TRANSLATE-TIMI 70

American College of Cardiology Scientific Sessions
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Brian Bergmark, MD

For the TRANSLATE-TIMI 70 Investigators

An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Disclosures

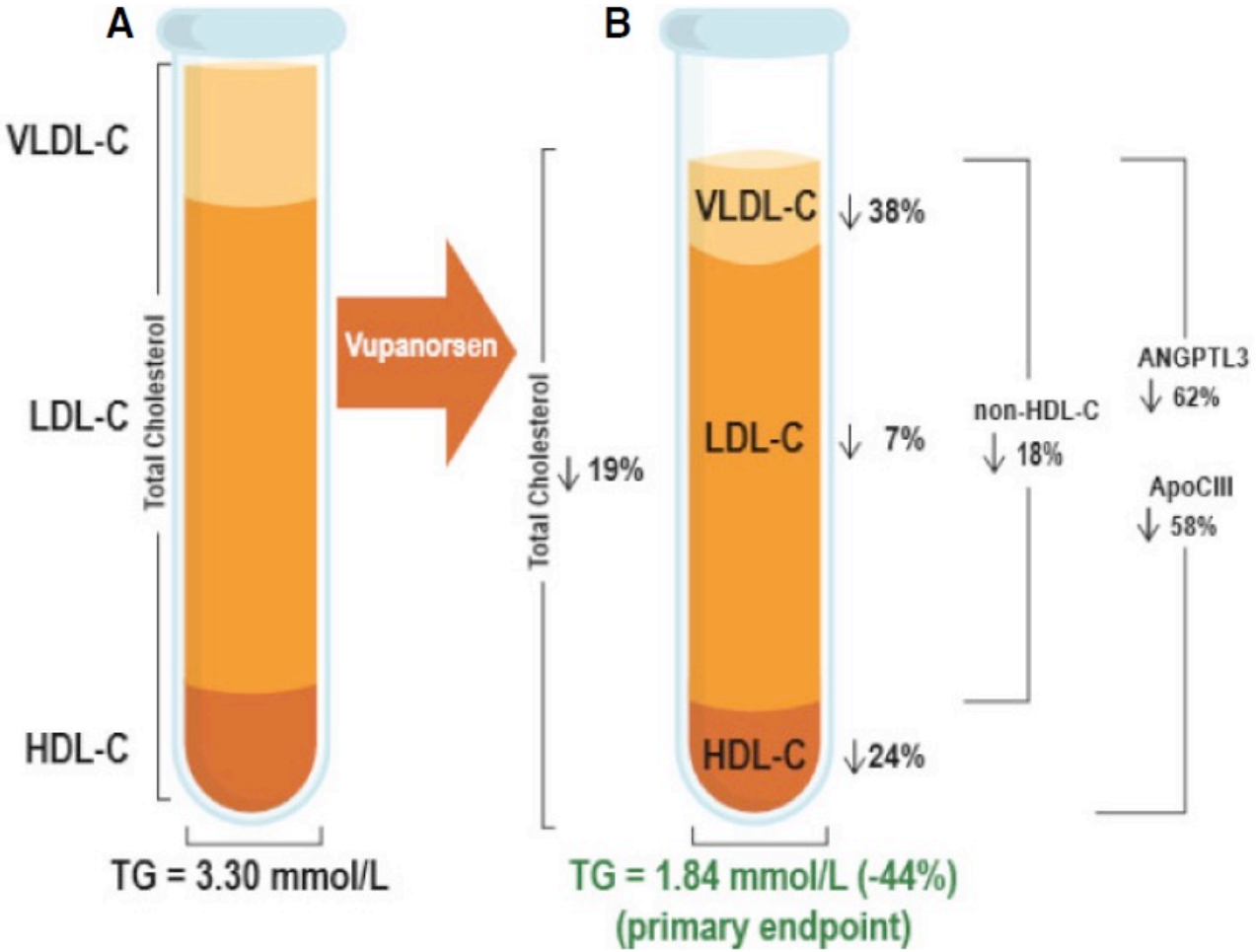
BAB – Grant support through Brigham and Women's Hospital: Pfizer, Ionis, AstraZeneca; consulting/personal fees: Abiomed, CSI, Philips, Abbott Vascular, Servier, Daiichi-Sankyo, Janssen, Quark. BAB is a member of the TIMI Study Group, which has received institutional grant support through the Brigham and Women's Hospital from: Abbott, Amgen, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Ionis, Janssen, MedImmune, Merck, Novartis, Pfizer, Poxel, Quark Pharmaceuticals, Roche, Takeda, The Medicines Company, Zora Biosciences.

The TRANSLATE-TIMI 70 Trial was supported by a grant from Pfizer to the Brigham and Women's Hospital.

Background

- Angiopoietin-like protein 3 (ANGPTL3) is a protein secreted by the liver that inhibits lipases, including lipoprotein lipase (LPL)
- Loss-of-function variants in *ANGPTL3* are associated with lower levels of plasma lipids
- mAb targeting ANGPTL3 is approved as an IV infusion for Rx of homozygous familial hypercholesterolemia
- Vupanorsen is a second-generation ASO targeting hepatic ANGPTL3 mRNA with a potential role for cardiovascular risk reduction

Background



Vupanorsen Ph 2a:

- Evaluated doses up to 80 mg/mo
- Treatment effects up to:
  - 62% ↓ in ANGPTL3
  - 44% ↓ in TG
  - 18% ↓ in non-HDL-C

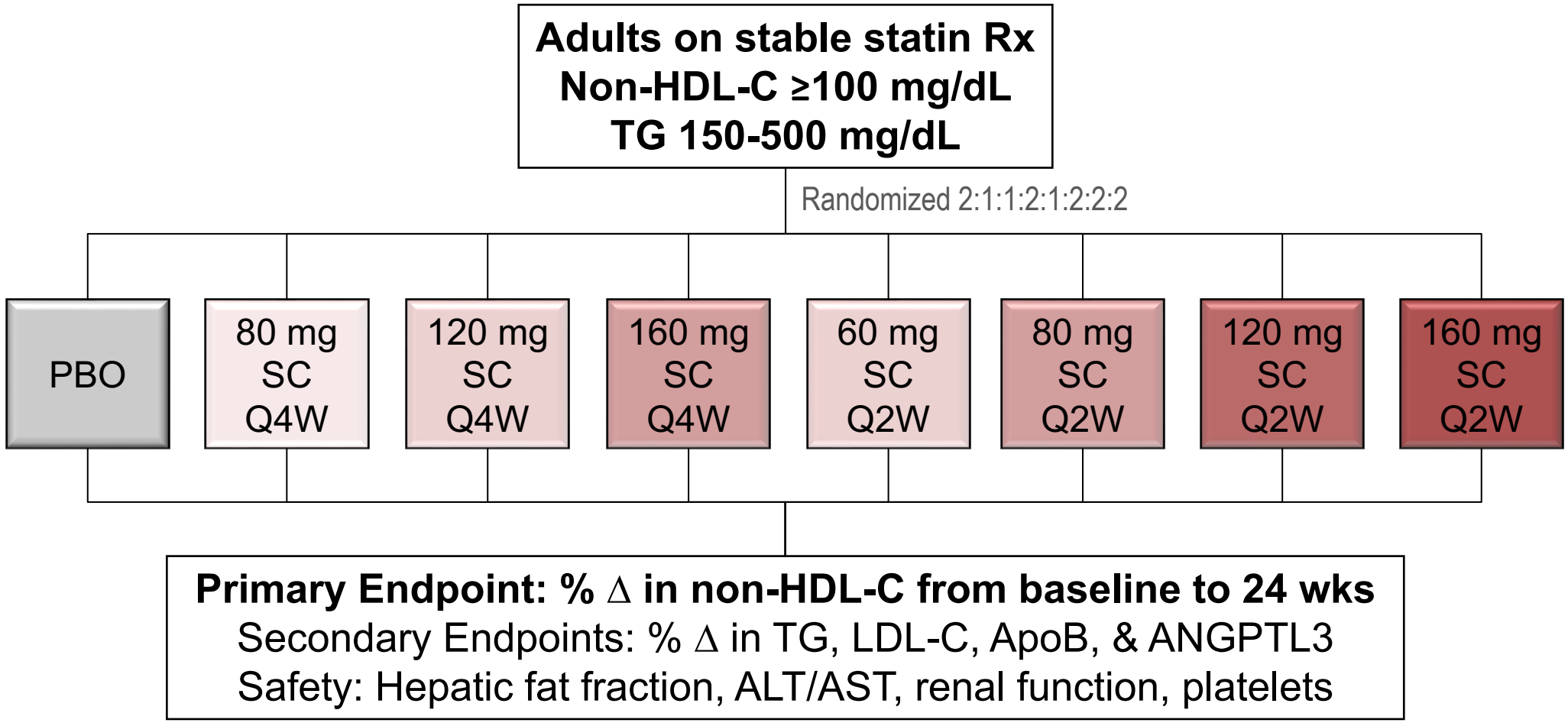
Are greater reductions in non-HDL-C possible?

Gaudet D, et al. *Eur Heart J*. 2020;41:3936-45.

Objective

Assess the effect of escalating doses of vupanorsen on non-HDL-C levels in statin-treated adults with hyperlipidemia.

Trial Design



Statistical considerations

- Mixed model for repeated measures (MMRM) used to generate placebo-adjusted LSM differences in non-HDL-C from baseline through 24 weeks for each vupanorsen arm
- Assuming common standard deviation of 17.5%, 20 subjects per arm anticipated to provide >90% power to detect a 20% difference in non-HDL-C from baseline to 24 weeks

Trial Organization

TIMI Study Group

Marc Sabatine (Chair)
Stephen Wiviott (Sr Investigator)
P. Fish & A. Jevne (Ops)

Brian Bergmark (PI)
Nicholas Marston (Investigator)
S. Murphy, J. Kuder, J.G. Park (Stats)

Sponsor: Pfizer

Steven Terra (Ex. Dir., Team Lead)
Madelyn Curto (Clinical Program Lead)
Tamara Morocco (Team Lead)

Candace Bramson (Dir., Clin. Res.)
Vesper Ramos (Global Prod. Dev.)
Karen Singletary (Lead Study Manager)

Independent Data Monitoring Committee

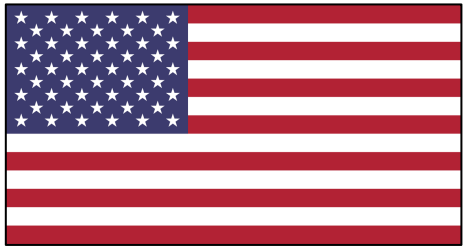
E. Magnus Ohman (Chair)
Jacques Genest

Sheryl Kelsey (Statistician)
Sidney Barritt

Global Enrollment

Enrollment:
October 2020 – April 2021

286 Patients
55 Sites

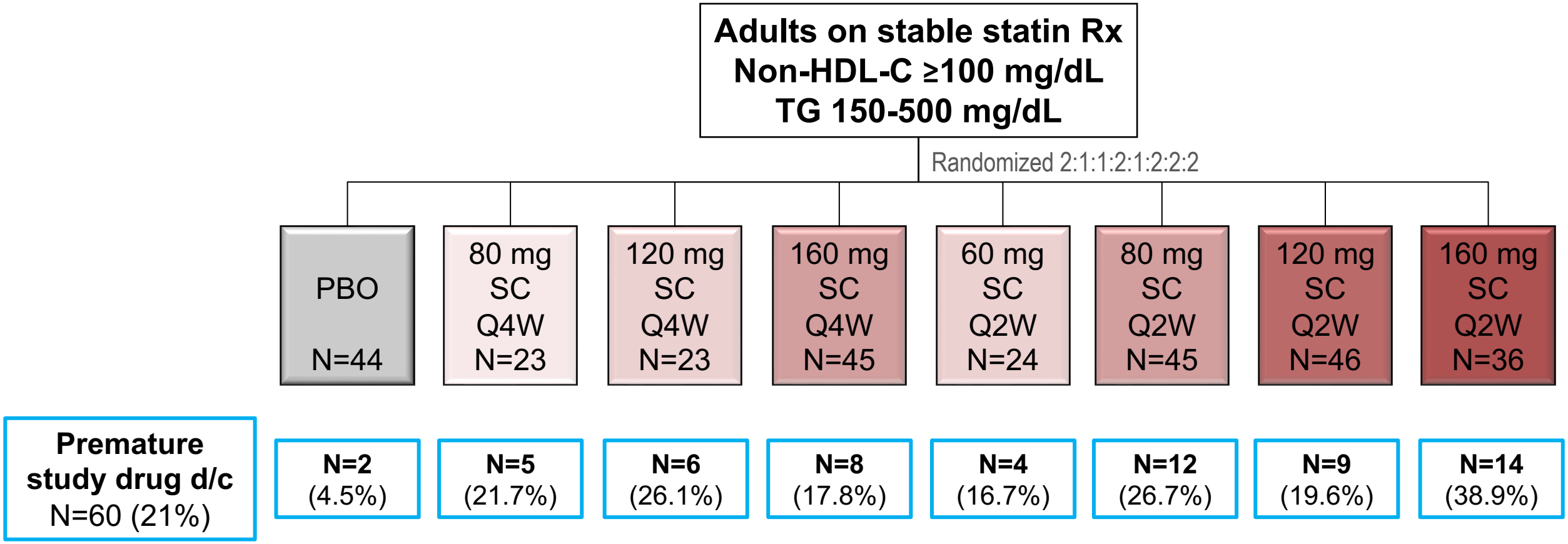


USA (Nicholas Marston)
127

Canada (Subodh Verma)
126

Poland (Wojtek Wojakowski)
33

Follow-up



99% (N=282) of patients completed study

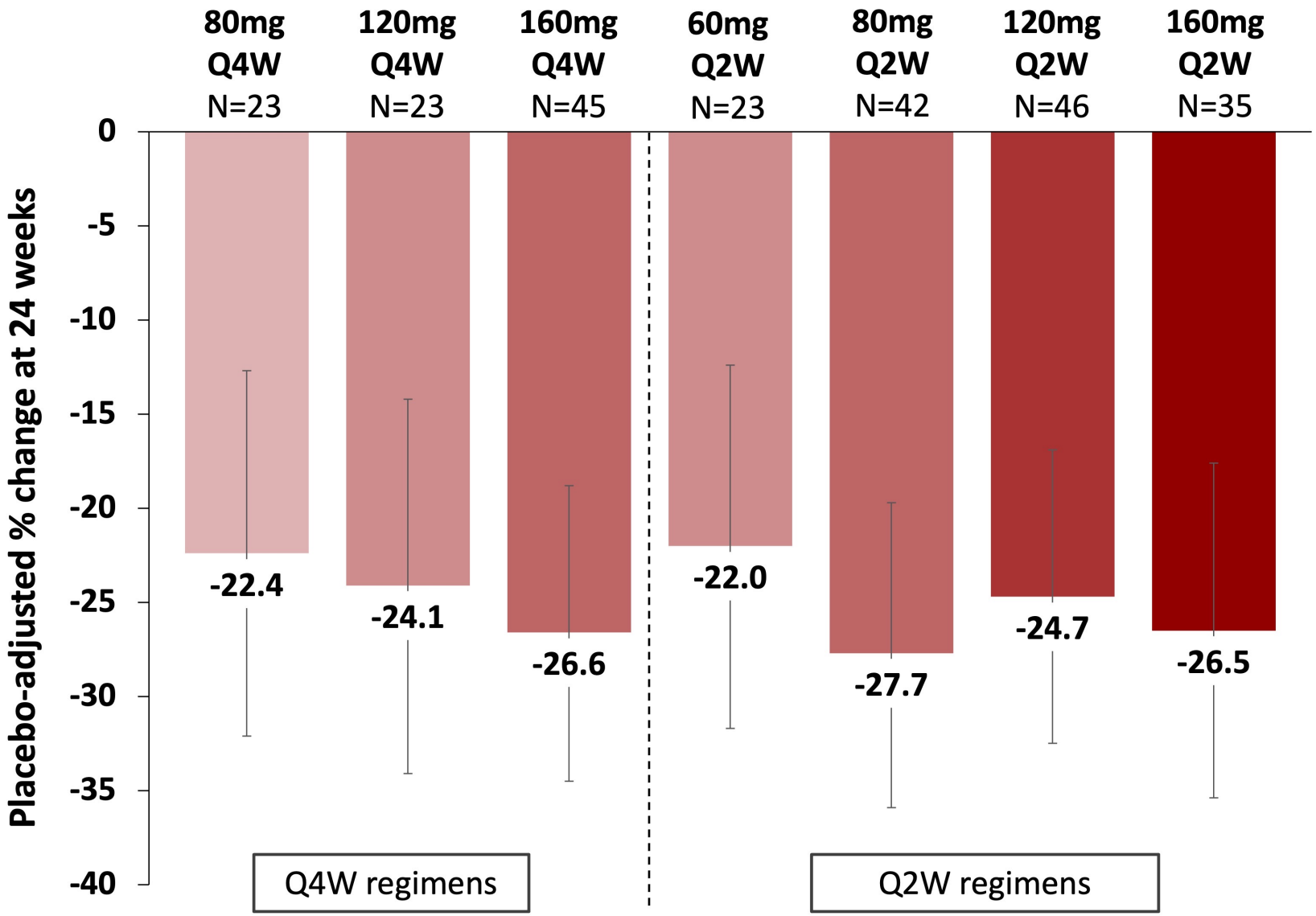
Baseline Characteristics

Characteristic	Overall N=286
Age, years	64 (58-69)
Female sex	44%
Race	
White	87%
Black	4%
Asian	7%
Type 2 diabetes	50%
Prior myocardial infarction	13%
Any statin	100%
High-intensity statin	51%
Ezetimibe	5%
Non-HDL-C, mg/dL	132 (118-154)
Triglycerides, mg/dL	216 (181-270)
LDL-C (direct), mg/dL	88 (73-109)
ApoB, mg/dL	96 (87-112)

No sig. Δ across study arms

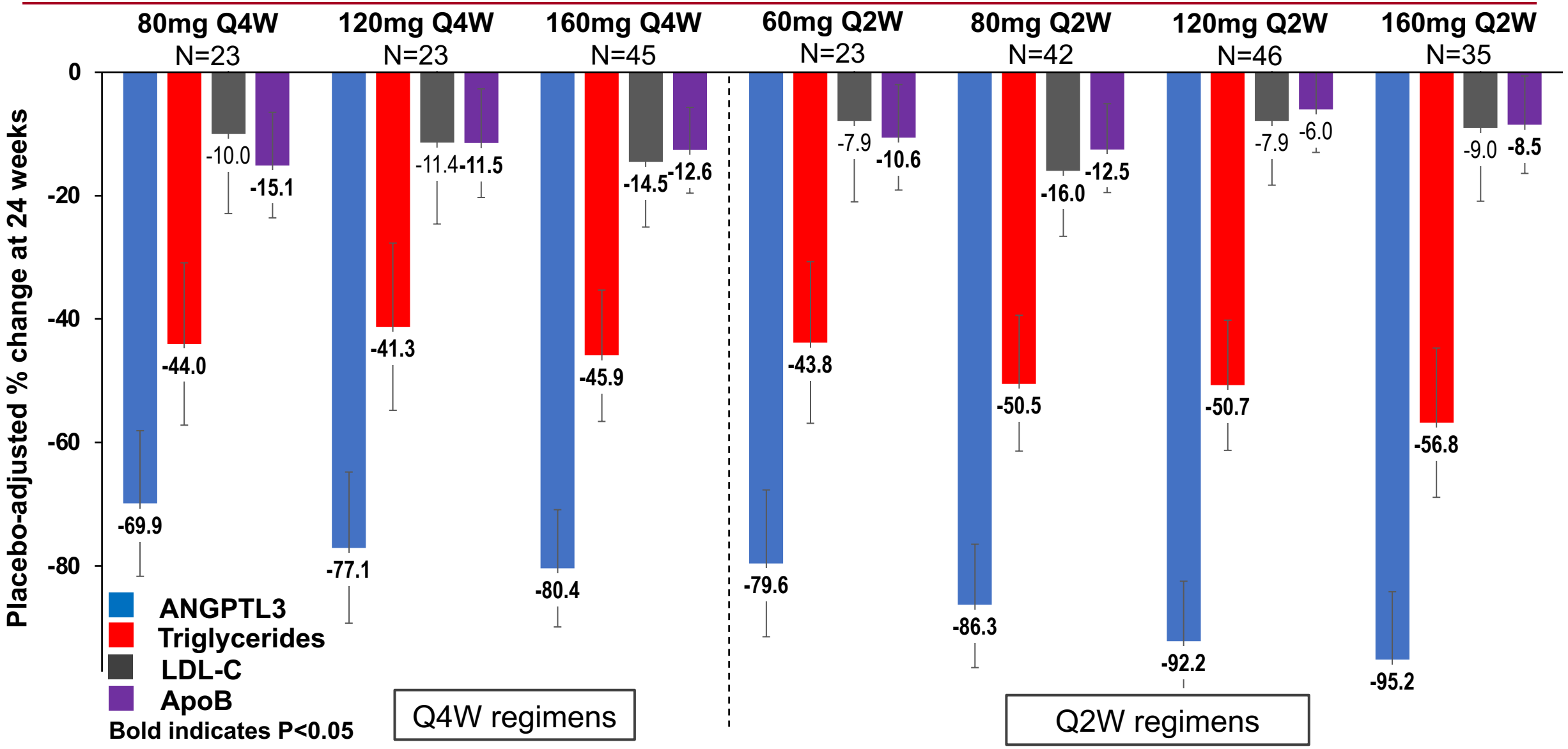
Values are median (IQR) or %

Non-HDL-C

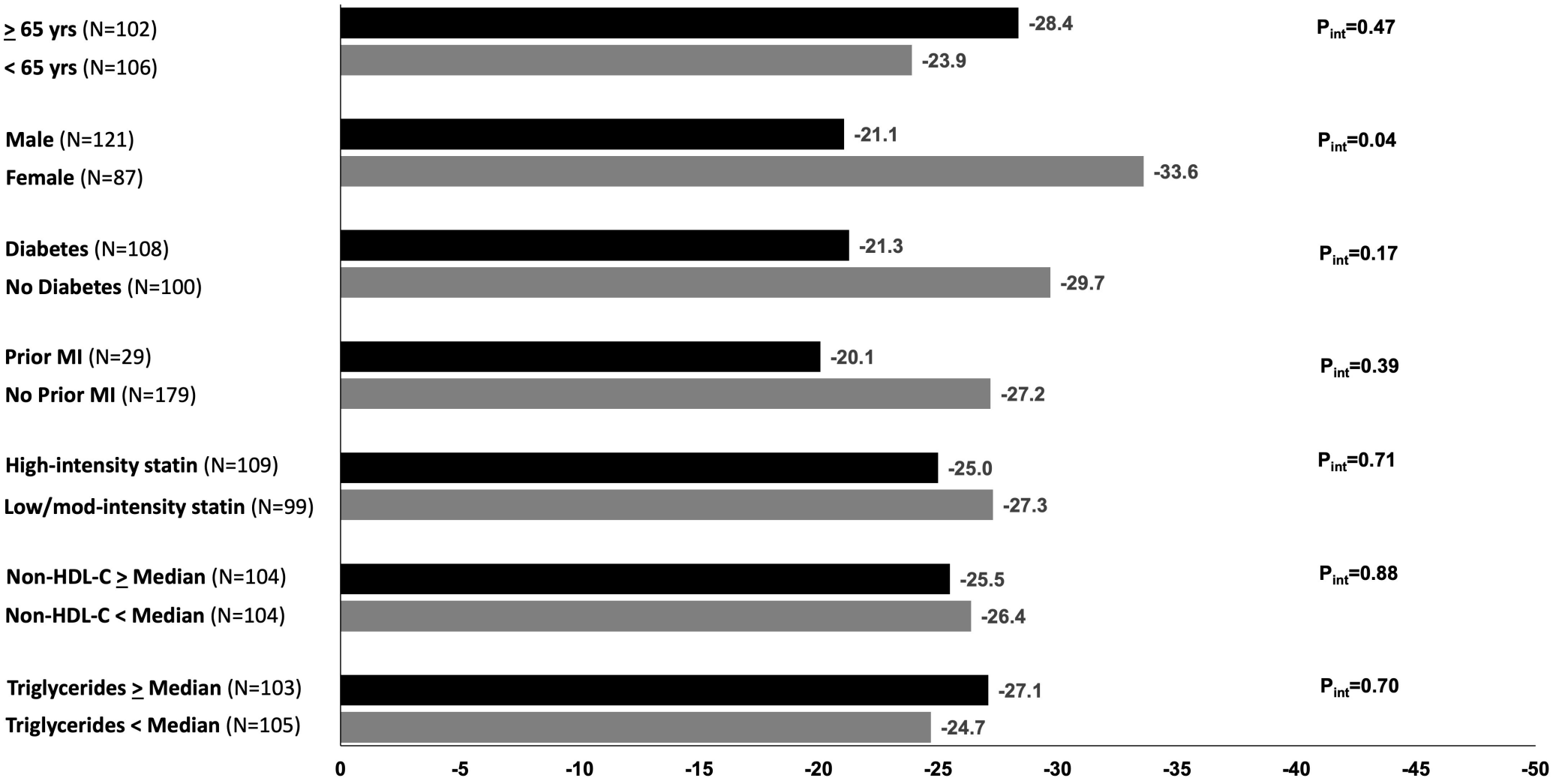


P<0.001 for all

Additional Lipid Parameters



Effect on non-HDL-C by subgroup



Safety and Tolerability

		Q4W regimens			Q2W regimens			
	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
Any AE	71%	65%	52%	62%	71%	69%	65%	86%

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Any AE	71%	65%	52%	62%	71%	69%	65%	86%
Worsening renal function*	0%	0%	0%	0%	0%	0%	0%	0%
Platelet count <100,000/mm^{3*}	0%	0%	0%	0%	0%	0%	0%	0%

*Confirmed values on repeat testing
^Indicates ISR occurring at a site of previous drug administration following subsequent injection at a different site
†Indicates P<0.05 for relative change compared to baseline

Safety and Tolerability

		Q4W regimens			Q2W regimens			
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Platelet count <100,000/mm^3*	0%	0%	0%	0%	0%	0%	0%	0%
Inj. site reaction								
Any	5%	17%	26%	16%	17%	13%	22%	33%
Recall^	0%	0%	4%	0%	8%	4%	11%	8%

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Inj. site reaction								
Any	5%	17%	26%	16%	17%	13%	22%	33%
Recall^	0%	0%	4%	0%	8%	4%	11%	8%
ALT or AST >3x ULN*	0%	0%	0%	9%	4%	2%	17%	39%
Hepatic fat fraction relative change	0.99	1.13	1.24†	1.24†	1.05	1.21†	1.40†	1.76†

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Hepatic fat fraction relative change	0.99	1.13	1.24†	1.24†	1.05	1.21†	1.40†	1.76†
Anti-drug antibodies	--	26%	17%	18%	38%	33%	33%	44%

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Limitations

- Trial conducted in general population of patients with elevated non-HDL-C, and results may not apply to patients with specific lipid disorders.

- A larger study would have allowed for more precise assessment of the relationships among ANGPTL3, non-HDL-C, and ApoB and for greater power for detecting differences in safety events.

Summary and Conclusions

In statin-treated adults with hyperlipidemia, vupanorsen:

- ***Significantly reduced non-HDL-C and triglyceride levels at all doses studied***
- ***Reduced additional lipid parameters at certain doses, but with a modest effect on ApoB***

Key safety and tolerability findings included:

- ***Frequent injection site reactions, including observation of recall reactions***
- ***More frequent liver enzyme elevations at higher total monthly doses***
- ***Dose-related increases in hepatic fat fraction***

Emphasizes the importance of rigorous evaluation of new lipid-lowering therapies and may provide mechanistic insight as additional metabolic targets are studied going forward.

Thank you

Circulation

ORIGINAL RESEARCH ARTICLE

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