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ORIGINAL RESEARCH ARTICLE

Effect of Vupanorsen on Non–High-Density Lipoprotein Cholesterol Levels in Statin-Treated Patients With Elevated Cholesterol: TRANSLATE-TIMI 70

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BACKGROUND: Genetic loss-of-function variants in *ANGPTL3* are associated with lower levels of plasma lipids. Vupanorsen is a hepatically targeted antisense oligonucleotide that inhibits Angiopoietin-like 3 (ANGPTL3) protein synthesis.

METHODS: Adults with non–high-density lipoprotein cholesterol (non-HDL-C) ≥100 mg/dL and triglycerides 150 to 500 mg/dL on statin therapy were randomized in a double-blind fashion to placebo or 1 of 7 vupanorsen dose regimens (80, 120, or 160 mg SC every 4 weeks, or 60, 80, 120, or 160 mg SC every 2 weeks). The primary end point was placebo-adjusted percentage change from baseline in non–HDL-C at 24 weeks. Secondary end points included placebo-adjusted percentage changes from baseline in triglycerides, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), and ANGPTL3.

RESULTS: Two hundred eighty-six subjects were randomized: 44 to placebo and 242 to vupanorsen. The median age was 64 (interquartile range, 58–69) years, 44% were female, the median non–HDL-C was 132.4 (interquartile range, 118.0–154.1) mg/dL, and the median triglycerides were 216.2 (interquartile range, 181.4–270.4) mg/dL. Vupanorsen resulted in significant decreases from baseline over placebo in non–HDL-C ranging from 22.0% in the 60 mg every 2 weeks arm to 27.7% in the 80 mg every 2 weeks arm (all $P<0.001$ for all doses). There were dose-dependent reductions in triglycerides that ranged from 41.3% to 56.8% (all $P<0.001$). The effects on LDL-C and ApoB were more modest (7.9%–16.0% and 6.0%–15.1%, respectively) and without a clear dose-response relationship, and only the higher reductions achieved statistical significance. ANGPTL3 levels were decreased in a dose-dependent manner by 69.9% to 95.2% (all $P<0.001$). There were no confirmed instances of significant decline in renal function or platelet count with vupanorsen. Injection site reactions and >3× elevations of alanine aminotransferase or aspartate aminotransferase were more common at higher total monthly doses (up to 33.3% and 44.4%, respectively), and there was a dose-dependent increase in hepatic fat fraction (up to 76%).

CONCLUSIONS: Vupanorsen administered at monthly equivalent doses from 80 to 320 mg significantly reduced non–HDL-C and additional lipid parameters. Injection site reactions and liver enzyme elevations were more frequent at higher doses, and there was a dose-dependent increase in hepatic fat fraction.

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Key Words: Angiopoietin-like proteins ■ antisense oligonucleotide ■ lipids ■ triglycerides

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Clinical Perspective

What Is New?

- Vupanorsen, an antisense oligonucleotide targeting ANGPTL3 (angiopoietin-like protein 3), reduced non–high-density lipoprotein cholesterol levels in statin-treated adults at all doses studied.
- Significant reductions in other lipid parameters, such as triglycerides, were also seen.
- Injection site reactions and liver enzyme elevations were more frequent at higher doses, and there was a dose-dependent increase in hepatic fat fraction.

What Are the Clinical Implications?

- Despite recent advances in lipid-modifying therapy, residual cardiovascular risk remains in many patients.
- Novel therapeutic targets such as ANGPTL3 may present new opportunities for cardiovascular risk reduction in at-risk patients.

Nonstandard Abbreviations and Acronyms

ANGPTL3	angiopoietin-like protein 3
ALT	alanine aminotransferase
ApoB	apolipoprotein B
AST	aspartate aminotransferase
Non-HDL-C	non-high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol

Recent advances in lipid-modifying therapy have demonstrated the clinical benefit of aggressive low-density lipoprotein cholesterol (LDL-C)–lowering beyond statin therapy.[1–3] Yet, residual cardiovascular risk remains in many patients.[1–3] Evidence suggests that lipid-mediated cardiovascular risk comes from atherogenic Apolipoprotein B (ApoB)–containing lipoproteins, including both cholesterol-rich low-density lipoproteins and triglyceride-rich very-low-density lipoproteins.[4,5]

Angiopoietin-like protein 3 (ANGPTL3) inhibits lipases, including lipoprotein lipase, and impairs metabolism of triglyceride-rich lipoproteins.[6] Lower levels of triglycerides and LDL-C have been observed with loss-of-function mutations in the *ANGPTL3* gene.[7–9] Vupanorsen is an N-acetyl galactosamine–conjugated antisense oligonucleotide targeting ANGPTL3 mRNA in the liver. A phase 2a trial of vupanorsen in patients with hypertriglyceridemia, hepatic steatosis, and type 2 diabetes showed significant reductions in triglycerides at all doses studied, as well as reductions in non–high-density lipoprotein cholesterol (non-HDL-C) at the highest doses.[10] However, the phase 2a study only evaluated vupanorsen doses up to 80 mg/mo.

Non–HDL-C is highly correlated with ApoB levels, suggesting potential for vupanorsen at higher doses than previously studied as a therapy for cardiovascular risk reduction. Therefore, the TRANSLATE (Targeting ANGPTL3 with an Antisense Oligonucleotide in Adults with Dyslipidemia)–TIMI (Thrombolysis in Myocardial Infarction) 70 trial was designed to assess the effect of escalating doses of vupanorsen on non–HDL-C levels in statin-treated adults with hyperlipidemia.

METHODS

Trial Design

TRANSLATE-TIMI 70 was a placebo-controlled, double-blind, randomized, phase 2b trial of vupanorsen at escalating doses in adults with hyperlipidemia on statin therapy. Subjects were randomly assigned 2:1:1:2:1:2:2:2 by a permuted block schedule to placebo or 1 of 7 doses of subcutaneous vupanorsen (80 mg, 120 mg, or 160 mg every 4 weeks, or 60 mg, 80 mg, 120 mg, or 160 mg every 2 weeks) (Supplemental Material and Figure S1). The study treatment period was 24 weeks, after which subjects were followed off study drug for an additional 12 weeks of safety monitoring after the last dose of study medication.

Study Population

Statin-treated adults ≥40 years old and with non–HDL-C ≥100 mg/dL and triglycerides 150 to 500 mg/dL were eligible for enrollment. Potential subjects with active liver disease other than hepatic steatosis, HbA1c ≥9.5%, estimated glomerular filtration rate <30 mL per min per 1.73 m^2, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level >2× the upper limit of normal, or a platelet count less than the lower limit of normal were excluded. Complete inclusion and exclusion criteria are provided in the Supplemental Material. The study protocol was approved by all relevant ethical oversight committees, and all subjects provided written, informed consent.

Study End Points

The primary end point was placebo-adjusted percent change in non–HDL-C at 24 weeks compared with baseline. Secondary end points included percent changes in triglycerides, LDL-C (direct), ApoB, and ANGPTL3 at 24 weeks as well as changes in non–HDL-C and these additional lipid values at 16 weeks. Safety end points included changes in renal function and platelet counts, incidence of liver enzyme elevations, change in hepatic fat fraction as determined by magnetic resonance imaging, and occurrence of antidrug antibodies. Abnormal renal function, hepatic enzyme, or platelet count results meeting prespecified criteria required repeat testing within 7 days (Supplemental Material). Liver magnetic resonance imaging for measurement of hepatic fat fraction was performed at baseline and at 24 weeks with subjects in a fasted state.

Statistical Analysis

The primary end point was assessed according to assigned treatment group in the population of subjects who received

at least 1 dose of study drug, had a baseline non–HDL-C level, and had at least 1 postbaseline non–HDL-C level available. Comparisons between each vupanorsen arm and placebo were made using a mixed model for repeated measures approach, generating placebo-adjusted least squares mean differences and 95% CIs. In the mixed model for repeated measures model, baseline value, treatment (categorical), visit (categorical), and interaction term of treatment (categorical) by visit (categorical) were treated as fixed effects, and an unstructured covariance matrix was used to account for the correlation among visits. The restricted maximum likelihood method along with Kenward-Roger adjustment for degrees of freedom were used for parameter estimation. For subjects who prematurely discontinued treatment, values after discontinuation were censored, and there was no imputation of missing data. The safety population was defined as all randomized subjects who received at least 1 dose of study medication. There was no adjustment for multiple testing. Assuming a common standard deviation in the primary end point of 17.5% on the basis of earlier phase data, we calculated that at least 20 subjects per arm would provide >90% power to detect a 20% placebo-adjusted change from baseline in non–HDL-C level in each vupanorsen arm at a 2-sided α of 0.05. To account for potential dropout, we aimed to enroll 260 subjects.

The effect of vupanorsen (pooled doses) on the primary end point was examined in key subgroups using an ANCOVA model adjusting for baseline value, treatment group, subgroup status, and an interaction term for treatment by subgroup. All analyses were performed by the TIMI Study Group on a complete, independently held database using commercially available software (SAS, version 9.4, Cary, NC). The trial database cannot be shared, but parties interested in collaborating should contact the corresponding author.

Table 1. Baseline Patient Characteristics

		Q4W regimens			Q2W regimens			
Characteristic	Placebo N=44	80 mg N=23	120 mg N=23	160 mg N=45	60 mg N=24	80 mg N=45	120 mg N=46	160 mg N=36
Age, y	64.0 (59.5–68.5)	66.0 (61.0–72.0)	60.0 (55.0–67.0)	64.0 (58.0–68.0)	65.5 (57.5–70.0)	64.0 (57.0–68.0)	63.0 (58.0–67.0)	65.0 (61.0–69.5)
Female sex	17 (38.6)	13 (56.5)	9 (39.1)	17 (37.8)	7 (29.2)	24 (53.3)	20 (43.5)	19 (52.8)
Race								
White	38 (86.4)	20 (87.0)	21 (91.3)	44 (97.8)	21 (87.5)	38 (84.4)	37 (80.4)	31 (86.1)
Black	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.2)	1 (4.2)	4 (8.9)	4 (8.7)	1 (2.8)
Asian	4 (9.1)	2 (8.7)	1 (4.3)	0 (0.0)	2 (8.3)	3 (6.7)	4 (8.7)	4 (11.1)
Not reported	2 (4.5)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)
Type 2 diabetes	20 (45.5)	11 (47.8)	11 (47.8)	27 (60.0)	10 (41.7)	24 (53.3)	25 (54.3)	14 (38.9)
Previous myocardial infarction	7 (15.9)	3 (13.0)	4 (17.4)	5 (11.1)	4 (16.7)	3 (6.7)	3 (6.5)	7 (19.4)
Previous coronary revascularization	13 (29.5)	5 (21.7)	3 (13.0)	12 (26.7)	7 (29.2)	5 (11.1)	6 (13.0)	8 (22.2)
Previous stroke	2 (4.5)	3 (13.0)	1 (4.3)	2 (4.4)	1 (4.2)	2 (4.4)	3 (6.5)	0 (0.0)
Peripheral artery disease	3 (6.8)	1 (4.3)	0 (0.0)	2 (4.4)	0 (0.0)	1 (2.2)	0 (0.0)	2 (5.6)
High-intensity statin	24 (54.5)	10 (43.5)	10 (43.5)	22 (48.9)	12 (50.0)	20 (44.4)	24 (52.2)	23 (63.9)
Ezetimibe	2 (4.5)	1 (4.3)	1 (4.3)	5 (11.1)	2 (8.3)	2 (4.4)	1 (2.2)	1 (2.8)
Measured values								
Non–HDL-C, mg/dL	127.2 (117.8–150.7)	139.4 (120.1–169.5)	134.0 (115.1–150.0)	124.9 (117.4–150.6)	136.9 (125.5–153.6)	133.4 (123.9–160.0)	129.5 (112.9–164.9)	130.0 (117.0–151.2)
Triglycerides, mg/dL	206.4 (182.1–246.7)	230.1 (196.9–281.9)	223.5 (187.2–295.6)	222.1 (183.2–278.3)	227.1 (178.8–274.6)	221.7 (182.3–286.7)	213.7 (181.9–256.2)	196.5 (176.8–267.7)
LDL-C (direct), mg/dL	86.7 (71.6–104.1)	91.1 (80.5–122.4)	84.6 (69.9–110.4)	85.5 (71.4–100.6)	95.9 (75.9–111.6)	90.0 (78.4–103.9)	83.9 (70.1–116.4)	85.2 (76.6–114.8)
ApoB, mg/dL	92.6 (84.9–112.1)	99.9 (90.5–113.5)	100.4 (88.2–110.5)	95.9 (90.7–109.0)	100.8 (90.5–114.5)	94.7 (87.9–110.5)	95.6 (81.8–115.5)	92.5 (87.1–109.0)
ANGPTL3, ng/mL	95.8 (73.5–109.0)	105.5 (76.0–137.0)	101.0 (76.5–124.0)	98.0 (79.0–113.0)	98.5 (78.0–117.0)	100.0 (82.0–109.0)	96.8 (83.5–122.0)	94.0 (72.0–111.0)
HbA1c, %	6.1 (5.6–7.2)	6.3 (5.7–7.7)	6.1 (5.8–7.7)	6.6 (6.0–8.1)	6.1 (5.7–6.9)	6.5 (5.8–7.5)	6.4 (5.7–7.2)	6.2 (5.7–7.3)
Hepatic fat fraction, %	9.3 (5.2–13.3)	5.7 (4.4–10.4)	7.7 (5.8–17.1)	9.9 (6.3–15.6)	8.8 (4.8–12.2)	8.4 (6.1–13.5)	8.6 (5.4–14.5)	7.6 (6.3–14.2)

Continuous variables are provided as median (interquartile range) and categorical variables as n (%). ANGPTL3 indicates angiopoietin-like protein 3; ApoB, apolipoprotein B; LDL-C, low-density lipoprotein cholesterol; HDL-C, non–high-density lipoprotein cholesterol; Q2W, every 2 weeks; and Q4W, every 4 weeks.

RESULTS

A total of 286 subjects were randomized at 55 sites in 3 countries (Supplemental Material) from October 2020 through April 2021. All patients received at least 1 dose of study drug, 2 (0.7%) withdrew consent, and 1 (0.3%) was lost to follow-up (Figure S1). Among subjects assigned to placebo, 2 (4.5%) permanently stopped study drug prematurely, and among subjects assigned to vupanorsen, 58 (24.0%) permanently stopped study drug prematurely (Figure S1). Of the 60 premature study drug discontinuations, 43 (71.7%) were a result of an adverse event, and the remainder for other reasons. Baseline patient characteristics were similar across treatment arms (Table 1). Overall, the median age was 64 (interquartile range, 58–69) years, 44% were women, 87% were White, 50% had type 2 diabetes, 51% were on a high-intensity statin regimen, and 5.2% were taking ezetimibe. The median non–HDL-C level was 132.4 (interquartile range, 118.0–154.1) mg/dL; triglycerides, 216.2 (interquartile range, 181.4–270.4) mg/dL; LDL-C, 87.5 (73.4–108.9) mg/dL; and ApoB, 95.9 (86.5–112.0) mg/dL.

Effect of Vupanorsen

Treatment with vupanorsen led to significant placebo-adjusted reductions in the primary end point of non–HDL-C at 24 weeks at all dose levels studied, ranging from 22.0% in the 60 mg every 2 weeks arm to 27.7% in the 80 mg every 2 weeks arm (all $P<0.001$; Figure 1, Table 2, and Figure S2). Reductions in non–HDL-C were evident within 4 weeks of treatment initiation and persisted through the study period (Figure S3). Therapeutic target engagement, as indicated by a dose-dependent placebo-adjusted reduction in ANGPTL3 level, ranged from 69.9% in the 80 mg every 4 weeks arm to 95.2% in the 160 mg every 2 weeks arm and was significant at all dose regimens (all $P<0.001$; Figure 2, Table 2, and Figure S4).

With regard to additional lipid end points, vupanorsen reduced triglyceride levels in a dose-dependent manner, ranging from 41.3% in the 120 mg every 4 weeks arm to 56.8% in the 160 mg every 2 weeks arm ($P<0.001$ for all; Figure 2 and Table 2). The effects of vupanorsen on LDL-C and ApoB were more modest and without a clear dose-response (Figure 2 and Table 2). Vupanorsen lowered HDL-C levels at all doses studied, and there was no significant change in hsCRP (high-sensitivity C-reactive protein) at any dose (Table 2). The effects of vupanorsen on lipid outcomes at 16 weeks are shown in Table S1.

The effect of vupanorsen on non–HDL-C was generally consistent across key clinical subgroups, including those on the basis of age, diabetes status, high versus low/intermediate statin intensity, and baseline non–HDL-C and triglyceride levels, though there was a nominally statistically significant interaction between sex and vupanorsen effect (Figure 3).

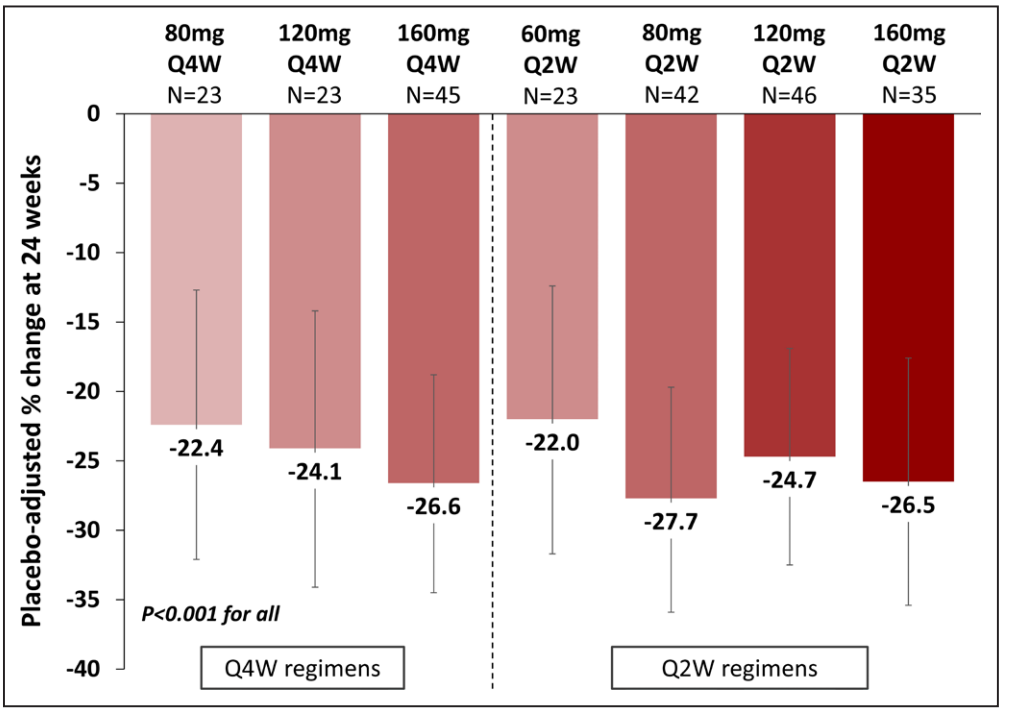

Figure 1. Effect of vupanorsen on non–high-density lipoprotein cholesterol at 24 weeks.
The effect of vupanorsen on the primary end point of percent change in placebo-adjusted non–high-density lipoprotein cholesterol level at 24 weeks is shown for each dose arm. Data shown are placebo-adjusted least squares mean differences and 95% CIs. Q2W indicates every 2 weeks; and Q4W, every 4 weeks.

Table 2. Effect of Vupanorsen on Lipid and Inflammatory Parameters at 24 Weeks

	Placebo N=44	Q4W regimens			Q2W regimens			
		80 mg N=23	120 mg N=23	160 mg N=45	60 mg N=23	80 mg N=42	120 mg N=46	160 mg N=35
Non–HDL-C (mg/dL)								
Baseline	135.7 (29.0)	146.7 (32.1)	142.1 (38.3)	135.9 (29.9)	148.5 (38.4)	143.0 (37.0)	143.0 (41.1)	138.1 (31.0)
24 wk	133.2 (31.3)	95.7 (24.2)	101.5 (32.4)	95.4 (22.7)	112.6 (24.5)	94.9 (23.8)	107.0 (39.2)	100.9 (35.2)
LSM change (95% CI)	−1.1 (−6.6 to 4.3)	−23.5 (−31.6 to −15.5)	−25.3 (−33.6 to −17.0)	−27.8 (−33.4 to −22.1)	−23.2 (−31.1 to −15.3)	−28.8 (−34.8 to −22.9)	−25.8 (−31.4 to −20.2)	−27.6 (−34.7 to −20.6)
PBO-adj LSM diff (95% CI)	–	−22.4 (−32.1 to −12.7)	−24.1 (−34.1 to −14.2)	−26.6 (−34.5 to −18.8)	−22.0 (−31.7 to −12.4)	−27.7 (−35.7 to −19.6)	−24.7 (−32.5 to −16.9)	−26.5 (−35.4 to −17.6)
P value	–	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
ANGPTL3 (ng/mL)								
Baseline	94.2 (32.2)	113.5 (58.1)	106.4 (35.1)	96.5 (23.1)	104.8 (32.5)	97.8 (23.1)	105.7 (39.8)	97.3 (33.5)
24 wk	101.2 (31.0)	35.3 (19.3)	34.2 (24.3)	31.0 (17.1)	34.5 (14.2)	25.9 (11.8)	20.2 (20.0)	22.2 (26.0)
LSM change	13.3 (6.7 to 19.9)	−56.6 (−66.3 to −46.9)	−63.8 (−74.1 to −53.5)	−67.1 (−73.9 to −60.3)	−66.3 (−76.2 to −56.5)	−73.0 (−80.4 to −65.6)	−78.9 (−86.0 to −71.9)	−81.9 (−90.7 to −73.1)
PBO-adj LSM diff (95% CI)	–	−69.9 (−81.6 to −58.1)	−77.1 (−89.4 to −64.9)	−80.4 (−89.9 to −70.9)	−79.6 (−91.5 to −67.7)	−86.3 (−96.2 to −76.3)	−92.2 (−101.9 to −82.6)	−95.2 (−106.2 to −84.2)
P value	–	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
TG (mg/dL)								
Baseline	228.6 (69.7)	236.0 (65.3)	249.2 (94.4)	236.6 (77.9)	241.1 (101.0)	245.7 (83.4)	224.4 (56.1)	228.4 (72.9)
24 wk	220.1 (81.0)	109.4 (41.9)	128.6 (61.5)	115.9 (42.9)	129.3 (54.9)	114.1 (62.8)	99.7 (33.8)	101.9 (41.6)
LSM change	−1.8 (−9.1 to 5.5)	−45.8 (−56.7 to −34.8)	−43.1 (−54.5 to −31.8)	−47.7 (−55.3 to −40.0)	−45.6 (−56.5 to −34.8)	−52.3 (−60.4 to −44.2)	−52.5 (−60.1 to −44.9)	−58.6 (−68.3 to −48.9)
PBO-adj LSM diff (95% CI)	–	−44.0 (−57.1 to −30.8)	−41.3 (−54.8 −27.8)	−45.9 (−56.5 to −35.2)	−43.8 (−56.9 to −30.7)	−50.5 (−61.4 to −39.6)	−50.7 (−61.2 to −40.1)	−56.8 (−68.9 to −44.7)
P value	–	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
LDL-C (direct) (mg/dL)								
Baseline	91.4 (27.2)	100.1 (33.7)	89.3 (29.2)	88.9 (26.9)	100.7 (34.2)	95.6 (37.2)	98.3 (40)	93.8 (27.8)
24 wk	89.6 (28.6)	73.7 (23.4)	75.8 (32.0)	74.0 (21.9)	87.5 (23.4)	72.2 (24.5)	87.1 (38)	80.6 (32.0)
LSM change	−1.2 (−8.5 to 6.0)	−11.2 (−21.9 to −0.6)	−12.7 (−23.8 to −1.6)	−15.7 (−23.4 to −8.0)	−9.1 (−20.0 to 1.8)	−17.3 (−25.1 to −9.4)	−9.1 (−16.6 to −1.7)	−10.2 (−19.5 to −0.8)
PBO-adj LSM diff (95% CI)	–	−10.0 (−22.9 to 2.9)	−11.4 (−24.7 to 1.8)	−14.5 (−25.1 to −3.9)	−7.9 (−21.0 to 5.2)	−16.0 (−26.7 to −5.3)	−7.9 (−18.3 to 2.5)	−9.0 (−20.8 to 2.9)
P value	–	0.129	0.090	0.008	0.238	0.004	0.136	0.138
HDL-C (mg/dL)								
Baseline	42.1 (8.0)	41.4 (10.8)	42.2 (8.4)	42.1 (9.7)	41.4 (7.9)	44.6 (9.5)	43.9 (9.7)	43.2 (8.2)
24 wk	40.9 (9.3)	35.8 (11.6)	32.9 (9.0)	30.4 (8.6)	34.6 (6.6)	34.4 (9.0)	28.4 (10.9)	28.6 (7.8)
LSM change	−1.1 (−5.8 to 3.6)	−13.2 (−20.1 to −6.4)	−21.8 (−28.9 to −14.7)	−24.8 (−29.6 to −19.9)	−14.2 (−21.0 to −7.4)	−23.6 (−28.7 to −18.5)	−35.3 (−40.1 to −30.5)	−36.2 (−42.2 to −30.3)
PBO-adj LSM diff (95% CI)	–	−12.1 (−20.4 to −3.8)	−20.7 (−29.2 to −12.3)	−23.7 (−30.4 to −17.0)	−13.1 (−21.4 to −4.9)	−22.5 (−29.4 to −15.6)	−34.3 (−41.0 to −27.6)	−35.1 (−42.7 to −27.6)
P value	–	0.004	<0.001	<0.001	0.002	<0.001	<0.001	<0.001
ApoB (mg/dL)								
Baseline	96.6 (17.7)	103.2 (17.5)	101.7 (21.8)	100.1 (16.8)	106.8 (22.3)	101.1 (23.0)	102.4 (26.3)	99.2 (18.5)
24 wk	96.4 (20.7)	80.9 (16.1)	86.2 (22.6)	86.0 (14.9)	94.1 (16.5)	83.9 (15.4)	98.0 (26.7)	92.6 (26.5)
LSM change	0.3 (−4.5 to 5.2)	−14.8 (−21.9 to −7.7)	−11.2 (−18.6 to −3.8)	−12.2 (−17.3 to −7.2)	−10.3 (−17.3 to −3.3)	−12.2 (−17.4 to −6.9)	−5.6 (−10.7 to −0.6)	−8.1 (−14.4 to −1.9)
PBO-adj LSM diff (95% CI)	–	−15.1 (−23.7 to −6.5)	−11.5 (−20.3 to −2.7)	−12.6 (−19.5 to −5.6)	−10.6 (−19.2 to −2.1)	−12.5 (−19.7 to −5.3)	−6.0 (−13.0 to 1.0)	−8.5 (−16.4 to −0.6)
P value	–	<0.001	0.011	<0.001	0.015	<0.001	0.095	0.036
hsCRP (mg/dL)								
Baseline	3.3 (7.6)	1.9 (1.4)	2.4 (2.1)	4.9 (5.8)	1.5 (1.1)	3.0 (2.7)	5.0 (7.2)	2.8 (3.1)

(*Continued*)

Table 2. Continued

	Placebo N=44	Q4W regimens			Q2W regimens			
		80 mg N=23	120 mg N=23	160 mg N=45	60 mg N=23	80 mg N=42	120 mg N=46	160 mg N=35
24 wk	3.3 (8.6)	1.3 (0.9)	2.4 (2.3)	2.6 (2.0)	1.3 (1.1)	4.3 (13.0)	3.4 (4.1)	1.6 (1.5)
LSM change	43.6 (−125.5 to 212.8)	−33.1 (−292.2 to 226.1)	6.8 (−252.2 to 265.9)	−2.9 (−183.4 to 177.6)	0.4 (−259.2 to 260.0)	231.8 (35.5 to 428.2)	49.4 (−123.8 to 222.6)	−18.8 (−254.7 to 217.2)
PBO-adj LSM diff (95% CI)	–	−76.7 (−386.1 to 232.6)	−36.8 (−346.1 to 272.4)	−46.6 (−294.1 to 201.0)	−43.3 (−352.9 to 266.4)	188.2 (−70.9 to 447.3)	5.8 (−236.5 to 248.0)	−62.4 (−352.7 to 227.9)
P value	–	0.625	0.815	0.711	0.783	0.154	0.963	0.672

Baseline and week 24 values are provided as mean and standard deviation. LSM change from baseline for each treatment arm and PBO-adj LSM diff for each vupanorsen arm were calculated using a mixed model for repeated measures and are shown as mean and 95% confidence interval. Adj indicates adjusted; ANGPTL3, angiopoietin-like protein 3; ApoB, apolipoprotein B; diff, difference; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LSM, least squares mean; PBO, placebo; TG, triglycerides; Q2W, every 2 weeks; and Q4W, every 4 weeks.

Safety and Tolerability

Safety and tolerability findings are shown in Table 3. A total of 19 (6.6%) subjects experienced a treatment-emergent serious adverse event. No serious adverse event was deemed related to study medication by the investigator, and there were no suspected unexpected serious adverse reactions. There were no confirmed instances of significant decline in renal function or platelet count with vupanorsen. Elevations in ALT or AST >3× the upper limit of normal were more common with vupanorsen than placebo and tended to be more common at higher total monthly doses, with 16 (44.4%) subjects in the 160 mg every 2 weeks arm having any instance of an ALT or AST value reaching this threshold, and 14 (38.9%) having an abnormal repeat value within 7 days. Placebo-adjusted changes in ALT and AST levels by treatment arm are shown in Table S2. There were no elevations in bilirubin or Hy's law cases among vupanorsen-treated subjects. There was a dose-dependent change in hepatic fat fraction with vupanorsen, with up to a 76% relative increase compared with baseline observed with the 160 mg every 2 weeks dose. The relative change at 24 weeks was −1.0% in the placebo arm. Antidrug antibodies were observed in 73 (30.2%) vupanorsen-treated patients, with no apparent difference in treatment effect in those with versus without antidrug antibodies (Table S3).

Injection site reactions were observed in 49 (20.2%) vupanorsen-treated patients compared with 2 (4.5%) placebo-treated patients and were more common at higher total monthly doses (33.3% at the highest dose). Injection site reactions occurring at a site of previous

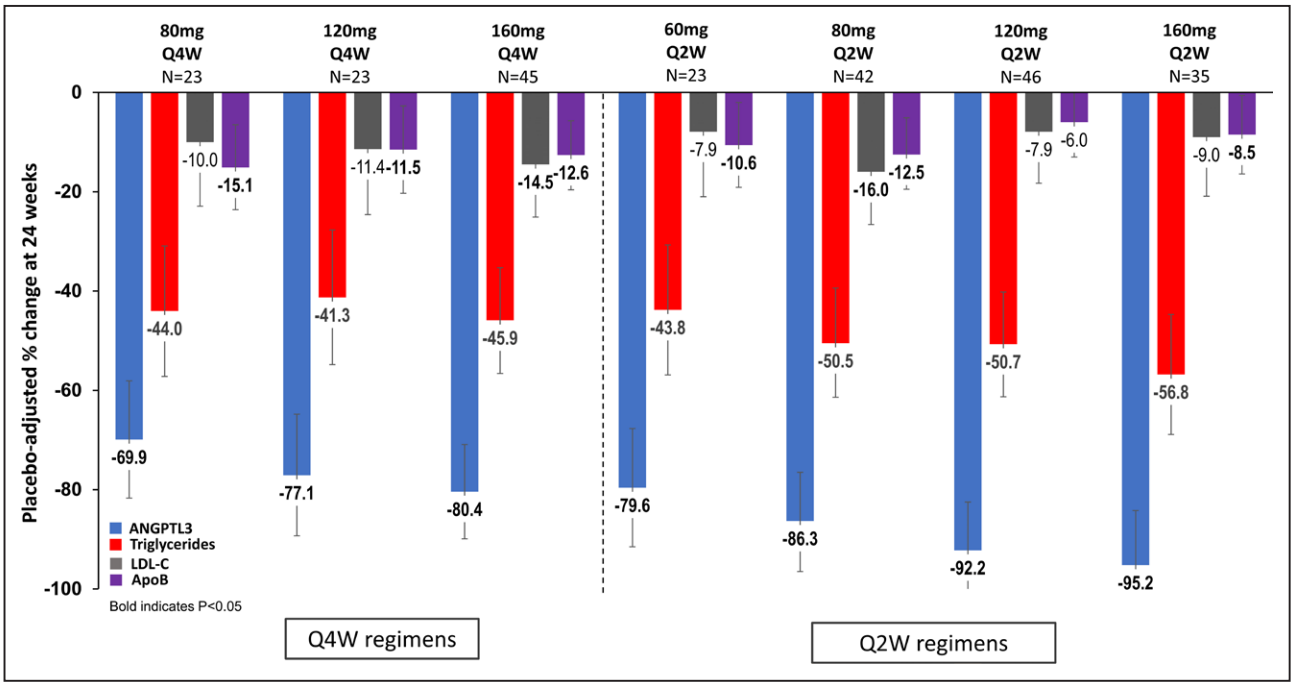

Figure 2. Effect of vupanorsen on additional lipid parameters at 24 weeks.
The effects of vupanorsen on the percent change in placebo-adjusted levels of ANGPTL3 (angiopoietin-like protein 3), triglycerides, low-density lipoprotein cholesterol (LDL-C), and ApoB (apolipoprotein B) at 24 weeks are shown for each dose arm. Data shown are placebo-adjusted least squares mean differences. Q2W indicates every 2 weeks; and Q4W, every 4 weeks.

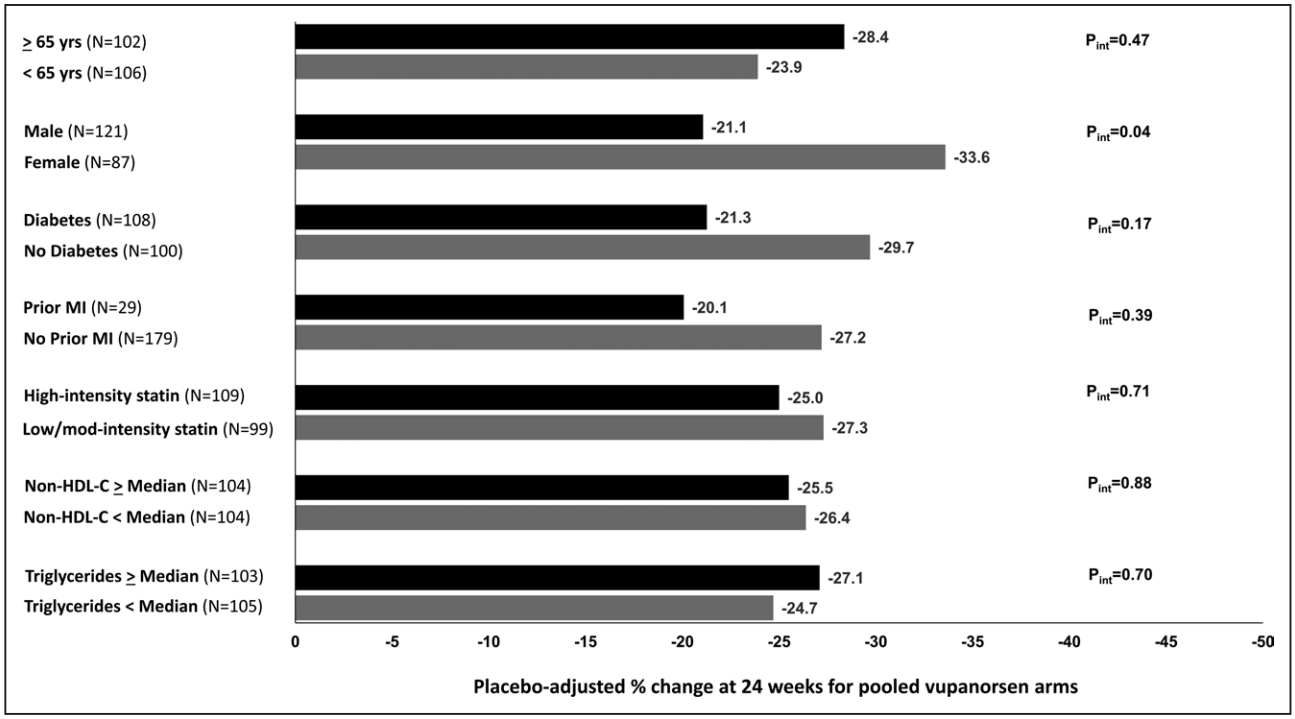

Figure 3. Effect of vupanorsen on non–HDL-C at 24 weeks in key subgroups.
Placebo-adjusted least squares mean difference reductions in non–HDL-C at 24 weeks with vupanorsen (pooled) are shown in key subgroups. MI indicates myocardial infarction; mod, moderate; non-HDL-C, non-high-density lipoprotein cholesterol; and Pint, *P* value for interaction.

drug administration after a subsequent injection at a separate site, referred to as "recall" injection site reactions, occurred in 13 (5.4%) vupanorsen-treated subjects and no placebo-treated subjects.

DISCUSSION

The principal finding of the TRANSLATE-TIMI 70 trial, a phase 2b study of a novel antisense oligonucleotide targeting hepatic ANGPTL3, is that treatment with vupanorsen resulted in significant reductions in non–HDL-C at 24 weeks at all doses studied. These reductions ranged from 22.0% to 27.7% and were accompanied by significant lowering of triglycerides and other lipid parameters. Liver enzyme elevations and injection site reactions were more frequent at higher total monthly doses, and there was a dose-related increase in hepatic fat fraction.

Lipid-lowering therapies are the centerpiece of cardiovascular risk reduction for primary and secondary prevention. However, substantial residual risk remains, for which numerous promising therapeutic targets are under investigation.[11] Among these is ANGPTL3, a hepatically produced protein that inhibits lipases, including lipoprotein lipase, and impairs metabolism of triglyceride-rich lipoproteins. In genetic studies, loss-of-function variants in *ANGPTL3* have been associated with lower levels of triglycerides and LDL-C and with lower rates of coronary artery disease.[7,9,12]

Vupanorsen, a second-generation N-acetyl galactosamine–conjugated antisense oligonucleotide, was studied with ascending doses in healthy adults, resulting in dose-dependent reductions in plasma ANGPTL3 levels of up to 85%.[8] In a phase 2a trial in adults with diabetes, hypertriglyceridemia, and hepatic steatosis, reductions in triglycerides up to 53% and in non–HDL-C up to 19% were seen with total monthly doses of 40 or 80 mg.[10] Given that a potential cardiovascular benefit of vupanorsen would best be reflected by its effects on non–HDL-C and ApoB, we designed the TRANSLATE-TIMI 70 trial to assess these parameters at higher doses than had been evaluated in the phase 2a study.

We found significant reductions in non–HDL-C at all doses studied. This effect of vupanorsen was observed on a background of statin therapy, including in those on a high-intensity statin regimen, and the study population reflects a typical cohort intended for cardiovascular risk reduction, with type 2 diabetes in approximately one-half of patients and prevalent atherosclerotic cardiovascular disease in a substantial portion. The effect of vupanorsen on non–HDL-C was generally consistent across key clinical subgroups, and it is not clear if the observed interaction between vupanorsen effect and patient sex reflects a true biological difference or is simply a result of chance.

Although previous genetic studies have suggested that reductions in LDL-C and ApoB require near-complete suppression of ANGPTL3 activity,[7,13] we did not observe a consistent dose-response relationship for these measures. In fact, whereas the reduction in ANGPTL3 levels increased with total monthly dose, there was no clear dose-response reduction in LDL-C or ApoB. Nor was there a clear relation-

Table 3. Safety and Tolerability

	Placebo N=44	Q4W regimens			Q2W regimens			
		80 mg N=23	120 mg N=23	160 mg N=45	60 mg N=24	80 mg N=45	120 mg N=46	160 mg N=36
Any AE	31 (70.5)	15 (65.2)	12 (52.2)	28 (62.2)	17 (70.8)	31 (68.9)	30 (65.2)	31 (86.1)
Mild	16 (36.4)	7 (30.4)	5 (21.7)	13 (28.9)	7 (29.2)	13 (28.9)	13 (28.3)	16 (44.4)
Moderate	10 (22.7)	6 (26.1)	7 (30.4)	13 (28.9)	6 (25.0)	14 (31.1)	15 (32.6)	13 (36.1)
Severe	5 (11.4)	2 (8.7)	0 (0.0)	2 (4.4)	4 (16.7)	4 (8.9)	2 (4.3)	2 (5.6)
Treatment-emergent SAE	4 (9.1)	2 (8.7)	0 (0.0)	1 (2.2)	2 (8.3)	6 (13.3)	3 (6.5)	1 (2.8)
Injection site reaction								
Any	2 (4.5)	4 (17.4)	6 (26.1)	7 (15.6)	4 (16.7)	6 (13.3)	10 (21.7)	12 (33.3)
Recall	0	0	1 (4.3)	0	2 (8.3)	2 (4.4)	5 (10.9)	3 (8.3)
Worsening renal function*								
Any instance	0	0	0	0	1 (4.2)	1 (2.3)	0	1 (2.8)
Abnormal repeat value†	0	0	0	0	0	0	0	0
Platelet count <100,000/mm^3								
Any instance	0	0	0	0	0	0	0	1 (2.8)
Abnormal repeat value†	0	0	0	0	0	0	0	0
ALT or AST >3× ULN‡								
Any instance	1 (2.3)	0	1 (4.3)	4 (8.9)	1 (4.2)	1 (2.3)	11 (23.9)	16 (44.4)
Abnormal repeat value†	0	0	0	4 (8.9)	1 (4.2)	1 (2.3)	8 (17.4)	14 (38.9)
Anti-drug antibodies	–	6 (26.1)	4 (17.4)	8 (17.8)	9 (37.5)	15 (33.3)	15 (32.6)	16 (44.4)
Hepatic fat fraction relative change§	0.99 (0.88–1.11)	1.13 (0.95–1.34)	1.24 (1.02–1.51)	1.24 (1.09–1.41)	1.05 (0.89–1.23)	1.21 (1.06–1.38)	1.40 (1.23–1.59)	1.76 (1.51–2.05)

Values shown are number and percent with the exception of hepatic fat fraction relative change. AE indicates adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; Q2W, every 2 weeks; Q4W, every 4 weeks; and SAE, serious adverse event.

*Greater than 50% decrease in eGFR compared with baseline or any instance of eGFR <15 mL per min per 1.73 m^2 regardless of starting eGFR.

†Repeat confirmatory testing was required within 7 days of an initial abnormal value meeting the protocol-defined monitoring criteria. "Abnormal repeat value" indicates that the repeat confirmatory test also met the prespecified renal, platelet count, or liver enzyme threshold.

‡Instances of protocol-defined significant ALT or AST elevations. For subjects with normal ALT and AST values at baseline, elevations >3× upper limit of normal (ULN) are reported. For subjects with abnormal baseline ALT or AST values, instances of ALT or AST >3× ULN also meeting the threshold of >2× baseline value are reported.

§Hepatic fat fraction was measured by MRI and is provided as least squares mean relative change at week 24 compared with baseline (week 24 value divided by baseline value). Hepatic fat fraction is only reported in subjects with baseline and week 24 MRI data (N=227).

ship between non–HDL-C and ApoB reductions across vupanorsen regimens. In comparison, evinacumab, a monoclonal antibody against ANGPTL3 that is thought to cause near-total suppression of ANGPTL3 activity,[7,14,15] reduces ApoB levels by >40% in adults with refractory hypercholesterolemia or homozygous familial hypercholesterolemia in its intravenous formulation administered at a dose of 15 mg/kg.[14,15] Conversely, reductions in triglycerides with vupanorsen showed a dose-response relationship, mirroring the reduction in ANGPTL3 and consistent with the expected increases in lipoprotein lipase activity. However, the relatively muted effect on ApoB levels suggests that vupanorsen is primarily decreasing the triglyceride, and, to a lesser extent, cholesterol content of very-low-density lipoprotein particles rather than reducing the number of such particles. These observations have important implications for the potential ability of this mechanism to reduce lipid-mediated cardiovascular risk, which largely appears to be a function of the number of ApoB-containing lipoproteins.[4]

With regard to safety, there were no confirmed instances of reduced renal function or platelet count with vupanorsen, 2 issues that have been observed with some first-generation antisense oligonucleotides.[16,17] Injection site reactions were more common at higher total monthly doses, as were recall injection site reactions, which have not previously been seen with vupanorsen, but have been reported with mipomersen, an antisense oligonucleotide targeting ApoB.[18]

More frequent elevations of ALT or AST occurred at higher total monthly vupanorsen doses, and there was a dose-related increase in hepatic fat fraction. Neither finding is readily explained given what is known about this metabolic pathway, although a significant increase in hepatic fat fraction was also seen in the 80 mg every 4 weeks dose arm in the phase 2a study of vupanorsen.[10] There is uncertainty about potential metabolic mechanisms for this finding. Fibrates, which also increase lipoprotein lipase activity,[19] have shown a strong trend toward increasing hepatic fat

fraction in patients with hypertriglyceridemia and nonalcoholic fatty liver disease.[20] Nonetheless, ANGPTL3 inhibition in mice with an antisense oligonucleotide led to a reduction in liver triglyceride content,[8] and no consistent associations have been observed between *ANGPTL3* loss-of-function mutations and liver disease[8,13] or between circulating ANGPTL3 levels and hepatic steatosis.[21] Ultimately, it is unclear whether the increases in hepatic fat fraction and liver enzymes reflect a metabolic effect of vupanorsen specifically or an off-target effect as a result of hepatic targeting of ANGPTL3. Regardless, these are medically meaningful findings with important safety ramifications.

These findings must be considered in the context of a rapidly evolving landscape of therapeutic targets and agents indented for cardiovascular risk reduction.[11] An antisense oligonucleotide targeting apolipoprotein C3, for example, has shown reductions in triglycerides up to 77% and in ApoB up to 30% in healthy volunteers without major safety concerns,[22] although the reductions in ApoB seen in patients with hypertriglyceridemia have been of lower magnitude.[23] How the efficacy and safety of vupanorsen will compare with compounds affecting these adjacent metabolic targets, such as apolipoprotein C3 or lipoprotein lipase, in larger trials is not presently known.

Limitations

Some limitations of this trial should be considered. First, the study was intended to enroll a population reflective of a large cardiovascular outcomes trial, and findings cannot necessarily be generalized to patients with specific lipid disorders. Testing for genetic disorders of lipid metabolism was not performed. Second, although the trial did have adequate power for its primary end point, a larger study would have allowed for a more precise assessment of the relationship between non–HDL-C and ANGPTL3 reductions across dose regimens. Third, there was an underrepresentation of subjects who do not self-identify as White, with 13% of subjects indicating race other than White in this trial compared with approximately 23% for the overall populations of the participating countries weighted for enrollment contribution.

Conclusions

In conclusion, vupanorsen, a second-generation N-acetyl galactosamine–conjugated antisense oligonucleotide targeting hepatic ANGPTL3, significantly reduced non–HDL-C and triglycerides at all doses studied as well as additional lipid parameters at certain doses. Key safety findings included more frequent liver enzyme elevations at higher total monthly doses and a dose-related increase in hepatic fat fraction.

ARTICLE INFORMATION

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Supplemental Material

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