EAS 93rd Congress

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Zodasiran (ARO-ANG3), an Investigational RNAi Therapeutic, Demonstrates Profound and Durable Reductions in LDL-Cholesterol and Other Atherogenic Lipoproteins in Patients with HoFH; GATEWAY Final Results

AUTHORS: Raal F , Bergeron J, Gaudet D, Rosenson RS, Sullivan D, Turner T, Fu R, Muhsin, M, Hellawell J, Hamilton J, Hegele RA, Ballantyne CM, Knowles JW[1], Leeper NJ, Goldberg I, Watts G F

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Disclosure Slide

	No, nothing to disclose
	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Frederick J Raal	x	x	x					

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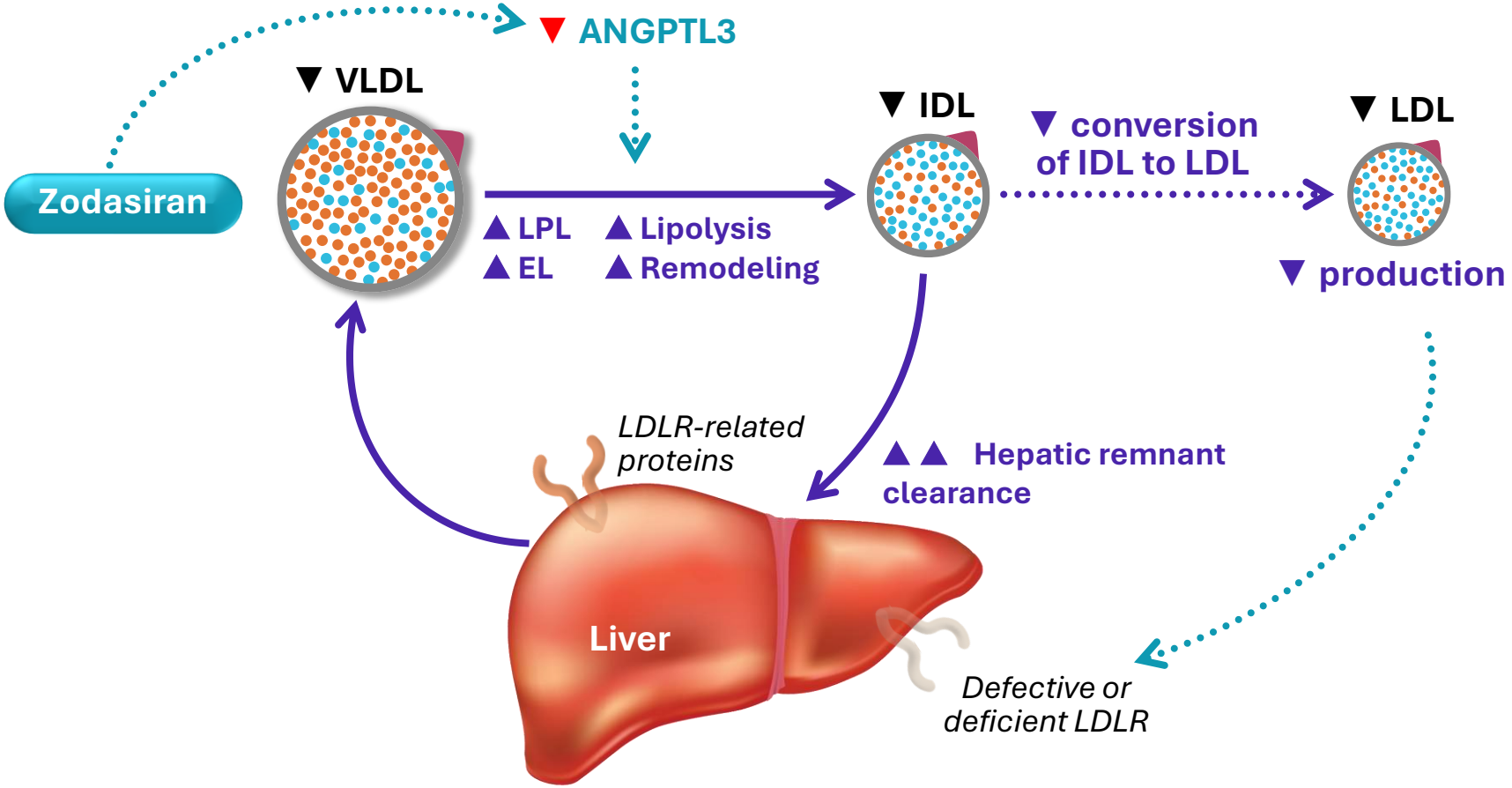
ANGPTL3 is a Key Regulator of Lipoprotein Metabolism and Clearance[1-6]



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

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

RNAi As A Therapeutic Modality

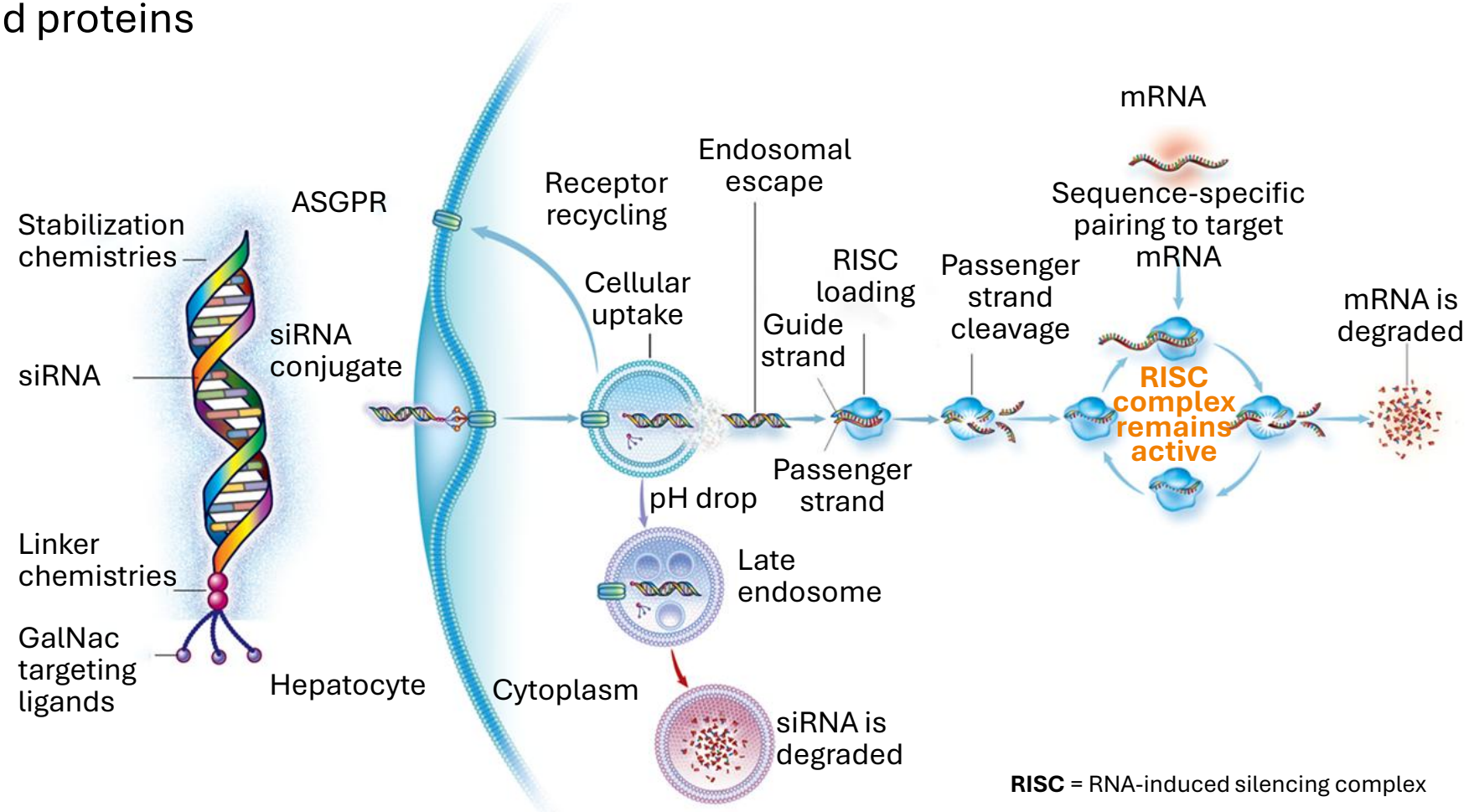
- Arrowhead's Targeted RNAi Molecule (TRiM™) technology leverages the RNAi mechanism
- RNAi is a natural process that uses short fragments of RNA molecules to interfere with mRNA translation into associated proteins

High Specificity:
Gene specific silencing

Potent Activity:
Deep and consistent silencing of target genes

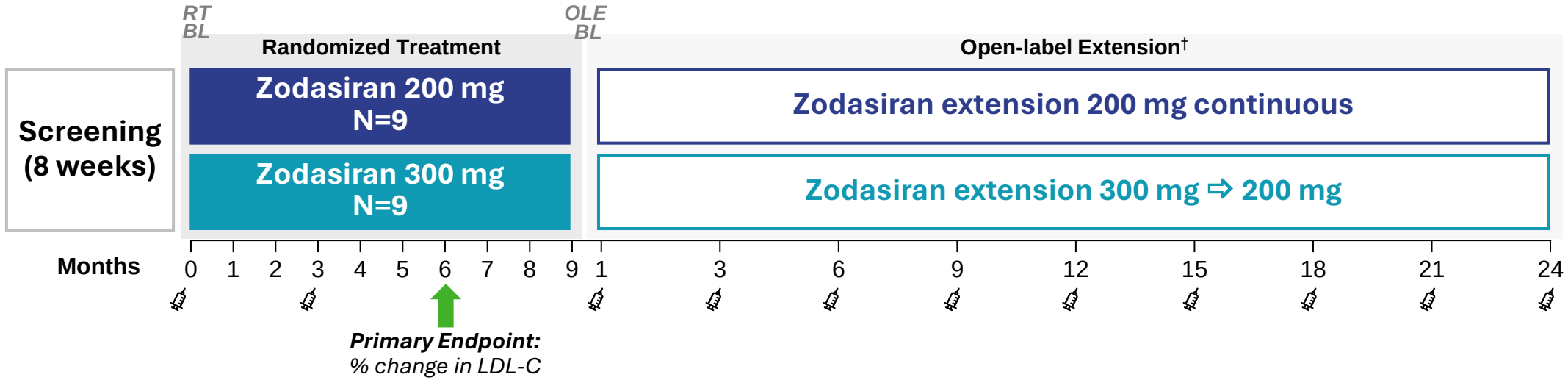
Safety:
Minimal off target adverse effects due to targeted delivery (GalNAc) and sequence specificity

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



RISC = RNA-induced silencing complex

GATEWAY: An Open-Label, Phase 2 Dose Ranging Study of Zodasiran in Patients With Homozygous Familial Hypercholesterolaemia



Study Objectives

- To evaluate safety and efficacy of zodasiran in patients with HoFH, and to explore optimal dosing

Study Population

- HoFH confirmed by genetic testing or clinical diagnosis
- Fasting LDL-C >2.6 mmol/L at screening
- On stable low-fat diet, lipid-lowering standard of care (including apheresis), statins, ezetimibe +/- PCSK9 inhibitors

Key Endpoints*

- **Primary endpoint:** % change from to Week 24 in fasting LDL-C (UC)
- **Key secondary PD endpoints:**
  - Percent and absolute change from baseline in LDL-C, ANGPTL3, total ApoB, HDL-C, TGs and non-HDL-C at each scheduled assessment (fasting)
- **Safety**

Randomization

- 18 eligible HoFH patients randomized to receive 200 mg or 300 mg zodasiran SC on Day 1 and Week 12

Open Label Extension (OLE)

- All patients were eligible to enroll in the OLE at the end of the study

*All samples taken after ≥10 hour fast. **ANGPTL3**, angiopoietin-like 3; †The open-label extension was terminated early due to sponsor considerations; however, nearly all patients completed at least one year of follow-up. **ApoB**, apolipoprotein B; **ARO-ANG3**, zodasarin; **BL**, baseline; **HDL-C**, high density lipoprotein cholesterol; **HoFH**, homozygous familial hypercholesterolaemia; **LDL-C**, low density lipoprotein cholesterol; **non-HDL-C**, non-high-density lipoprotein cholesterol; **OLE,** open label extension period; **RT**, randomized treatment period; **SC**, subcutaneous; **TG**, triglyceride; **UC**, preparative ultracentrifuge.

Baseline Characteristics

	Zodasiran 200 mg (N=9)	Zodasiran 300 mg (N=9)	Total (N=18)
Age (years), mean (SD)	49.6 (19.5)	36.4 (18.1)	43.0 (19.4)
Sex at birth, n (%)			
Female	7 (77.8)	6 (66.7)	13 (72.2)
Race, n (%)			
White	6 (66.7)	8 (88.9)	14 (77.8)
BMI (kg/m^2), mean (SD)	25.8 (5.8)	28.0 (6.1)	26.9 (5.9)
LDL-C (UC) (mmol/L), mean (SD)	8.7 (5.8)	10.9 (5.6)	9.8 (5.7)
Total ApoB (mg/dL), mean (SD)	231.2 (138.0)	256.3 (104.4)	243.8 (119.4)
HDL-C (mmol/L), mean (SD)	1.2 (0.4)	1.1 (0.5)	1.2 (0.4)
Non-HDL-C (mmol/L), mean (SD)	9.6 (6.5)	11.7 (5.7)	10.7 (6.0)
VLDL-C (UC) (mmol/L), mean (SD)	1.0 (0.9)	0.7 (0.5)	0.8 (0.7)
Total cholesterol (mmol/L), mean (SD)	10.9 (6.5)	12.8 (5.5)	11.8 (5.9)
TG (mmol/L)[a], geometric median (Q1, Q3)	1.2 (1.0, 1.7)	0.9 (0.9, 1.6)	1.1 (0.9, 1.7)
Lp(a) (nmol/L), median (Q1, Q3)	135.7 (79.9, 275.4)	149.9 (66.4, 231.7)	168.6 (66.4, 245.5)
ANGPTL3 (ng/mL), mean (SD)	72.3 (31.3)	98.5 (64.9)	85.4 (51.2)
HbA1C (%), mean (SD)	5.4 (0.5)	5.3 (0.3)	5.4 (0.4)
Concomitant PCSK9 inhibitor use, n (%)	3 (33.3)	3 (33.3)	6 (33.3)
Concomitant statin use, n (%)			
High intensity	8 (88.9)	9 (100.0)	17 (94.4)
Low intensity	1 (11.1)	0 (0.0)	1 (5.6)

[a]Mean value at baseline is defined as the average (i.e. geometric mean) of Day 1 predose assessment and the fasting TG value collected during the Screening period. If only one value was available, then this value was used. For other lipid related parameters, baseline was defined as the predose value on Day 1. % = 100 x n/N, N = number of subjects in the population, **n** = number of subjects reporting event; **SD**, standard deviation

Genotype Analysis

Genotype, N (%)	Total (N=18)	Zodasiran 200 mg (N=9)	Zodasiran 300 mg (N=9)
LDLR Non-null			
	9 (50)	4 (44)	5 (56)
LDLR Null-null			
	8 (44)	4 (44)	4 (44)
LDLR plus APOB*			
	1 (6)	1 (12)*	0 (0)

*One patient was a double heterozygote (digenic) for APOB and LDLR

Zodasiran Demonstrated Substantial and Durable Reductions in LDL-C and ApoB Throughout the Randomized Treatment Period and OLE

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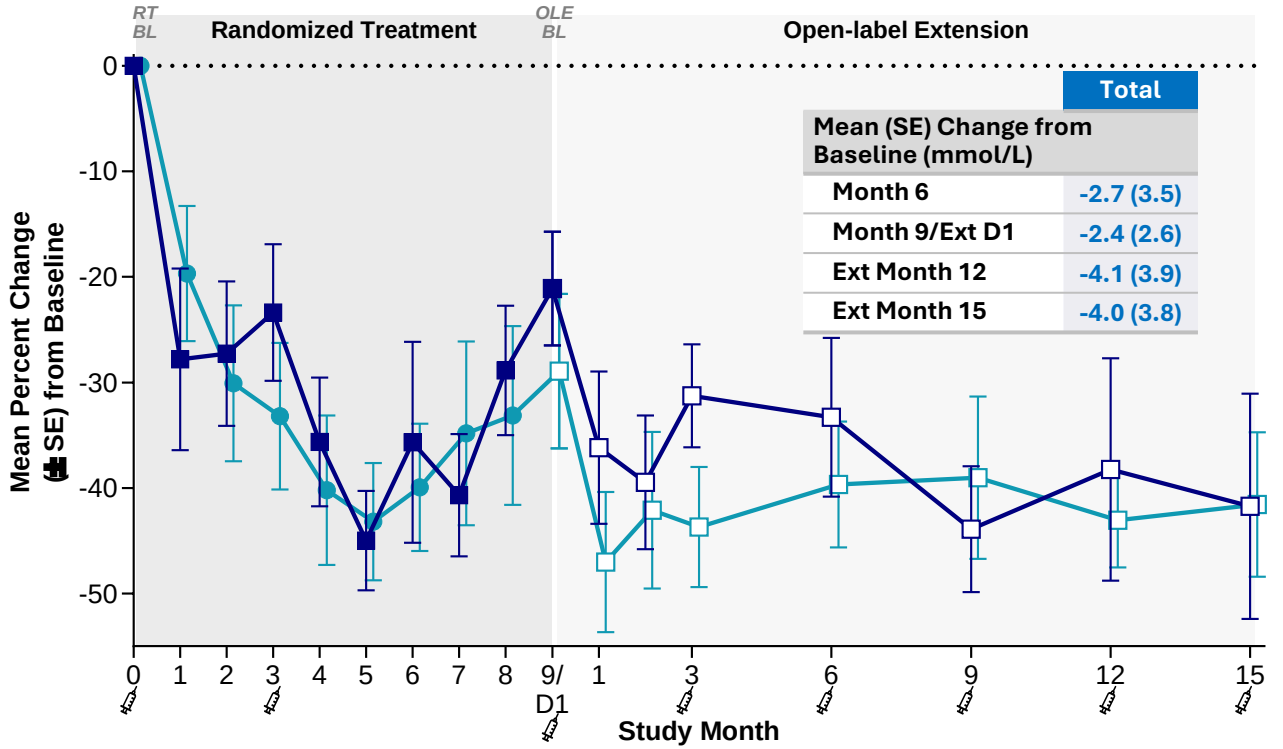
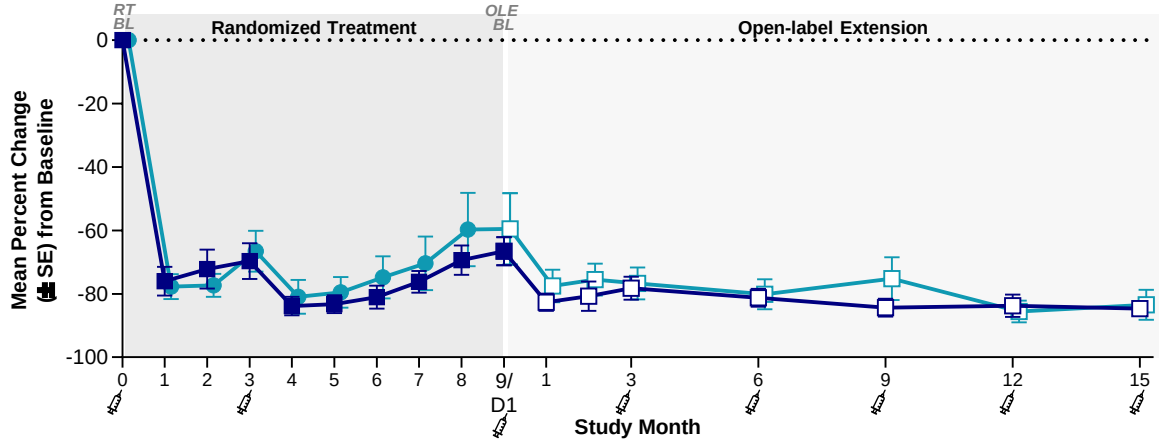
LDL-C



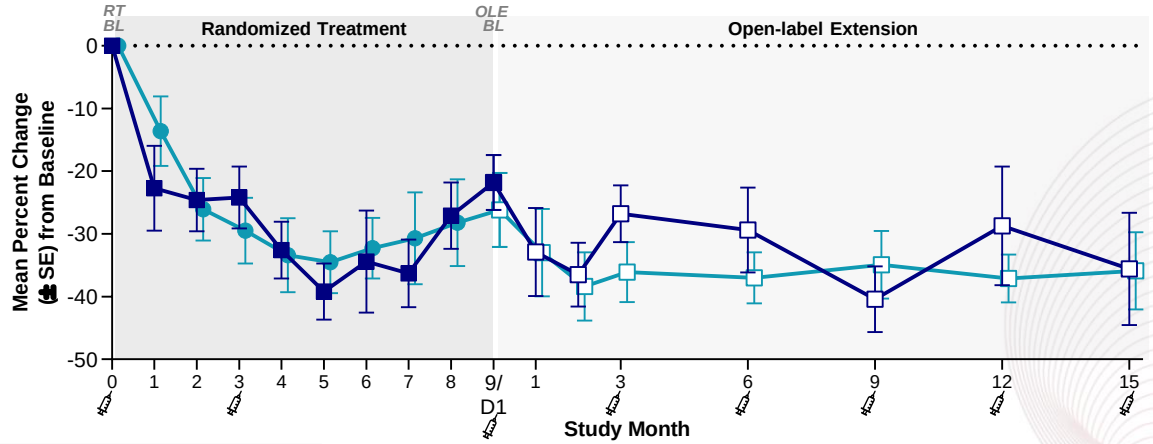
Mean (SE) Change from Baseline (mmol/L)	Total
Month 6	-2.7 (3.5)
Month 9/Ext D1	-2.4 (2.6)
Ext Month 12	-4.1 (3.9)
Ext Month 15	-4.0 (3.8)

200 mg	9	9	9	9	9	8	9	8	9	9				
200 mg Ext										9	9	9	9	9	8	6
300 mg	9	9	8	9	8	9	9	9	9	9				
300 mg Ext										8	8	9	8	8	8	8

ANGPTL3



ApoB

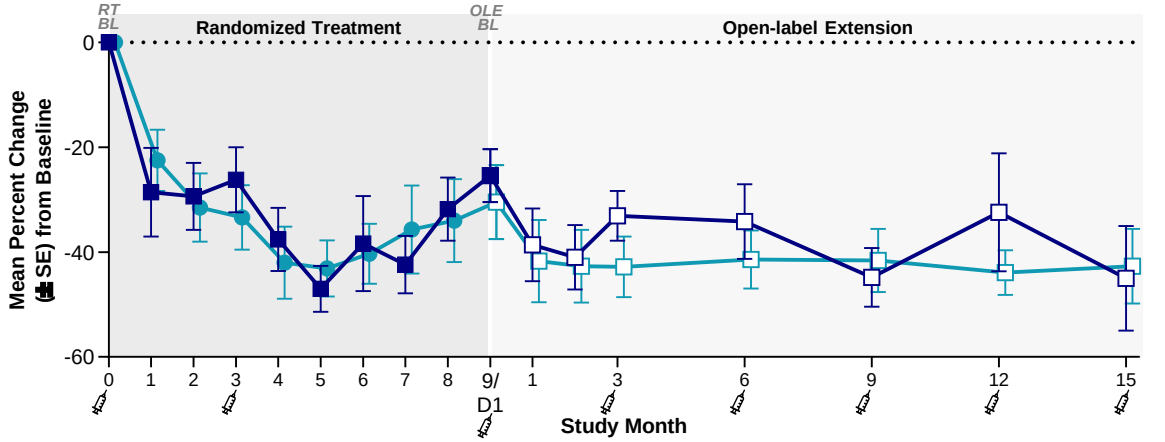


Zodasiran 200 mg | Zodasiran 300 mg | Zodasiran extension 200 mg continuous | Zodasiran extension 300 mg ⇨ 200 mg

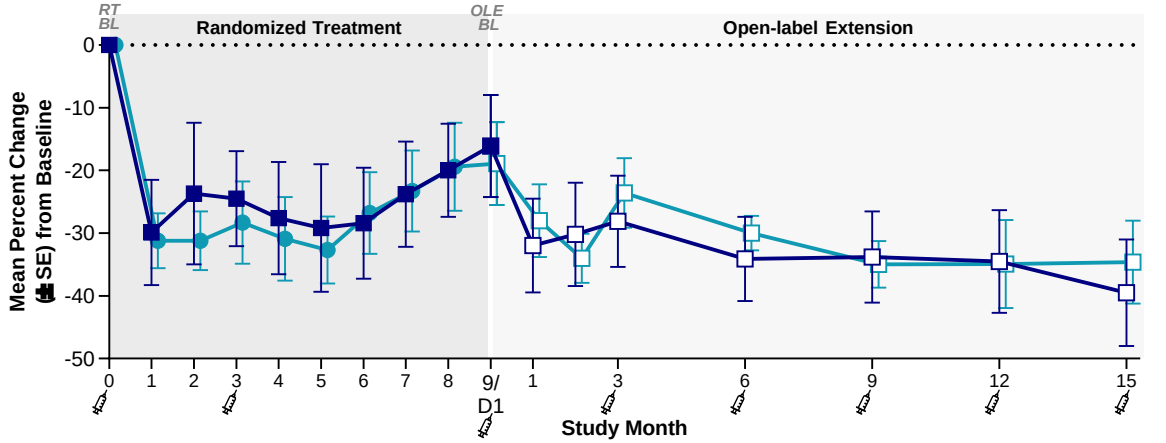
Analysis of Covariance (ANCOVA) with repeated measures modeling was used for statistical modeling. **ANGPTL3**, angiopoietin-like protein 3; **ApoB**, apolipoprotein B; **BL**, baseline; **D1**, day 1 of OLE; **Ext**, extension; **LDL-C**, low-density lipoprotein cholesterol; **OLE**, open-label extension;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

Zodasiran Affected Multiple Atherogenic Lipid Parameters Including Non-HDL-C, Lp(a), TGs and HDL-C in Patients with HoFH Throughout the RT and OLE Periods

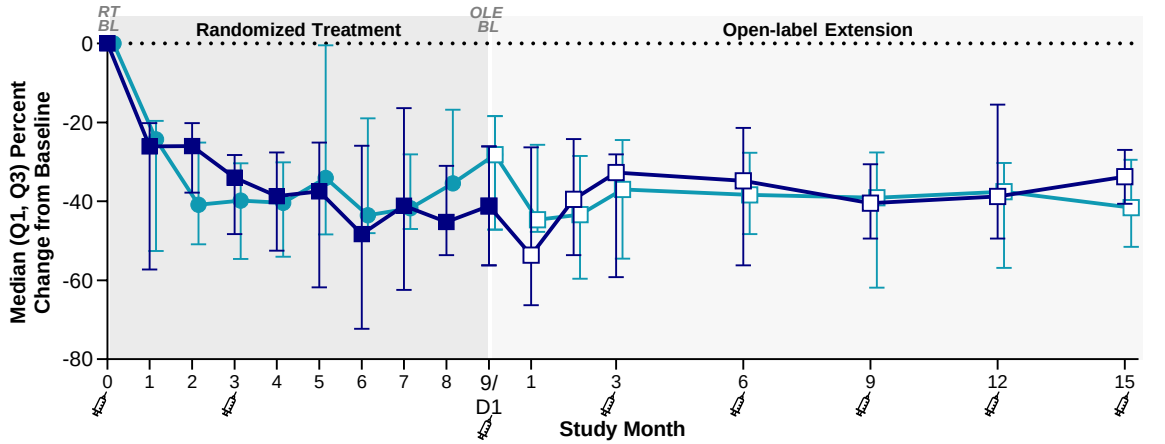
Non-HDL-C



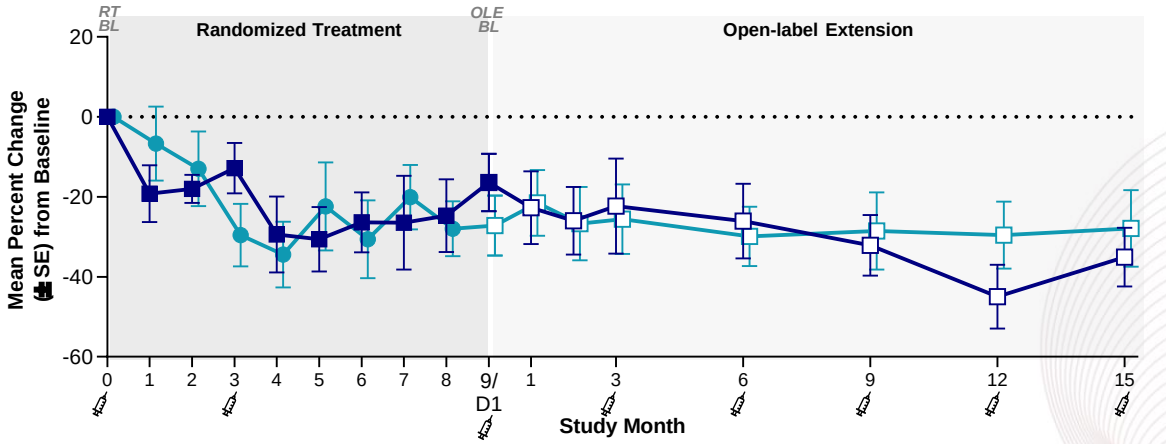
HDL-C



Triglycerides



Lp(a)

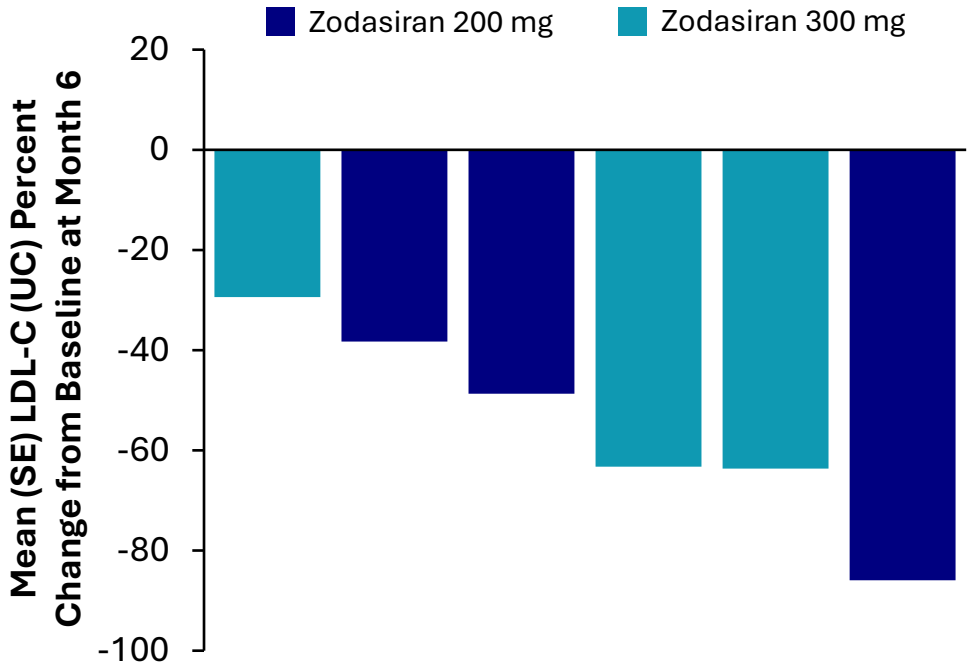


Zodasiran 200 mg
Zodasiran 300 mg
Zodasiran extension 200 mg continuous
Zodasiran extension 300 mg ⇨ 200 mg

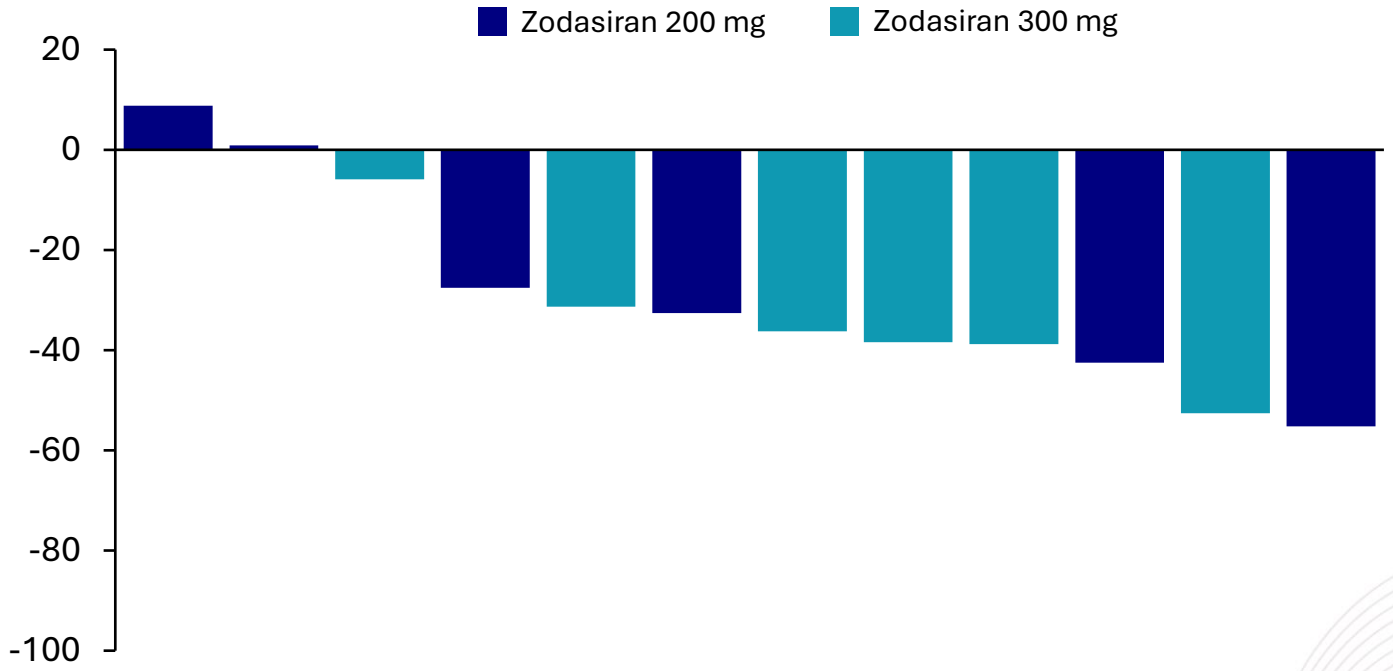
Triglycerides at baseline was defined as the average (i.e. geometric mean) of Day 1 predose assessment and the fasting TG value collected during the Screening period. If only one value was available, then this value was used. Baseline was the last observed value prior to the first administration of study treatment.

Reductions in LDL-C and % of Patients Attaining LDL-C Below Risk Thresholds and Potential Enhanced Effect With PCSK9i in Fasting LDL-C (UC)

LDL-C in Patients Using PCSK9 Inhibitors



LDL-C in Patients Not Using PCSK9 Inhibitors



HoFH patients on PCSK9i administered zodasiran reached LDL-C levels as low as 0.75 mmol/L

	With PCSK9i (n=6)	Total (n=18)
Patients attaining LDL-C < 1.8 mmol/L at Month 6	3 (50%)	3 (17%)
Patients attaining LDL-C < 2.6 mmol/L at Month 6	4 (67%)	4 (22%)
Patients attaining LDL-C < 3.4 mmol/L at Month 6	4 (67%)	6 (33%)

Summary of Adverse Events

	Zodasiran 200 mg (N=9)	Zodasiran 300 mg (N=9)	Total (N=18)
Number of subjects with at least one:			
Treatment-emergent adverse events	7 (77.8)	7 (77.8)	14 (77.8)
Serious TEAEs	2 (22.2)	1 (11.1)	3 (16.7)
Severe TEAEs[a]	1 (11.1)	1 (11.1)	2 (11.1)
Study drug-related TEAEs[b]	1 (11.1)	4 (44.4)	5 (27.8)
TEAEs leading to study drug discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Injection site reactions[c]	1 (11.1)	4 (44.4)	5 (27.8)
Most common TEAE			
COVID-19	2 (22.2)	3 (33.3)	5 (27.8)
Nasopharyngitis	2 (22.2)	3 (33.3)	5 (27.8)
Upper respiratory tract infection	1 (11.1)	3 (33.3)	4 (22.2)
Dizziness	2 (22.2)	1 (11.1)	3 (16.7)

- No TEAEs leading to study drug discontinuation
- No drug related SAEs
- No AEs related to elevations in liver enzymes or glycemic control

Data shown as n (%). [a]Severe TEAEs were an event of coronary artery disease in the 200 mg group and an event of vertebral foraminal stenosis in the 300 mg group. [b]Study drug-related TEAEs were all injection site reactions. [c]Injection site reactions were assessed at every visit starting on Day 1 and included any Preferred Term containing 'Injection Site'. All ISRs were grade 1 or less, none were serious and all resolved/recovered without sequelae and none were persistent (i.e. lasted > 2 weeks). A TEAE is defined as an AE that occured following investigational product (IP) administration or a pre-existing condition exacerbated following IP administration. **AE**, adverse event; **IP**, investigational product; **ISR**, injection site reaction; **TEAE**, treatment-emergent adverse event.

Zodasiran Demonstrated Potent and Durable Reductions in LDL-C in Subjects with HoFH

- By silencing ANGPTL3, zodasiran significantly reduced LDL-C by a mean of 41% with continuous Q3M dosing throughout the OLE in patients with HoFH
- Treatment with background PCSK9i appeared to be associated with an enhanced effect with atherogenic LDL-C reduced by a mean of 62% at month 15 of OLE
- Zodasiran also reduced other atherogenic lipids and lipoproteins, including ApoB, non-HDL-C, and TGs as well as Lp(a)
- Zodasiran demonstrated a positive benefit-risk ratio and safety profile in HoFH patients
- Zodasiran is a promising potential treatment for patients with HoFH. A Phase 3 HoFH trial is planned to start later this year

ANGPTL3, angiopoietin-like 3; **ApoB**, apolipoprotein B; **LDL-C**, low density lipoprotein cholesterol; **Lp(a)**, lipoprotein(a); **non-HDL-C**, non-high-density lipoprotein cholesterol; **TGs**, triglycerides.

thank you

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