Safety and Efficacy of Zodasiran, a Hepatic siRNA Targeting ANGPTL3, in Mixed Hyperlipidemia Patients: 2 Year Open Label Extension (OLE) Results from ARCHES-2

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BACKGROUND

ANGPTL3 is a Key Regulator of TRL 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:
  - ▼ 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]

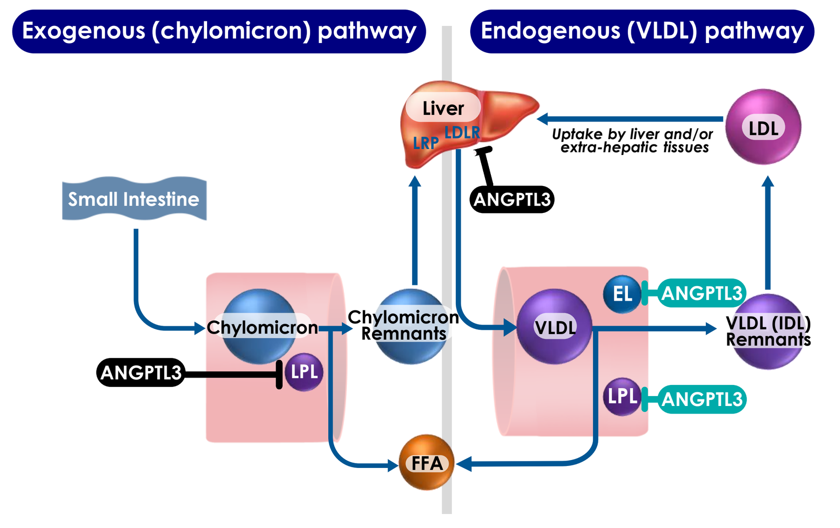
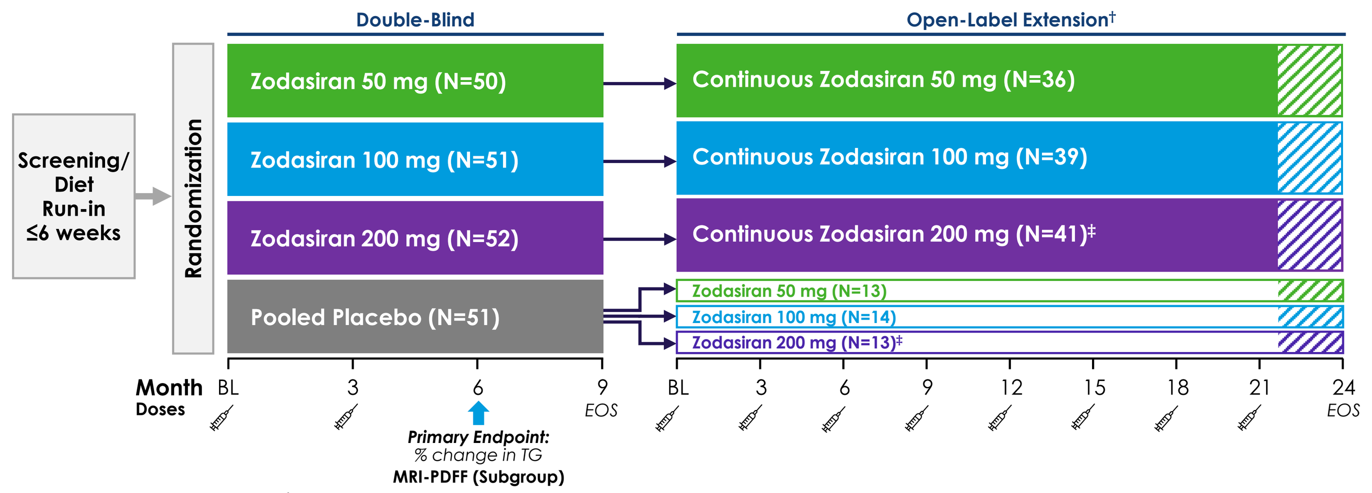


Figure adapted from: Rosenson RS, Shaik A, Song W. *J Am Coll Cardiol*. 2021;78(18):1817-1830. ▼=Reductions in.

METHODS

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

- **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 1.69–5.63 mmol/L and:
  - Either LDL-C ≥1.81 mmol/dL **or** non-HDL-C ≥2.59 mmol/L
  - 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 Month 6
  - Safety
- **Data Analysis:** Phase 2 study data to 9 months, EOS
- **OLE:** All patients were eligible to enroll in the OLE at the end of the study over 2 years



*All samples taken after ≥10 hour fast. †Study ended early due to sponsor decision; last dose administered was 27 Jun 2024. ‡Participants in the 200 mg dose groups were transitioned to 100 mg Zodasiran after 07 Nov 2022.

TABLE 1. BASELINE CHARACTERISTICS

	Placebo to Zodasiran 50mg (N=13)	Continuous Zodasiran 50mg (N=36)	Placebo to Zodasiran 100mg (N=14)	Continuous Zodasiran 100mg (N=39)	Placebo to Zodasiran 200mg (N=13)	Continuous Zodasiran 200mg (N=41)	Total (N=156)
Mean (SD) age, years	62.4 (9.0)	60.6 (12.3)	57.1 (12.1)	60.9 (9.9)	61.9 (11.2)	62.0 (12.4)	61.0 (11.3)
Female, n (%)	6 (46.2)	15 (41.7)	5 (35.7)	16 (41.0)	6 (46.2)	18 (43.9)	90 (57.7)
White, n (%)	12 (92.3)	36 (100.0)	12 (85.7)	37 (94.9)	13 (100.0)	39 (95.1)	149 (95.5)
Mean (SD) BMI, kg/m²	31.7 (4.3)	33.3 (4.1)	32.7 (8.3)	31.9 (5.2)	34.9 (4.9)	31.5 (5.2)	32.4 (5.3)
Mean (SD) ANGPTL3, ng/mL	87.7 (15.8)	95.7 (36.6)	102.4 (35.6)	92.5 (27.6)	90.0 (30.1)	100.1 (36.4)	95.5 (32.3)
Median (Q1, Q3) TG[a], mmol/L	2.6 (2.1, 3.1)	2.5 (2.2, 4.0)	2.7 (1.8, 3.1)	2.6 (2.1, 3.0)	2.6 (2.5, 2.8)	2.5 (2.1, 3.6)	2.6 (2.1, 3.3)
Mean (SD) remnant cholesterol (UC)[b], mmol/L	1.1 (0.5)	1.3 (0.4)	1.2 (0.6)	1.3 (0.9)	1.5 (1.5)	1.3 (0.7)	1.3 (0.8)
Mean (SD) non-HDL-C, mmol/L	3.1 (0.9)	3.8 (1.0)	3.7 (0.9)	4.0 (1.4)	4.1 (1.4)	3.7 (1.1)	3.8 (1.1)
Mean (SD) ApoB, g/L	0.8 (0.2)	1.0 (0.2)	1.0 (0.2)	1.0 (0.3)	1.1 (0.3)	1.0 (0.3)	1.0 (0.3)
Mean (SD) HDL-C, mmol/L	1.0 (0.4)	1.1 (0.4)	1.0 (0.2)	1.0 (0.3)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)
Mean (SD) LDL-C (UC), mmol/L	2.0 (0.7)	2.6 (0.8)	2.4 (0.6)	2.6 (1.3)	2.6 (1.1)	2.4 (0.9)	2.5 (1.0)
Mean total cholesterol, mmol/L	4.1 (0.9)	4.9 (0.9)	4.7 (0.9)	5.0 (1.4)	5.2 (1.4)	4.8 (1.1)	4.9 (1.1)
Mean Lp(a), nmol/L	38.5 (18.1)	78.5 (21.3)	184.7 (84.0)	92.0 (18.9)	90.7 (36.1)	65.9 (16.2)	85.8 (144.7)
Mean (SD) HbA1c, %	6.8 (1.0)	6.2 (1.1)	6.5 (1.5)	6.3 (1.0)	6.6 (1.1)	6.6 (1.1)	6.4 (1.1)

	Placebo to Zodasiran 50mg (N=13)	Continuous Zodasiran 50mg (N=36)	Placebo to Zodasiran 100mg (N=14)	Continuous Zodasiran 100mg (N=39)	Placebo to Zodasiran 200mg (N=13)	Continuous Zodasiran 200mg (N=41)	Total (N=156)
Receiving statins, n (%)	12 (92.3)	36 (100)	12 (85.7)	38 (97.4)	12 (92.3)	40 (97.6)	150 (96.2)
High-intensity statins, n (%)	6 (46.2)	16 (44.4)	6 (42.9)	17 (43.6)	5 (38.5)	10 (24.4)	60 (38.5)
Receiving PCSK9 inhibitors, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.9)	2 (1.3)
Receiving GLP-1 receptor agonists,[c] n (%)	1 (7.7)	1 (2.8)	1 (7.1)	4 (10.3)	1 (7.7)	3 (7.3)	11 (7.1)
Diabetes[d], n (%)	10 (76.9)	17 (47.2)	6 (42.9)	19 (48.7)	5 (38.5)	23 (56.1)	80 (51.3)
10-year CHD risk >20%[e], n (%)	0 (0.0)	6 (16.7)	2 (14.3)	6 (15.4)	3 (23.1)	8 (19.5)	25 (16.0)
Tobacco use, n (%)	3 (23.1)	5 (13.9)	3 (21.4)	10 (25.6)	3 (23.1)	6 (14.6)	30 (19.2)
Genotype, n (%)							
Consistent with MCS	1 (7.7)	7 (19.4)	2 (14.3)	5 (12.8)	6 (46.2)	3* (4.9)	23 (14.7)
LPL mutation	1† (7.7)	1† (2.8)	1 (7.1)	4‡ (10.3)	2§ (15.4)	1† (2.4)	10 (6.4)
LDLR mutation	0 (0.0)	1 (2.8)	1 (7.1)	1 (2.6)	0 (0.0)	2 (4.9)	5 (3.2)
LDLRAP1 mutation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.6)
ABCG5 mutation	0 (0.0)	0 (0.0)	1** (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
ABCG8 mutation	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)

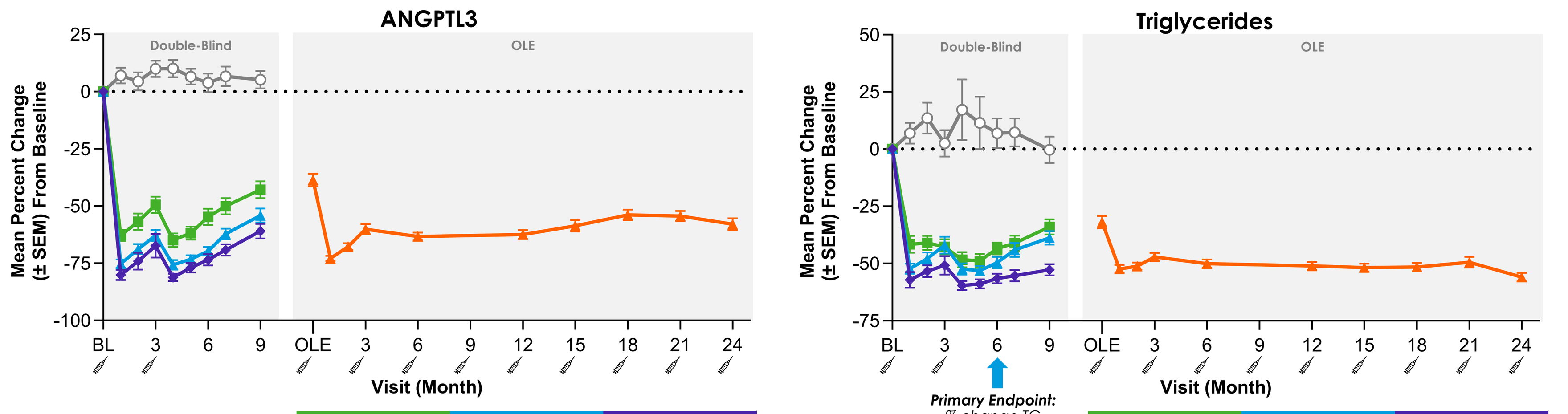
*Cmpd het, 1 benign, 1 VUS; †Likely benign; ‡3 benign, §1 pathogenic, 1 benign; 1 VUS; **VUS; Data are reported as mean (±SD) unless otherwise noted. [a]Mean value at baseline is defined as the geometric mean of Day 1 predose assessment and two fasting TG values collected during the Screening period. If fewer than 3 predose assessments are available, the geometric mean will be taken from the available results. [b]Remnant Cholesterol = (Total cholesterol – HDL-C – LDL-C). [c]Includes albiglutide (Tanzeum), dulaglutide (Trulicity), exenatide (Byetta), exenatide extended-release (Bydureon), liraglutide (Victoza), semaglutide (Ozempic). [d]Diabetic subjects are defined as having HbA1c ≥6.5% or fasting glucose ≥6.99 mmol/L or with medical history of 'diabetes' or receiving diabetic medications at baseline. [e]10-year coronary heart disease (CHD) risk is based on ATPIII Guidelines. 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 50 mg, 100 mg and 200 mg.

ABBREVIATIONS

ANGPTL3, angiopoietin-like 3; ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BL, baseline; BMI, body mass index; CHD, coronary heart disease; DM, diabetes mellitus; EOS, end of study; HbA1c, glycosylated hemoglobin; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; Lp, lipoprotein; Lp(a), lipoprotein (a); LPL, lipoprotein lipase; LS, least squares; MCS, multifactorial chylomicronemia syndrome; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; Non-HDL-C, non-high density lipoprotein cholesterol; OLE, open-label extension; Q, quartile; SAEs, serious adverse events; SC, subcutaneous; SD, standard deviation; SEM, standard error of mean; TEAEs, treatment emergent adverse events; TG, triglyceride; TRL, triglyceride rich lipoproteins; UC, ultracentrifuge; VLDL-C, very low-density lipoprotein cholesterol.

RESULTS

Figure 1. Zodasiran Demonstrated Substantial and Durable Decreases in ANGPTL3 and Consequently in TG[7]



ANGPTL3	50 mg	100 mg	200 mg
LS Mean % Change from Baseline Difference vs Placebo			
6 months	-56**	-70**	-74**
Mean (SEM) % Change from Baseline			
OLE Month 12	-55 (24)	-70 (20)	-62 (24)
OLE Month 24	-49 (28)	-61 (21)	-63 (17)

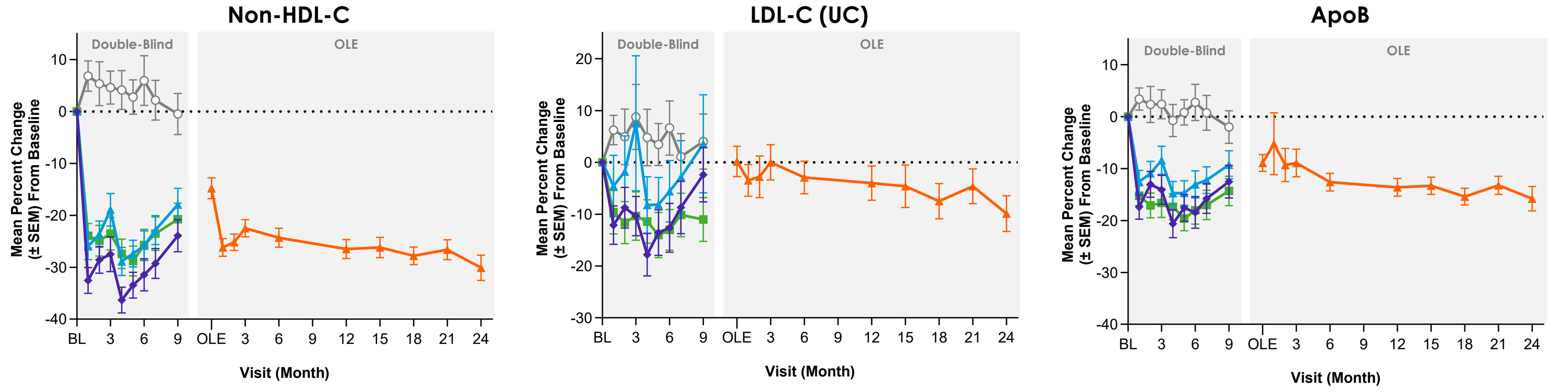
Triglycerides	50 mg	100 mg	200 mg
LS Mean % Change from Baseline Difference vs Placebo			
6 months	-51**	-57**	-63**
Mean (SEM) % Change from Baseline			
OLE Month 12	-45 (24)	-51 (25)	-56 (13)
OLE Month 24	-53 (18)	-57 (16)	-57 (15)

Placebo; Zodasiran 50 mg; Zodasiran 100 mg; Zodasiran 200 mg; OLE Pooled Zodasiran

Similar reductions were achieved in the OLE as in the double-blind portion of the study

*P<0.05; **P<0.0001.

Figure 2. Zodasiran Affected Multiple Lipid Parameters and Demonstrated Decreases in Non-HDL-C, ApoB, and LDL-C in Patients with Mixed Hyperlipidemia



Non-HDL-C	50 mg	100 mg	200 mg
LS Mean Difference vs Placebo (%)			
6 months	-29**	-29**	-36**
Mean (SEM) % Change from Baseline			
OLE Month 12	-20 (27)	-29 (22)	-30 (16)
OLE Month 24	-28 (25)	-33 (18)	-29 (22)

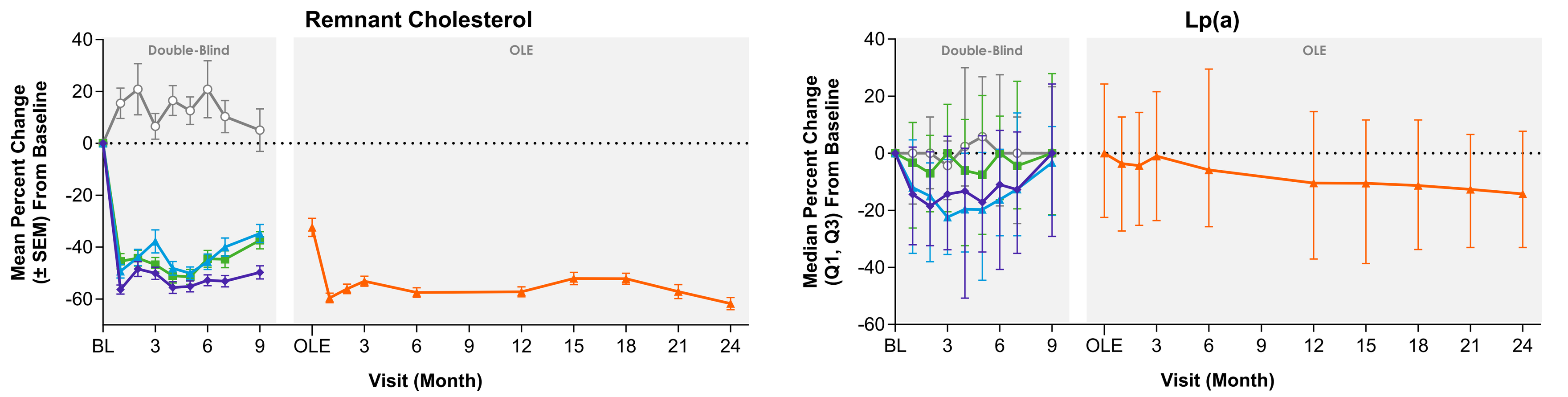
LDL-C (UC)	50 mg	100 mg	200 mg
LS Mean Difference vs Placebo (%)			
6 months	-16*	-9	-20*
Mean (SEM) % Change from Baseline			
OLE Month 12	0 (39)	-7 (42)	-4 (37)
OLE Month 24	-10 (35)	-14 (25)	-7 (33)

ApoB	50 mg	100 mg	200 mg
LS Mean Difference vs Placebo (%)			
6 months	-19**	-15*	-22**
Mean (SEM) % Change from Baseline			
OLE Month 12	-10 (24)	-15 (21)	-15 (16)
OLE Month 24	-13 (24)	-18 (17)	-16 (21)

Placebo; Zodasiran 50 mg; Zodasiran 100 mg; Zodasiran 200 mg; OLE Pooled Zodasiran

*P<0.05; **P<0.0001.

Figure 3. Zodasiran Affected Remnant Cholesterol and Lipoprotein(a)



RC	50 mg	100 mg	200 mg
LS Mean Difference vs Placebo (%)			
6 months	-73**	-76**	-82**
Mean (SEM) % Change from Baseline			
OLE Month 12	-53 (5)	-58 (5)	-60 (4)
OLE Month 24	-61 (6)	-60 (6)	-64 (4)

Lp(a)	50 mg	100 mg	200 mg	Total, median (Q1, Q3) % change from baseline
LS Mean Difference vs Placebo (%)				
6 months	-7	-20*	-17*	
Mean (SEM) % Change from Baseline				
OLE Month 12	-10 (37)	5 (85)	2 (65)	-10 (-37, 15)
OLE Month 24	-15 (28)	6 (102)	9 (105)	15 (4, 96)

Placebo; Zodasiran 50 mg; Zodasiran 100 mg; Zodasiran 200 mg; OLE Pooled Zodasiran

*P<0.05; **P<0.0001.

Table 2. Summary of Adverse Events in the OLE

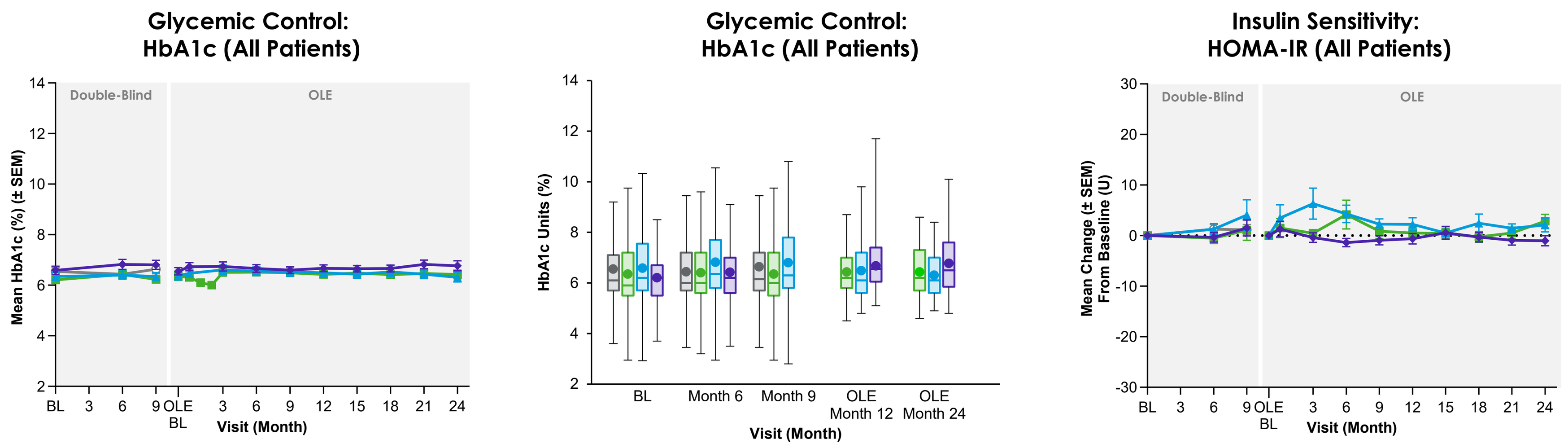
Preferred Term, n (%)	Zodasiran 50mg (N=49)	Zodasiran 100mg (N=53)	Zodasiran 200mg (N=54)	Total (N=156)
TEAEs				
COVID-19	8 (16.3)	9 (17.0)	9 (16.7)	26 (16.7)
Upper respiratory tract infection	5 (10.2)	8 (15.1)	8 (14.8)	21 (13.5)
Urinary tract infection	5 (10.2)	4 (7.5)	5 (9.3)	14 (9.0)
SAEs	7 (14.3)	7 (13.2)	7 (13.0)	21 (13.5)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	0 (0.0)	3 (5.7)	2 (3.7)	5 (3.2)
TEAEs associated with death	0 (0.0)	1 (1.9)*	0 (0.0)	1 (0.6)
HbA1c (%), mean (SD), baseline	6.4 (0.2)	6.4 (0.2)	6.6 (0.1)	6.4 (0.1)
HbA1c (%), mean (SD) at Month 24	6.4 (0.2)	6.3 (0.2)	6.8 (0.2)	6.5 (0.1)
Platelets (10^9/L), mean (SD), baseline	222.1 (57.4)	249.1 (51.1)	231.5 (71.2)	234.5 (61.3)
Platelets (10^9/L), mean (SD) at Month 24	232.9 (65.5)	259.8 (53.6)	233.9 (70.9)	241.8 (64.5)

- TEAEs reported reflect comorbidities and underlying conditions of the study population
- All SAEs were recovered/resolved (except 1 SAE with an outcome of death in the treated group)
- TEAEs leading to discontinuation due to AEs remained low (3.2%)
- Minimal changes in HbA1c
- No changes in platelets
- No safety findings related to elevated transaminases

*Cause of death unknown.

Note: TEAEs in OLE are defined as AEs that start on or after the first dose date of study drug during OLE. Diabetic patients are defined as having HbA1c ≥6.5% or fasting glucose ≥6.99 mmol/L or with medical history of 'diabetes' or receiving diabetic medications at baseline.

Figure 4. Minimal Change in Mean HbA1c or HOMA-IR



Placebo; Zodasiran 50 mg; Zodasiran 100 mg; Zodasiran 200 mg

CONCLUSIONS

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

- **By silencing ANGPTL3, zodasiran significantly reduced TGs and atherogenic lipoproteins in patients with mixed hyperlipidemia**
  - **In the RCT at 6 months:**
    - **ANGPTL3 ⬇ to -74%**
    - **TG ⬇ to -63%**
    - **Remnant cholesterol ⬇ to -82%**
    - **ApoB ⬇ to -22%**
    - **Non-HDL-C ⬇ to -36%**
    - **LDL-C ⬇ to -20%**
  - **In the OLE, reductions were maintained over 2 years:**
    - **TG reductions were maintained over -50%,**
    - **Non-HDL-C reductions were maintained at -30% and**
    - **APOB reductions were maintained over -15%**
- **3.2% of subjects discontinued for an adverse event (AE)**
- **AEs were consistent with prior observations, with no increase in mean HbA1c, supporting long-term safety of repeated dosing**
- **Zodasiran is a promising potential treatment for patients with increased risk for ASCVD**

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REFERENCES

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. 7. Rosenson RS. et al. N Engl J Med 2024;391:913-925. DOI: 10.1056/NEJMoa2404147

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