A Randomized, Double-Blind, Placebo-Controlled Trial of the Safety and Efficacy of a Monoclonal Antibody to PCSK9, SAR236553/REGN727, in Patients with Primary Hypercholesterolemia

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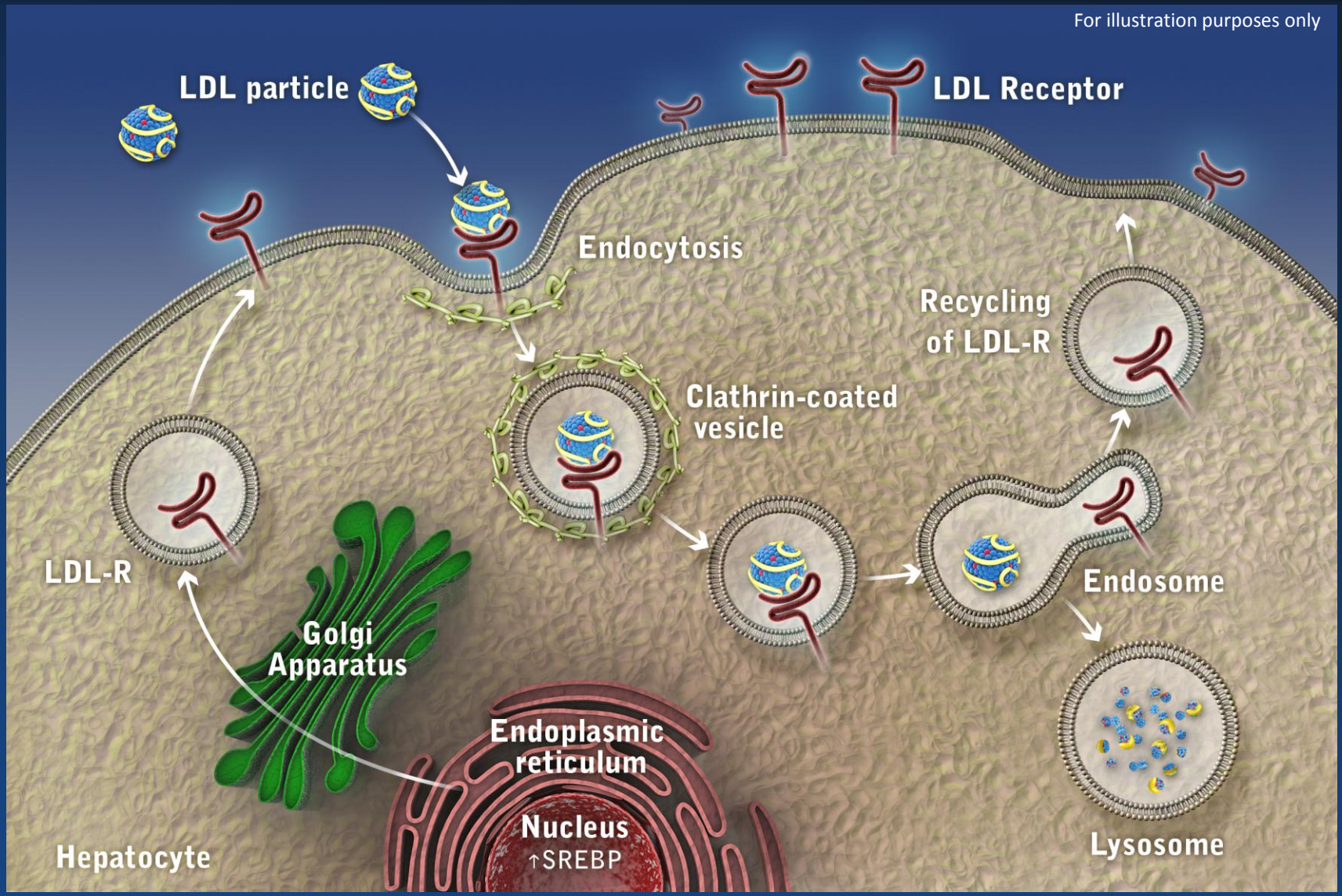
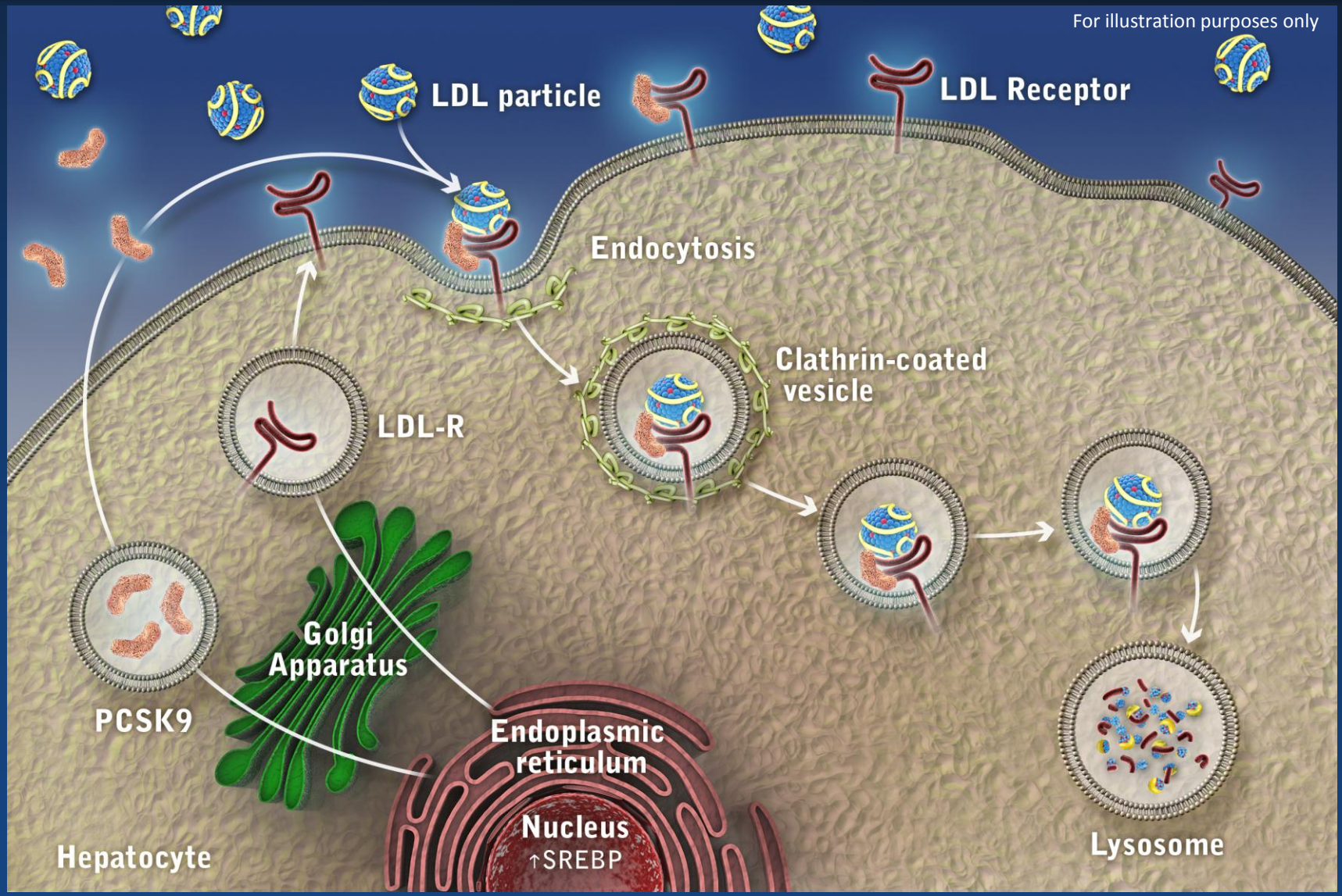
Industry Relationships and Institutional Affiliations

Author	Disclosure
James M. McKenney	Is an employee of a research company that has received research funding from Regeneron and/or Sanofi
Michael J. Koren	
Dean J. Kereiakes	Has no relationships to disclose
Corinne Hanotin	Are employees of Sanofi
Anne-Catherine Ferrand	
Evan A. Stein	Is an employee of a research company that has received research funding from Regeneron and/or Sanofi, as well as consultancy fees from Sanofi

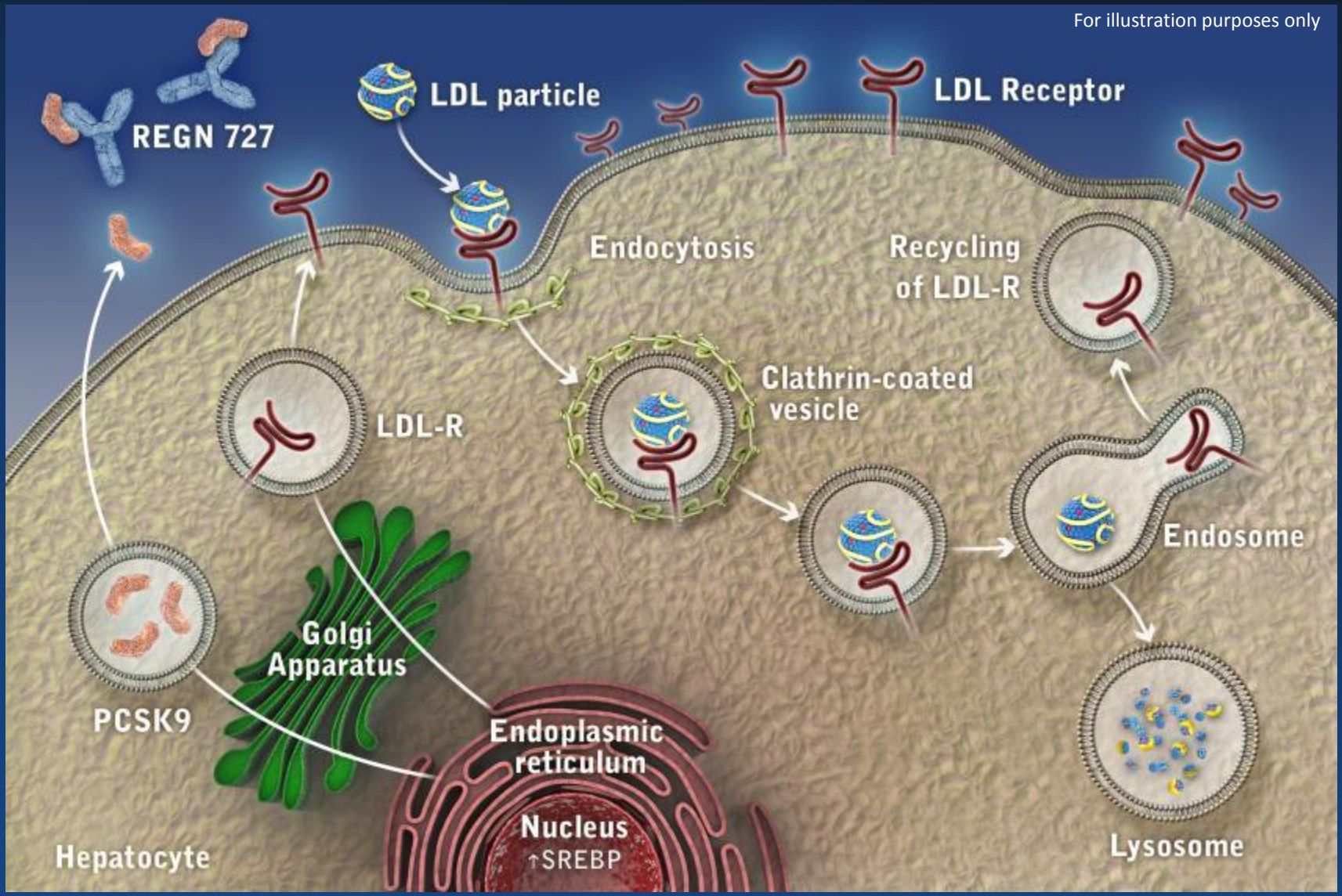
LDL Receptor Function and Life Cycle



The Role of PCSK9 in the Regulation of LDL Receptor Expression



Impact of an PCSK9 mAb on LDL Receptor Expression

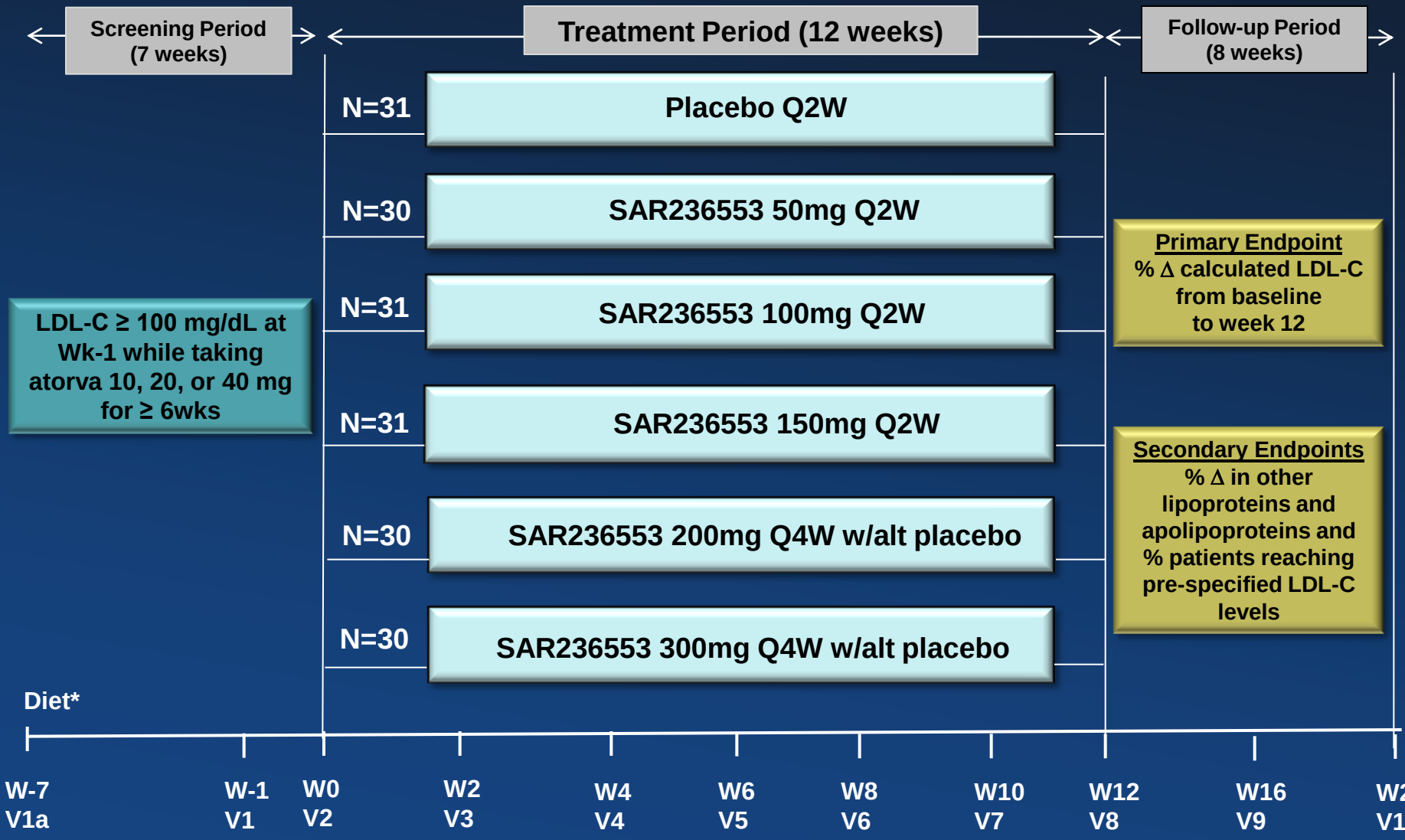


Background and Rationale

- Despite the widespread availability of statins, many patients fail to reach recommended LDL-C targets in clinical practice, even in combination with other lipid lowering agents
- In PCSK9 human population studies:
  - Gain-of-function mutations result in hypercholesterolemia
  - Loss-of-function mutations associated with low LDL-C and low prevalence of CHD events
- SAR236553/REGN727 is a highly specific, fully human monoclonal antibody (mAb) to PCSK9
- A SAR236553/REGN727 Phase 1 trial* in familial and non-familial hypercholesterolemia:
  - Demonstrated dose dependently reduced LDL-C by 36% to 58% either with or without atorvastatin
  - Safe and well-tolerated

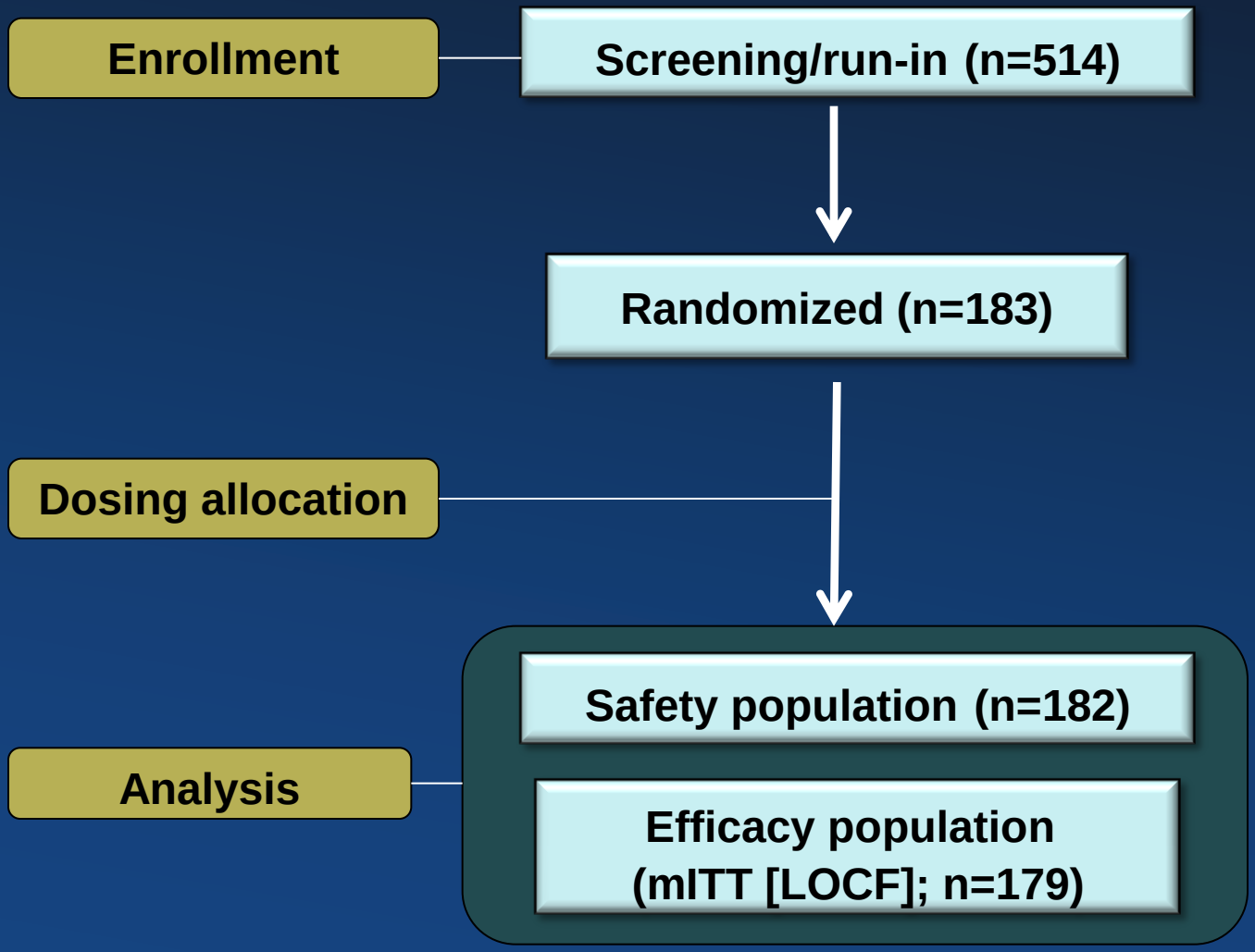
*Stein EA, Mellis S, Yancopoulos GD et al. NEJM 2012; 366: 1108-1118.

Study Design



*NCEP ATP-III TLC or equivalent diet

Patient Disposition



Patient Demographic and Baseline Characteristics

Age, mean	57 years
Female	52%
White race	86%
Hispanic/ Latino ethnicity	22%
On lipid-lowering treatment	86%
Coronary artery disease	5%
Type 2 diabetes	12%
Peripheral vascular disease	3%
Hypertension	45%
Current smoker	20%

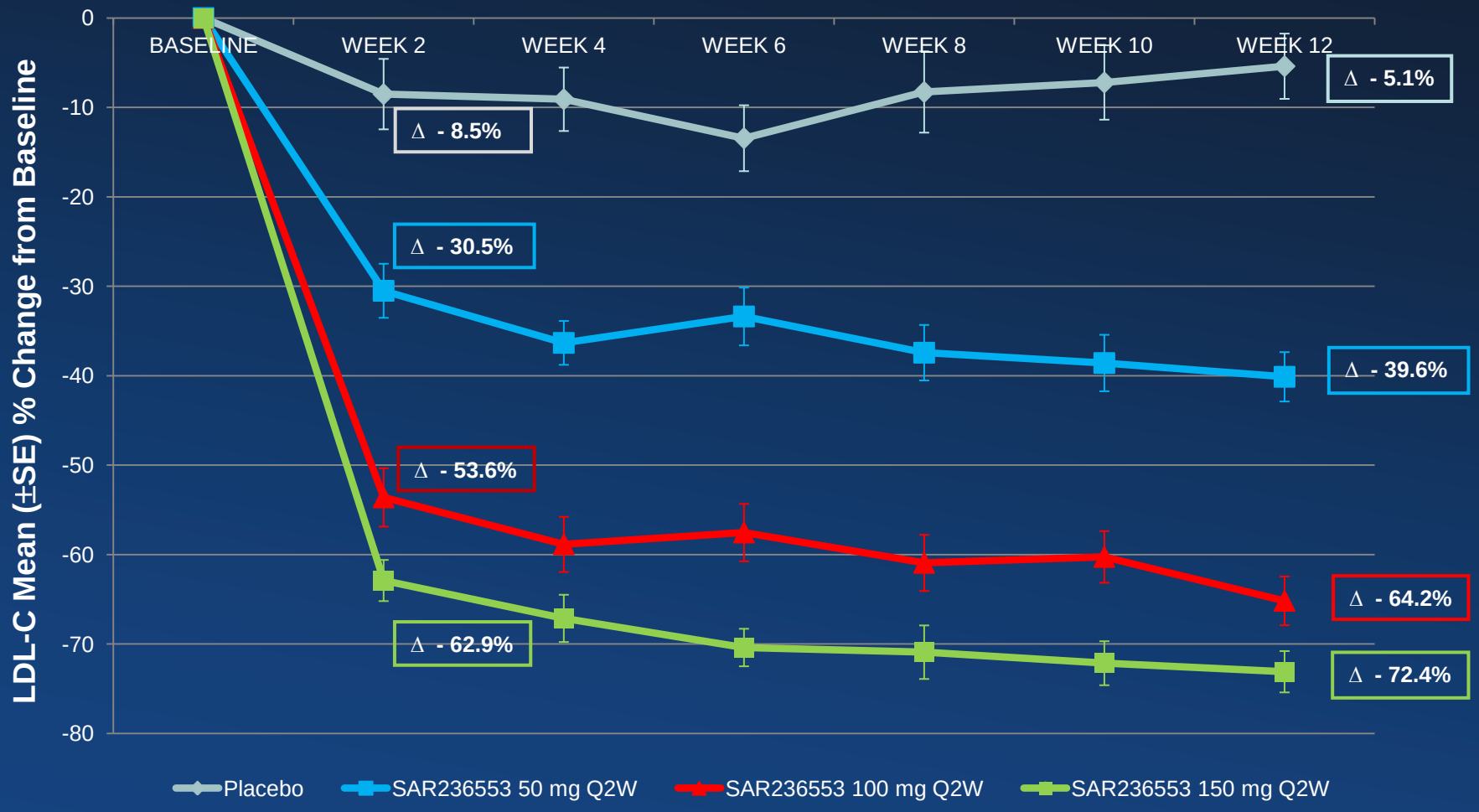
Changes in LDL-C from Baseline to Week 12 by Treatment Group (mITT Population)

Intervention	Baseline LDL-C (mg/dL)	% Change LDL-C[1]
Placebo	130.2	–5.1 (3.1)
SAR236553 50mg Q2W	123.2	–39.6 (3.2)*
SAR236553 100mg Q2W	127.0	–64.2 (3.1)*
SAR236553 150mg Q2W	123.9	–72.4 (3.2)*
SAR236553 200mg Q4W	128.2	–43.2 (3.3)*
SAR236553 300mg Q4W	131.6	–47.7 (3.2)*

*P<0.0001 for % change SAR236553 vs. placebo

[1]LS mean (SE), using LOCF method

Change in Calculated LDL-C at 2 Weekly Intervals from Baseline to Week 12



Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, and 12 in the modified intent-to-treat (mITT) population, by treatment group. Week 12 estimation using LOCF method.

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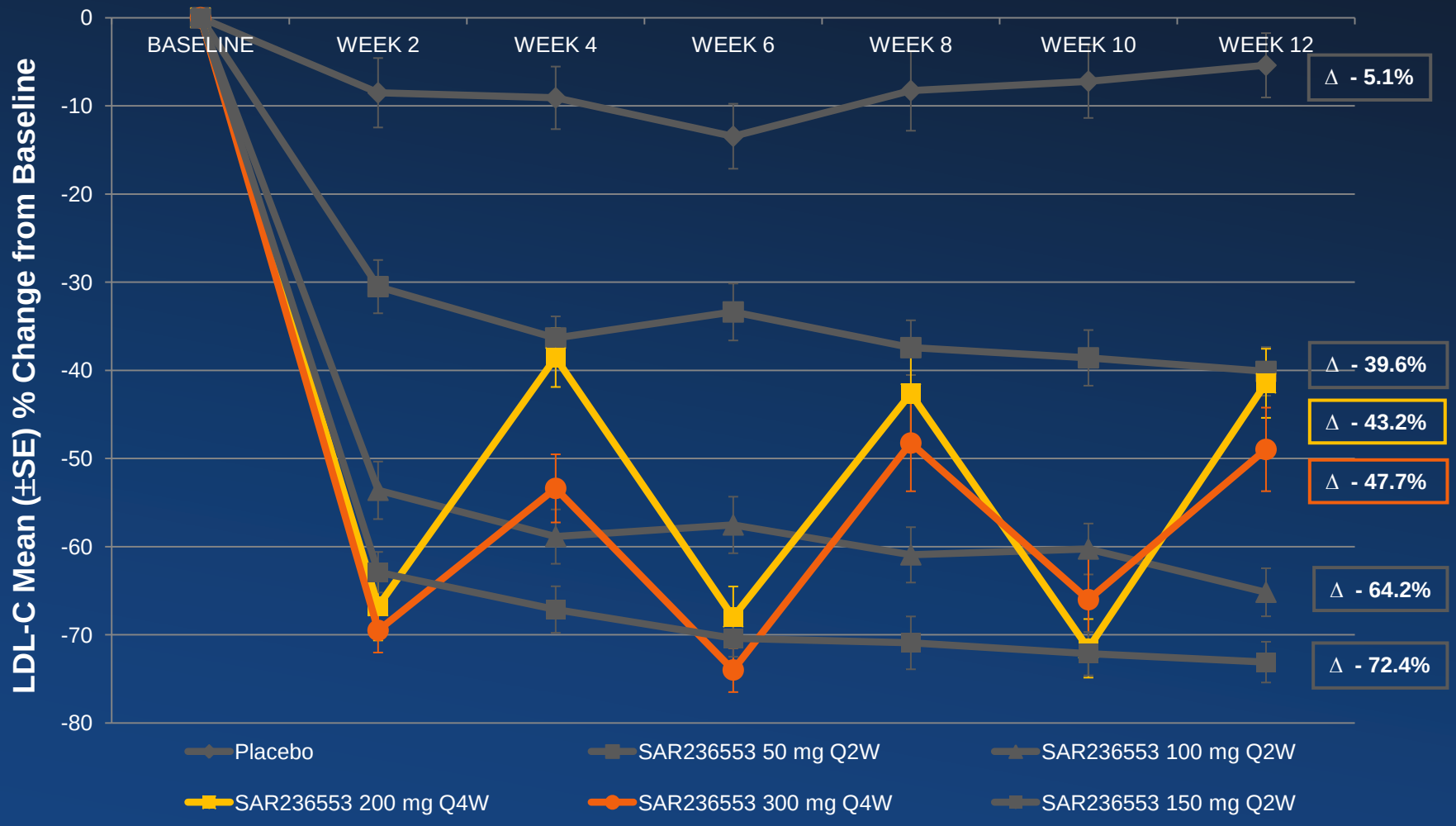

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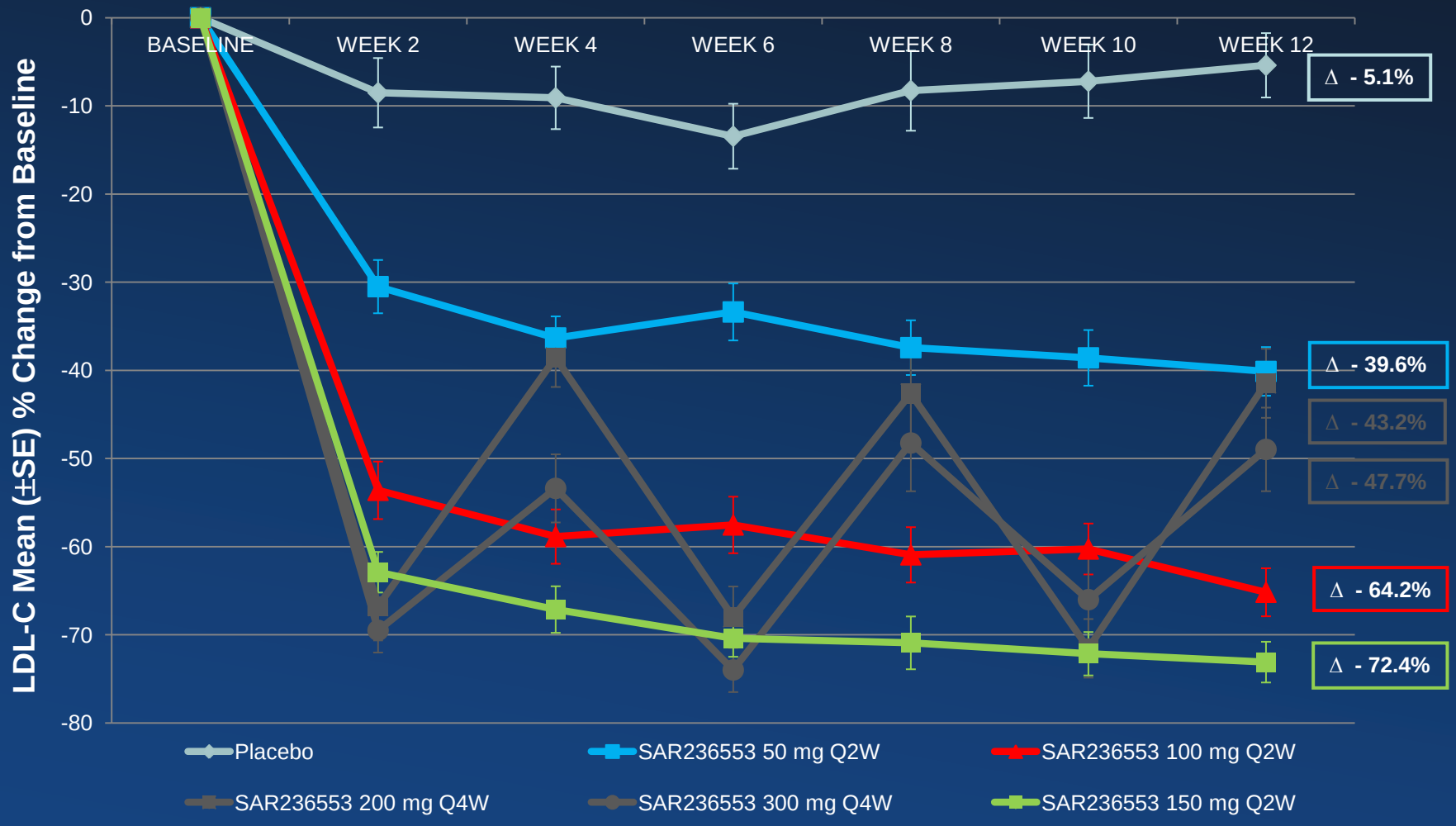
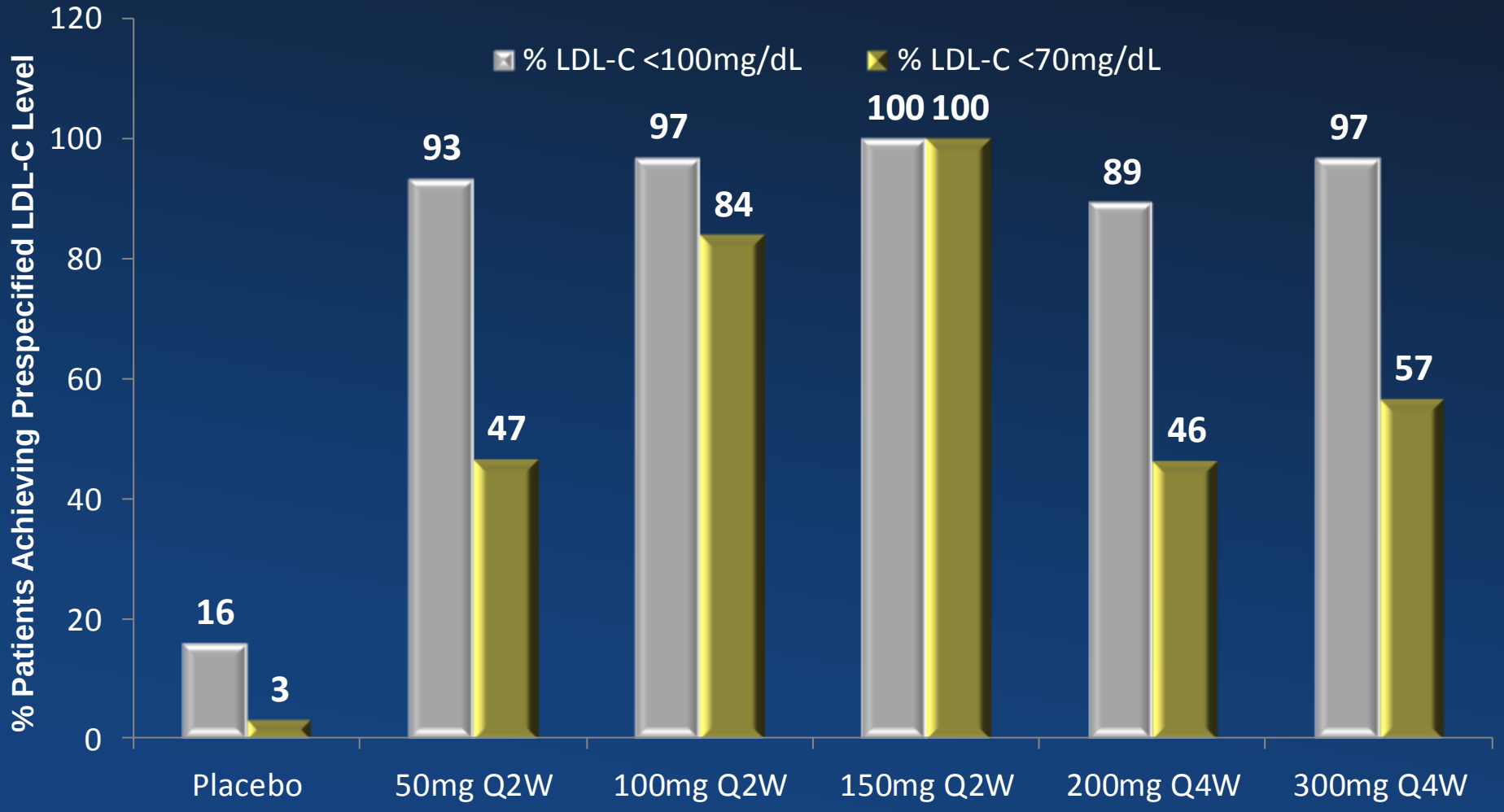


Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, and 12 in the modified intent-to-treat (mITT) population, by treatment group. Week 12 estimation using LOCF method.

Attainment of Prespecified LDL-C Levels at Week 12 (mITT Population)



Changes in Apo B, Non–HDL-C and Lp (a) from Baseline to Week 12 by Treatment Group (mITT Population)

Intervention	% Change Apo B	% Change Non–HDL-C	% Change Lp (a)
Placebo	2.2	–2.2	0.0
SAR236553 50mg Q2W	–27.3*	–33.6*	–13.3†
SAR236553 100mg Q2W	–48.1*	–55.6*	–26.1*
SAR236553 150mg Q2W	–56.1*	–62.5*	–28.6*
SAR236553 200mg Q4W	–28.7*	–37.4*	–16.7†
SAR236553 300mg Q4W	–33.1*	–40.7*	–7.9†

*P<0.0001 for % change SAR236553 vs. placebo
†P=0.05 for % change SAR236553 vs. placebo
P values are not adjusted for multiplicity (descriptive only)

Changes in TG, HDL-C, and Apo AI from Baseline to Week 12 by Treatment Group (mITT Population)

[1]LS mean (SE)
[2]median (Q1-Q3)

Summary of Treatment-Emergent Adverse Events (TEAEs) (Safety Population)

		Q2W dosing			Q4W dosing	
	Placebo (N=31)	50mg (N=30)	100mg (N=31)	150mg (N=31)	200mg (N=30)	300mg (N=30)
Overview of all TEAEs – no.						
Any TEAE	14	18	20	19	20	14
Any treatment-emergent SAE	1	0	1	0	1	1
Any TEAE leading to permanent treatment d/c	0	0	1	1	3	1
AEs of special interest — no.						
ALT or AST >3 x ULN	0	0	0	0	0	0
Muscle (including pain, weakness)	1	1	2	1	1	2
CK >10 x ULN	1	0	0	0	0	0

Injection-site reactions occurred in the SAR236553 groups only and were generally mild and non-progressive.

Serious Adverse Events

57-year-old male developed diarrhea followed by rash on his arms, legs, and abdomen 9 days after receiving his first injection of SAR236553 300mg.

- Leukocytoclastic vasculitis diagnosed by biopsy
- Prednisone begun with full resolution
- No organ involvement per signs and symptoms
- No anti-drug antibodies 2 weeks before or after the incident
- ANA, IgG, IgA, IgM, IgE, tryptase, anti-dsDNA, complement 5 WNL
- Investigator considered this a “significant medical event” related to IP

Summary and Conclusions

- SAR236553 produced significant, dose-dependent LDL-C reductions
  - Up to 72% LDL-C reduction with 150mg Q2W
  - Improved ability to achieve LDL-C goal cut points
  - LDL-C reductions were generally unaffected by baseline atorvastatin dose
- Consistent and robust reductions for all other Apo B–containing lipoproteins
  - Important reduction in Lp (a), consistent with prior studies
- Trend towards decreases in TG and increases in HDL-C and Apo AI vs placebo
- More sustained efficacy with Q2W vs. Q4W regimen
- SAR236553 was well tolerated during this short study
  - No signals for persistent or prevalent clinical or laboratory adverse events including hepatic and muscle assessments.
  - One patient experienced an occurrence of leukocytoclastic vasculitis; no similar reactions reported in prior studies
- These results support further evaluation of SAR236553 in larger, more diverse patient populations with different background therapies to fully assess its efficacy and safety.

Q&A