EAS

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Zodasiran Silences Hepatic ANGPTL3 Leading to Deep and Durable Reductions in Atherogenic Lipids and Lipoproteins in Mixed Hyperlipidemia Patients: Final Results From ARCHES-2, Double-blind Period

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Icahn School of Medicine at Mt Sinai on behalf of the ARCHES-2 Study Team

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Disclosure

Arches-2

	No, nothing to disclose
X	**Yes, please specify:**

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research	Royalties/ Patent	Stock Options	Ownership / Equity Position	Employee	Other (please specify)
Amgen	X	X	X					Grants
Arrowhead	X	X	X					Grants
Novartis	X	X	X					Grants
Eli Lilly	X	X	X					Grants
Regeneron	X	X	X					Grants
CRISPR	X	X						Grants
Editas	X	X						Grants

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research	Royalties/ Patent	Stock Options	Ownership / Equity Position	Employee	Other (please specify)
Lipigon	X	X						Grants
Precision Bio	X	X						Grants
Ultragenyx	X	X						Grants
Verve	X	X						Grants
Meda Pharma	X							
Wolters Kluwer (Up to Date)				X Significant				
MediMergent LLC					X Significant			

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

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- *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:
  - ▼ TG, LDL-C, 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]

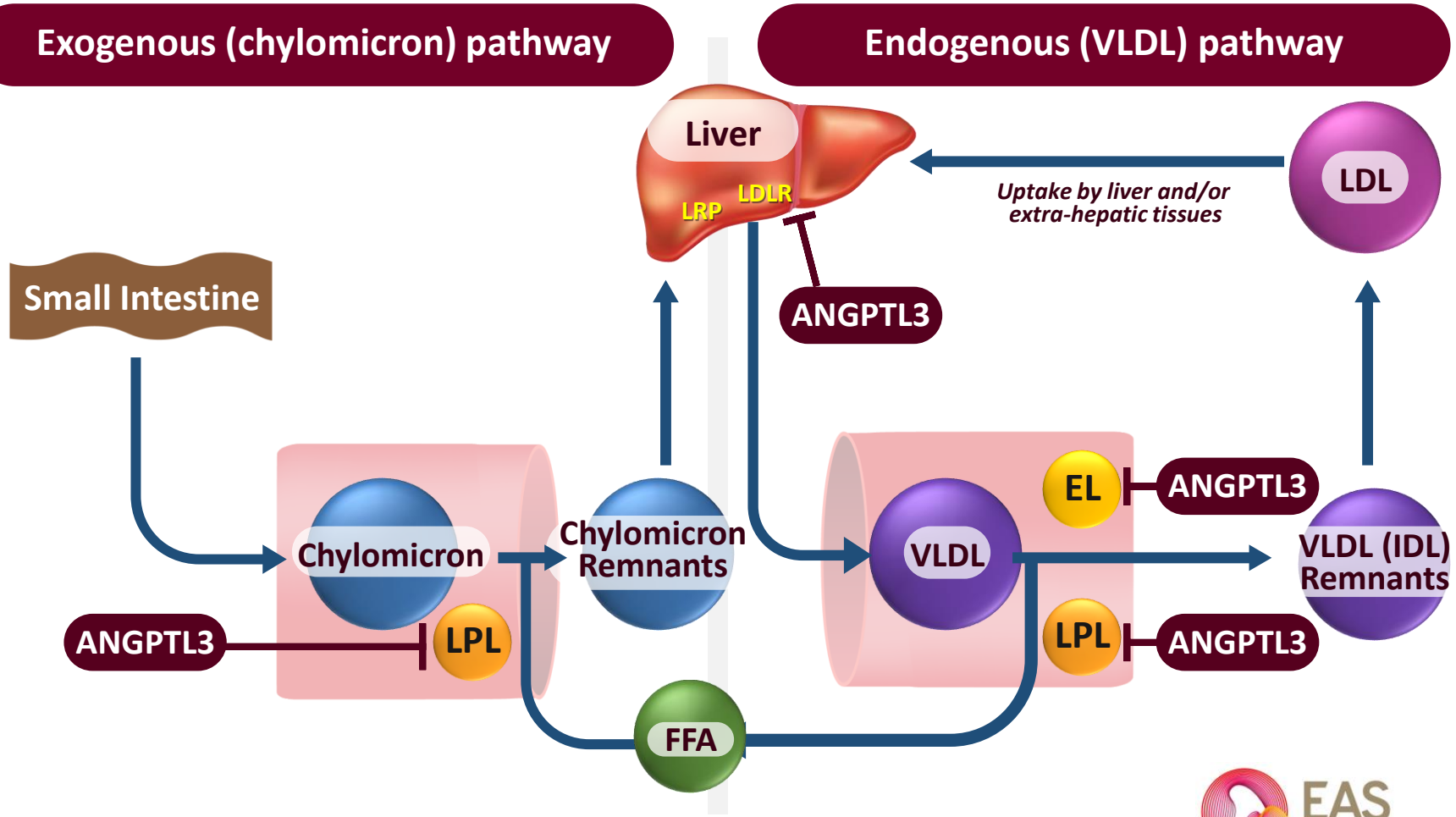

Figure adapted from: Rosenson RS, Shaik A, Song W. *J Am Coll Cardiol.* 2021;78(18):1817-1830.

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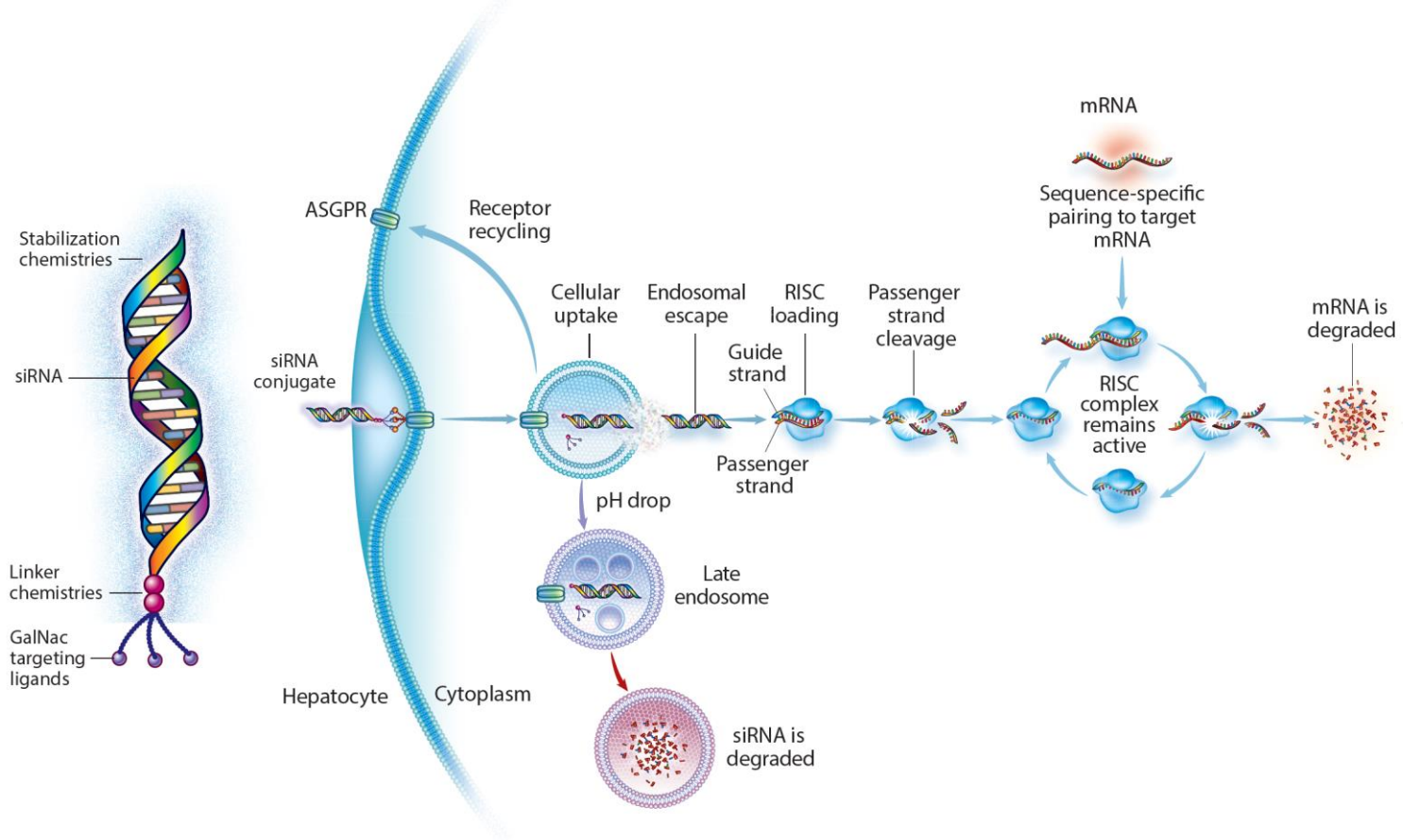
▼=Reductions in. **1.** Adam, et al. *J Lipid Res.* 2020;61(9): 1271-86. **2.** Rosenson. *J Lipid Res.* 2021:62:100060. **3.** Dewey, et al. *N Engl J Med.* 2017;377 (3):211-21. **4.** Minicocci, et al. *J Lipid Res.* 2013;54(12): 3481-90. **5.** Musunuru, et al. *N Engl J Med.* 2010; 363(23):2220-7. **6.** Stitziel, et al. *J Am Coll Cardiol.* 2017; 69(16):2054-63. **ANGPTL3**, angiopoietin-like 3; **ASCVD**, atherosclerotic cardiovascular disease; **CR**, chylomicron remnants; **HDL-C**, high density lipoprotein cholesterol; **IDL**, intermediate density lipoprotein; **LDL**, low density lipoprotein; **LDL-C**, low density lipoprotein cholesterol; **LDLR**, low density lipoprotein receptor; **LRP**, low density lipoprotein receptor related protein; **TG**, triglyceride; **VLDL**, very low-density lipoprotein; **VLDL-C**, very low-density lipoprotein cholesterol.

Key Features Of Using RNAi As A Therapeutic Modality

- Arrowhead's Targeted RNAi Molecule (TRiM™) technology leverages the RNAi mechanism
- RNAi is a natural process that uses short fragments of RNA molecules to interfere with mRNA translation into associated proteins.



High Specificity:
Allowing to suppress the expression of a specific gene

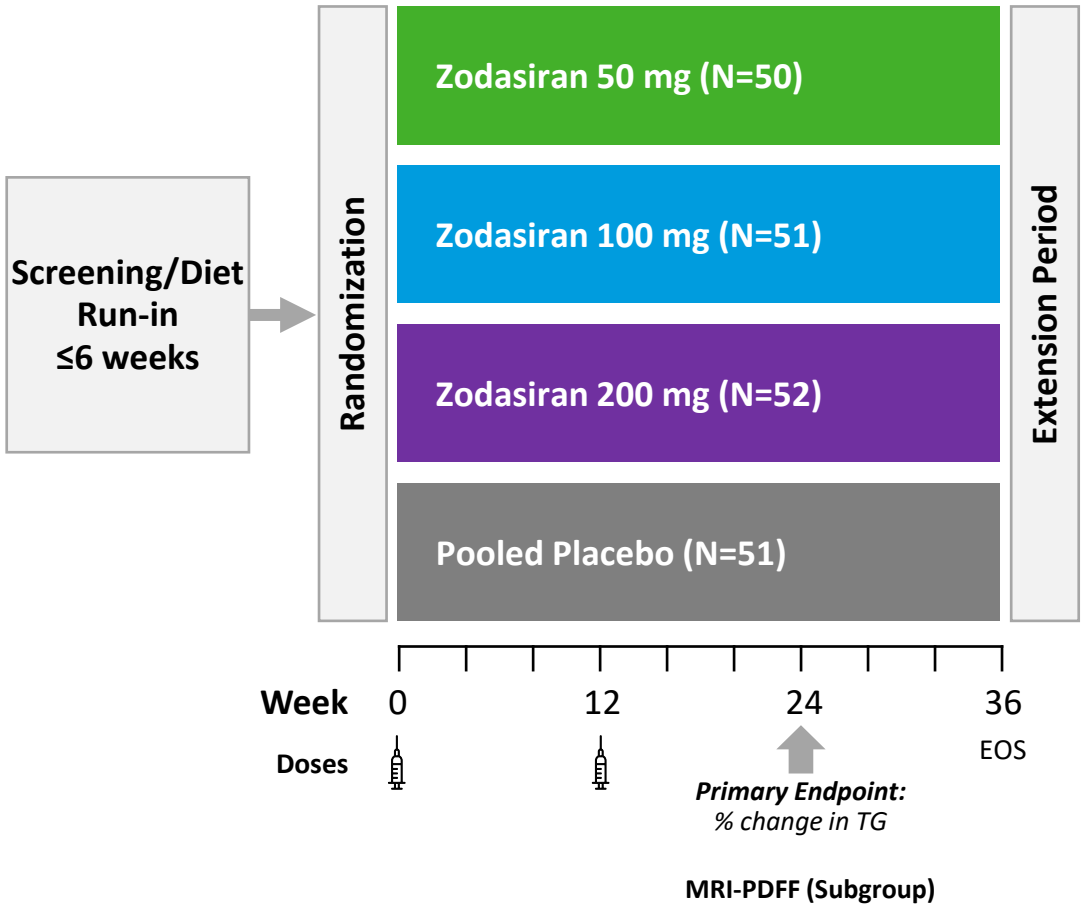
Potent Activity:
Deep and consistent silencing of target genes

Safety:
Minimal off target adverse effects due to targeted delivery (GalNAc) and sequence specificity

Infrequent Dosing:
Long tissue PK/PD, on target effect

ARCHES-2: A Double-Blind, Phase 2b Placebo-Controlled, Dose Ranging Study of Zodasiran (ARO-ANG3) in Patients With Mixed Hyperlipidemia

Arches-2



- **Study Objectives:** To evaluate safety and efficacy for lowering TG and atherogenic lipoproteins in patients with Mixed Hyperlipidemia, and to explore optimal dosing
- **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 and over time in:
  - Primary endpoint: TG
  - Key secondary and exploratory endpoints:
    - ANGPTL3, non-HDL-C, LDL-C, ApoB, remnant cholesterol, Lp(a), HDL-C
  - Liver Fat fraction (LFF) in 61 steatotic patients (MRI-PDFF subgroup; LFF 8% at baseline) at Week 24
  - Safety
- **Data Analysis:** Phase 2 study data to 36 Weeks, EOS
- **OLE:** All patients were eligible to enroll in the OLE at the end of the study

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*All samples taken after ≥10 hour fast. **ANGPTL3**, angiopoietin-like 3; **ApoB**, apolipoprotein B; **EOS**, end of study; **HDL-C**, high density lipoprotein cholesterol; **LDL-C**, low density lipoprotein cholesterol; **Lp**, lipoprotein; **Lp(a)**, lipoprotein (a); **MRI-PDFF**, magnetic resonance imaging-proton density fat fraction; **Non-HDL-C**, non-high-density lipoprotein cholesterol; **TG**, triglyceride.

Baseline Characteristics

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	Placebo (N=51)	ARO-ANG3 50 mg (N=51)	ARO-ANG3 100 mg (N=51)	ARO-ANG3 200 mg (N=51)	All Patients (N=204)
Mean (SD) Age, years	60 (11)	60 (13)	60 (10)	62 (13)	61 (12)
Female, n (%)	24 (47)	25 (49)	22 (43)	24 (47)	95 (47)
White, n (%)	48 (94)	49 (96)	49 (96)	49 (96)	195 (96)
Mean (SD) BMI, kg/m^2	33 (7)	33 (5)	33 (6)	32 (6)	33 (6)
Type 2 Diabetes, n (%)	20 (39)	19 (37)	22 (43)	25 (49)	86 (42)
Mean (SD) ANGPTL3, μg/L	93 (29)	99 (36)	93 (27)	101 (36)	97 (32)
Mean (SD) Triglyceride, mg/dL	234 (90)	239 (74)	248 (103)	260 (95)	245 (91)
Mean (SD) LDL-C (UC), mg/dL	94 (31)	103 (29)	101 (45)	92 (34)	97 (36)
Mean (SD) Non-HDL-C, mg/dL	139 (42)	151 (36)	150 (47)	143 (40)	146 (41)
Mean (SD) ApoB, mg/dL	96 (24)	105 (24)	100 (26)	94 (25)	99 (25)
Mean (SD) Remnant cholesterol,[a] mg/dL	45 (34)	49 (19)	49 (31)	51 (28)	48 (29)
Mean (SD) HDL-C, mg/dL	42 (12)	43 (13)	40 (11)	42 (14)	42 (12)

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[a]Based on calculation: remnant cholesterol = (total cholesterol) - (HDL-C) - (LDL-C [UC]); Data are reported as mean (±SD) unless otherwise noted. One patient in 50 mg treatment group was randomized to assigned treatment group but incorrectly received 200 mg for both injections of plozasiran at Day 1 and Week 12 administrations. This patient is classified into the ARO-ANG3 200 mg for Safety Analysis Set and PK Analysis Set. For efficacy analysis on FAS, the number of patients are 51 in each group, for the safety analysis on safety population, the patients are 50, 51, 52 in 50mg, 100mg and 200mg. **ANGPTL3**, angiopoietin-like 3; **ApoB**, apolipoprotein B; **BMI**, body mass index; **HDL-C**, high density lipoprotein cholesterol; **LDL-C**, low density lipoprotein cholesterol; **Non-HDL-C**, non-high-density lipoprotein cholesterol; **SC**, subcutaneous; **SD**, standard deviation; **UC**, ultracentrifuge.

Zodasiran Demonstrated Substantial and Durable Decreases in ANGPTL3 and Consequently in TG and TRL

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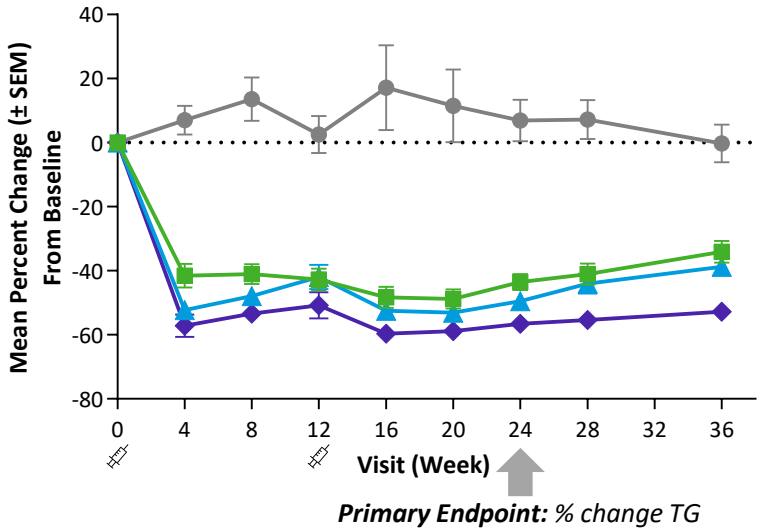
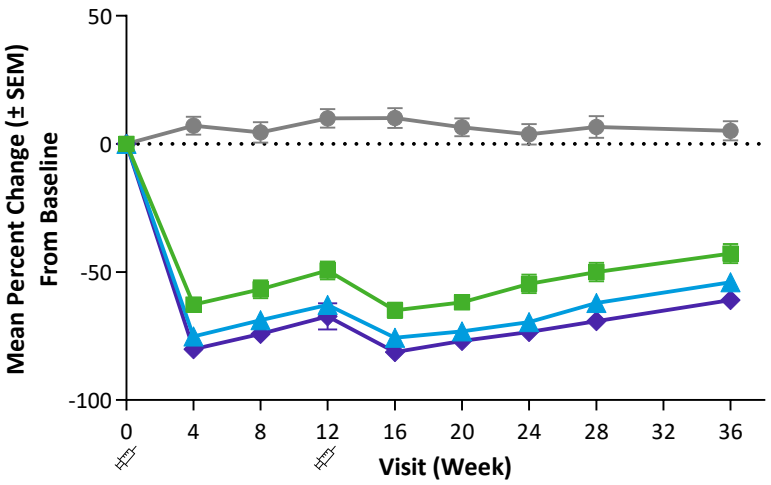
Triglycerides



Primary Endpoint: *% change TG*

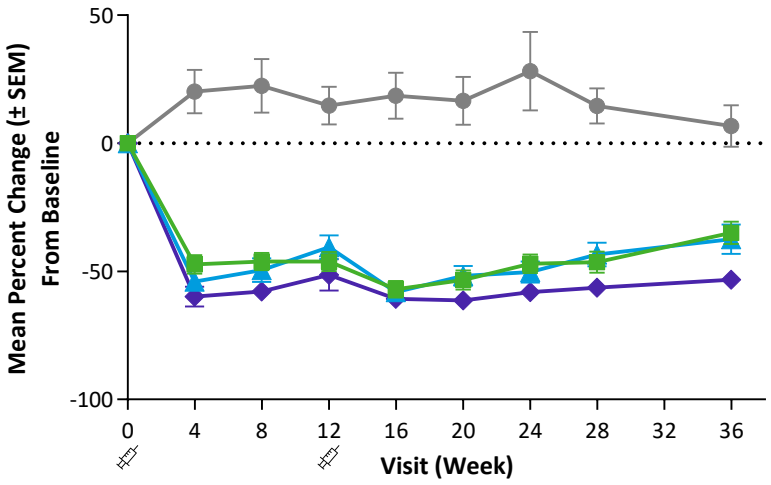
LS Mean* % Change from Baseline Difference vs Placebo			
24 Weeks	-51 p<0.0001	-57 p<0.0001	-63 p<0.0001
36 Weeks	-34	-38	-51

ANGPTL3



LS Mean* % Change from Baseline Difference vs Placebo			
24 Weeks	-54	-70	-74
36 Weeks	-45	-57	-64

Remnant Cholesterol[a]



LS Mean* % Change from Baseline Difference vs Placebo			
24 Weeks	-73	-76	-82
36 Weeks	-43	-45	-58

Placebo

Zodasiran 50 mg Q12W

Zodasiran 100 mg Q12W

Zodasiran 200 mg Q12W

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*Least Square Mean Difference vs Placebo (%); [a]Based on calculation: remnant cholesterol = (total cholesterol) - (HDL-C) - (LDL-C (Ultracentrifugation [UC]). Analysis of Covariance (ANCOVA) with repeated measures modeling was used for statistical modeling **ANGPTL3**, angiopoietin-like 3; **LS**, least squares; **SEM**, standard error of mean; **W**, week.

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Zodasiran Affected Multiple Lipid Parameters and Demonstrated Decreases in Atherogenic TRL and LDL-C in Patients with Mixed Hyperlipidemia

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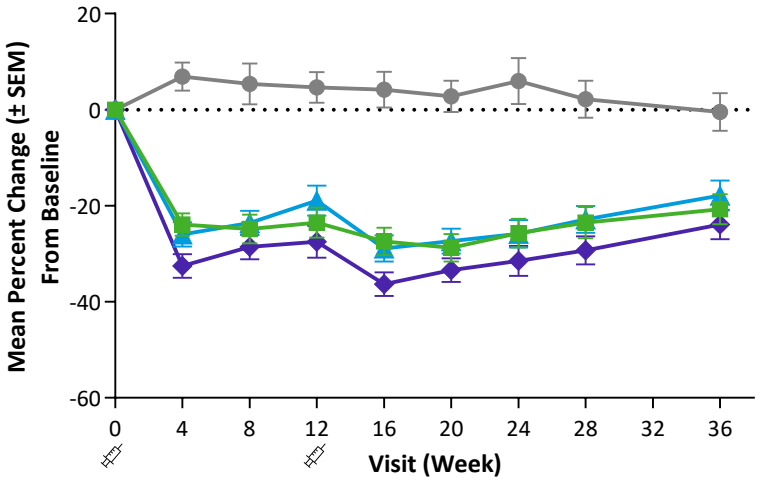
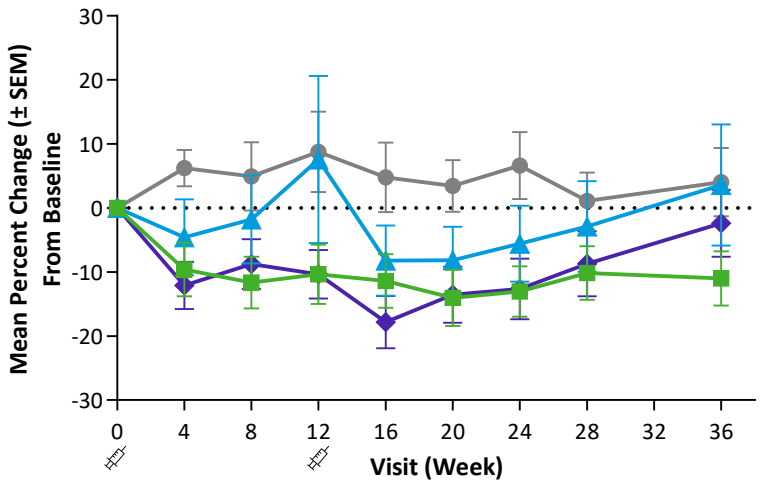
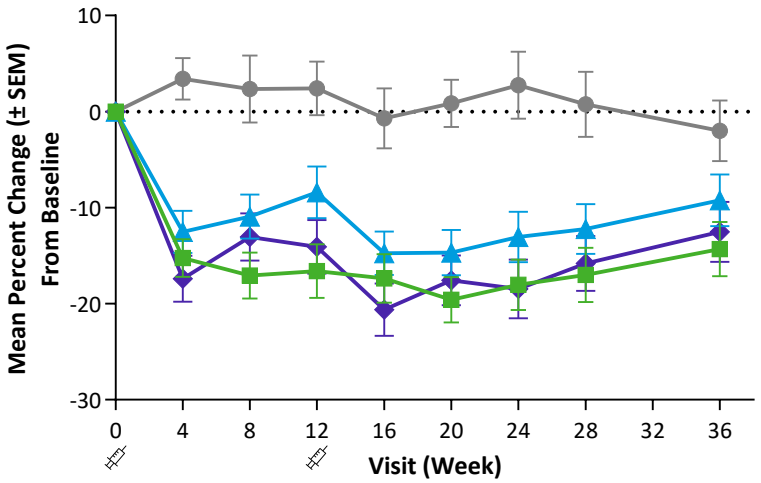
Non-HDL-C*



LDL-C (UC)*



ApoB*



Non-HDL-C Difference vs Placebo (%)			
24 Weeks	-29	-29	-36
36 Weeks	-19	-16	-23

LDL-C (UC)† Difference vs Placebo (%)			
24 Weeks	-16	-14	-20
36 Weeks	-12	-7	-7

ApoB Difference vs Placebo (%)			
24 Weeks	-19	-15	-22
36 Weeks	-11	-7	-11

Placebo Zodasiran 50 mg Zodasiran 100 mg Zodasiran 200 mg

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*Least Square Mean Difference vs Placebo (%); †One patient with baseline value at 17 mg/dL was removed from the analysis; Analysis of Covariance (ANCOVA) with repeated measures modeling was used for statistical modeling **ApoB**, apolipoprotein B; **LDL-C**, low density lipoprotein cholesterol; **Non-HDL-C**, non-high-density lipoprotein cholesterol; **SEM**, standard error of mean; **TRL**, Triglyceride Rich Lipoproteins; **UC**, ultracentrifuge.

Zodasiran Affected Liver Fat, HDL-C and Lipoprotein(a)

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- Liver fat median percent decrease from baseline to Week 24[†] measured by MRI-PDFF in a subset of patients with baseline >8% (N=61) is -10%, -16% and -27%* vs placebo (50 mg, 100 mg and 200 mg, zodasiran treatment, respectively)

- HDL-C least square mean difference vs placebo (%) at Study Week 24 is -12.0*, -21.6** and -24.5** and -7.8*, -20.1** and -15.8** at Week 36 for 50 mg, 100 mg and 200 mg zodasiran treatment, respectively

- Lipoprotein (a), least square mean difference vs placebo (%) at Study Week 24 is -7, -20* and -17* and -3, -12, -6 at Week 36 for 50 mg, 100 mg and 200 mg zodasiran treatment, respectively

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(*P<0.05);** (P<0.0001; [†] Liver fat is only assessed to week 24; **HDL-C**, high density lipoprotein cholesterol; **MRI-PDFF**, magnetic resonance imaging-proton density fat fraction.

Summary of Adverse Events

N (%)	Placebo	ARO-ANG 50 mg	ARO-ANG 100 mg	ARO-ANG 200 mg
TEAEs				
Covid-19	9 (18%)	10 (20%)	12 (24%)	11 (21%)
Upper respiratory tract infection	4 (8%)	5 (10%)	1 (2%)	5 (10%)
Headache	2 (4%)	5 (10%)	2 (4%)	7 (14%)
Urinary tract infection	2 (4%)	3 (6%)	3 (6%)	6 (12%)
Diabetes (Diabetes mellitus, T2 DM)	2 (4%)	2 (4%)	2 (4%)	7 (13%)
Injection site pain	0 (0%)	5 (10%)	4 (8%)	2 (4%)
Nausea	2 (4%)	3 (6%)	3 (6%)	3 (6%)
Back pain	0 (0%)	3 (6%)	2 (4%)	6 (12%)
Dizziness	3 (6%)	2 (4%)	4 (8%)	1 (2%)
SAEs	4 (8%)	5 (10%)	0 (0%)	1 (2%)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	1 (2%)	0 (0%)	1 (2%)	0 (0%)
TEAEs associated with death	1 (2%)	0 (0%)	0 (0%)	0 (0%)
HbA1c, % Baseline mean (SD)	6.5 (1.2)	6.2 (1.0)	6.4 (1.1)	6.6 (1.2)
HbA1c, % Mean (SD) Week 24 (%)	6.4 (1.0)	6.4 (1.0)	6.4 (1.1)	6.8 (1.4)
Platelets, Mean (SD) change from baseline at Week 24	11.1 (40.3)	18.0 (31.8)	4.6 (34.8)	10.7 (41.4)

- TEAEs reported reflect comorbidities and underlying conditions of the study population
- No Changes in Platelets
- All SAEs were recovered/resolved (except 1 SAE with an outcome of death in the placebo group)
- Overall favorable safety profile.
- All TEAEs manageable
- Minimal changes in HbA1c

Note: Diabetic patients are defined as having HbA1c ≥6.5% or Fasting Glucose ≥126 mg/dL or with medical history of 'diabetes' or receiving diabetic medications at baseline; [a]MRI-PDFF analysis set; ANCOVA model includes covariates treatment arm, stratification factor, and baseline value for liver fat; Statistical significance of A1C was determined. **DM**, diabetes mellitus; **LS**, least squares; **MRI-PDFF**, magnetic resonance imaging-proton density fat fraction; **SAEs**, serious adverse events; **SD**, standard deviation; **TEAEs**, treatment emergent adverse events.

Minimal Change in Mean HbA1C or HOMA-IR

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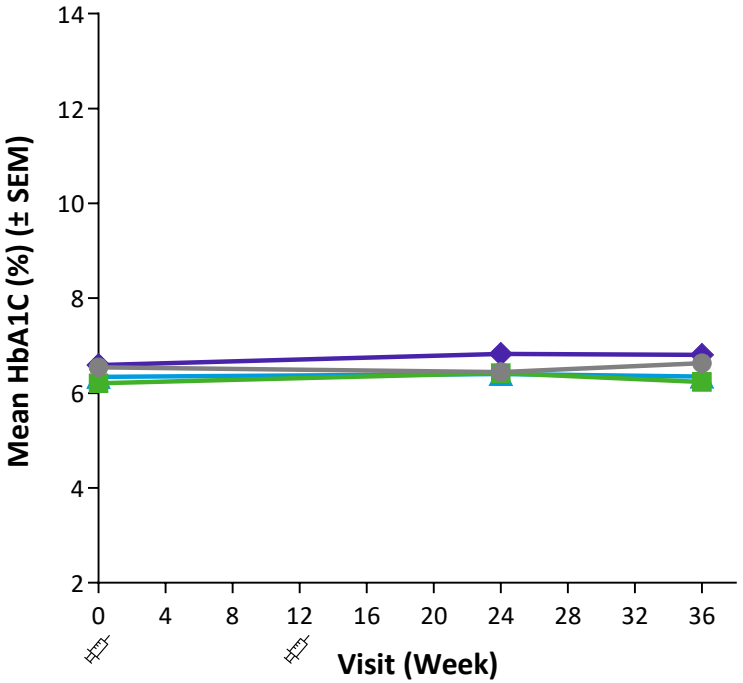
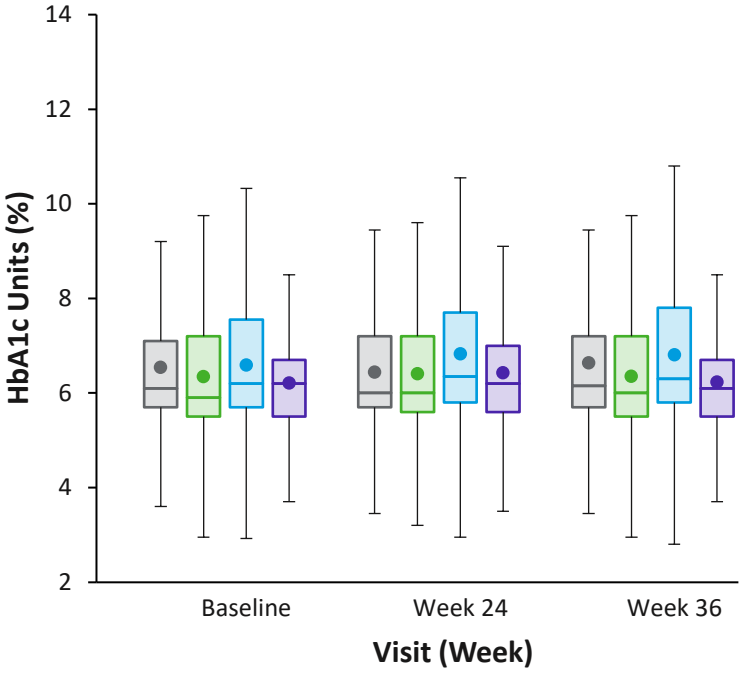
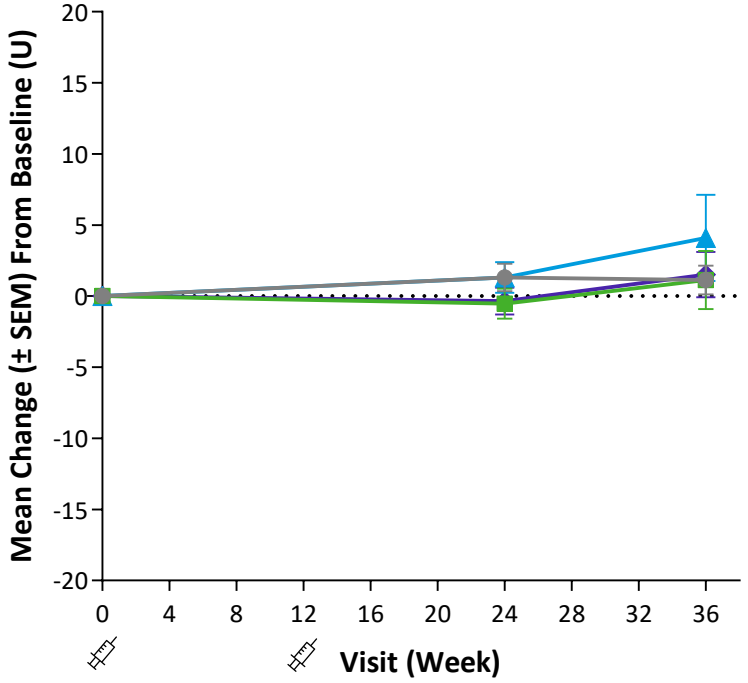
Glycemic Control: HbA1C (All Patients)



Glycemic Control: HbA1C (All Patients)



Insulin Sensitivity: HOMA-IR (All Patients)



Placebo | Zodasiran 50 mg | Zodasiran 100 mg | Zodasiran 200 mg

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SEM, standard error of mean.

Zodasiran Demonstrated Potent and Durable Reductions of Atherogenic Lipoproteins in Mixed Hyperlipidemia

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- By silencing ANGPTL3, zodasiran significantly reduced TGs and atherogenic triglyceride rich lipoproteins, across all dose levels at Week 24 in patients with mixed hyperlipidemia
  - ANGPTL3 ↓ to -74%
  - TG ↓ to -63%
  - Remnant cholesterol ↓ to -82%
  - ApoB ↓ to -22%
  - Non-HDL-C ↓ to -36%
  - LDL-C ↓ to -20%
- ARCHES-2 data demonstrate a favorable safety profile for zodasiran in this study with patients with mixed hyperlipidemia
- The reductions in serum lipids and lipoproteins and favorable safety profile seen in ARCHES-2 support the potential of zodasiran to treat residual ASCVD risk in patients with elevated TRLs
- Zodasiran is a promising potential treatment for patients with increased risk for ASCVD due to elevated TRL and these data support further development of zodasiran in Phase 3 programs including a cardiovascular outcomes trial

We would like to thank the patients and caregivers who participated in this study

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ANGPTL3, angiopoietin-like 3; **ApoB**, apolipoprotein B; **ASCVD**, atherosclerotic cardiovascular disease; **LDL-C**, low density lipoprotein cholesterol; **Non-HDL-C**, non high density lipoprotein cholesterol; **SD**, standard deviation; **TG**, triglyceride; **TGs**, triglycerides; **TRLs**, triglyceride-rich lipoproteins, **UC**, ultracentrifuge.

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Arches-2

ORIGINAL ARTICLE

Zodasiran, an RNAi Therapeutic Targeting ANGPTL3, for Mixed Hyperlipidemia

Robert S. Rosenson, M.D., Daniel Gaudet, M.D., Ph.D., Robert A. Hegele, M.D., Christie M. Ballantyne, M.D., Stephen J. Nicholls, M.B., B.S., Ph.D., Kathryn J. Lucas, M.D., Javier San Martin, M.D., Rong Zhou, Ph.D., Ma'an Muhsin, M.D., Ting Chang, Ph.D., Jennifer Hellawell, M.D., and Gerald F. Watts, D.Sc., Ph.D., M.D., for the ARCHES-2 Trial Team*