 mg Cohort 1b n = 5**	**25 mg Cohort 4b n = 5**	**50 mg Cohort 2b n = 7**	**100 mg Cohort 3b n=8**	**Pooled Placebo N=8**	**50 mg Cohort 5 n=16**	**Total Active n = 41**
Injection site reaction – erythema, rash, discoloration, pain, bruising	0	2 (40%)	2 (28.5%)	2 (25%)	0	2 (12.5%)	8 (19.5%)
ALT, LFT, transaminase increased, Liver function test increased	0	1 (20%)	1 (14%)	2 (25%)	0	3 (19%)	7 (17%)
Headache	1 (20%)	2 (40%)	2 (28.5%)	1 (12.5%)	0	0	6 (15%)
Upper respiratory tract infection	0	1 (20%)	2 (28.5%)	0	0	1 (6%)	4 (10%)
Rash	0	0	0	2 (25%)	0	1 (6%)	3 (7%)
Abdominal distention	0	2 (40%)	0	0	0	0	2 (5%)
Diarrhea	1 (20%)	0	1 (14%)	0	0	0	2 (5%)
Hyperglycemia	0	1 (20%)	1 (14%)	0	0	0	2 (5%)
Paresthesia	1 (20%)	0	0	1 (12.5%)	0	0	2 (5%)

- **AEs at injection site were all mild**
- **ALT elevations were generally asymptomatic and transient, returning towards baseline by end of study**
  - Only two subjects had ALT >3X ULN at two sequential visits with return to pre-dose baseline by Day 113 (EOS).
  - The highest ALT was in a subject with a history of cholelithiasis and biliary colic. Baseline ALT of 22 U/L, elevation on Day 85 to 230 U/L with return to 36 U/L on Day 99 and 33 U/L at Day 113 (EOS) Subject subsequently underwent elective cholecystectomy
- **No clinically significant adverse changes in platelets, total bilirubin or creatinine**
- **No drug discontinuations**
- **1 SAE of pancreatitis**
  - Not related to ARO-APOC3
  - History of pancreatitis, type 2 diabetes mellitus and gall stones
  - MRCP/endoscopic ultrasound indicated pancreatolithiasis as probable cause

Safety data cutoff 11 Sep 2020

ARO-APOC3 results in favorable lipid changes

- In patients with **hypertriglyceridemia**, 10 mg, 25 mg, 50 mg and 100 mg SC doses of ARO-APOC3, resulted in **robust and sustained reductions in TGs and Non-HDL-C, with HDL-C increases**
  - Maximal mean reduction of -80% to -99% in APOC3
  - Maximal mean reduction of **-**74% to -92% in TG, -39% to -62% in non-HDL-C
  - Maximal mean increase of +95% to +116% in HDL-C
- In patients with **chylomicronemia,** 50 mg ARO-APOC3 SC achieves similar levels of **reduction of APOC3 and changes in key lipid parameters**
  - Maximal mean reduction of -98% in APOC3
  - Maximal mean reduction of -88% in TG, -59% in non-HDL-C
  - Maximal mean increase of +120% in HDL-C
- The effect of ARO-APOC3 is **maintained >12 weeks post second dose** regardless of patient population
- ARO-APOC3 **safety profile** supportive of later stage clinical development based on interim Phase 1 study results

ARO-APOC3 may prove useful as a therapeutic option in patients with HTG, SHTG, and FCS

ARO-APOC3 Proposed Development Plan

	Est. Initiation Date 1H 2021		Est. Initiation Date 2H 2023	
FCS	**Phase 3**	• N=60 • **Prim EP: TG** • Second EP: APOC3, HDL-C, non- HDL-C, Safety Pancreatitis		
sHTG (TG>500mg/dl)	**Phase 2 Dose Finding**	• N=300 • **Prim EP: TG/Dose** • Second EP: HDL-C, non-HDL-C, ApoB, LDL-C, Safety Pancreatitis	**Phase 3**	• N=900 • **Prim EP: TG** • Second EP: HDL-C, non-HDL-C, ApoB, LDL-C, Safety Pancreatitis
HTG (TG>150mg/dl)	**Phase 2 Dose finding**	• N=300 • **Prim EP: TG/Dose** • Second EP: HDL-C, non-HDL-C, ApoB, LDL-C, Safety		

Wrap Up

Chris Anzalone, Ph.D

ARO-APOC3: A Compelling Market Opportunity

- **Substantial CV risk driven by high TGs**
- **APOC3 is a validated target for Hypertriglyceridemia**
  - Loss-of-function mutations in APOC3 are associated with lower TG and CVD
- **Competitive landscape is attractive**
  - ARO-APOC3 is the *only* RNAi candidate currently in clinical development against the target
    - ASOs and fish oils are the primary competition at this point
  - ARO-APOC3 has shown substantially better TG lowering than fish oils
  - We don't expect to see the ASO-related safety issues, such as thrombocytopenia
  - Expect ARO-APOC3 to have better durability than ASOs
    - Anticipate dosing every 4-6 months vs. monthly with ASOs

Clinical and Commercial Plans

- **Begin next clinical steps in 1h 2021**
  - Plan on P3 in FCS
  - Plan P2b in severe hypertriglyceridemic patients (TGs >500mg/dL)
    - Enable P3 in this population
  - Plan P2b in patients with TGs >150mg/dL
    - Provides optionality for possible future P3 in this population
- **Staged commercial approach**
  - Address FCS unmet medical need relatively quickly
  - Expand into ~4m population of sHTG (TGs >500mg/dL)
  - Retain optionality to possibly expand further into patients with TG >150mg/dL

Q&A Session
Panel