Long-term Treatment With Evolocumab in Patients With Homozygous Familial Hypercholesterolaemia (HoFH): Interim Results from the Trial Assessing Long-Term Use of PCSK9 Inhibition in Subjects With Genetic LDL Disorders (TAUSSIG) Study

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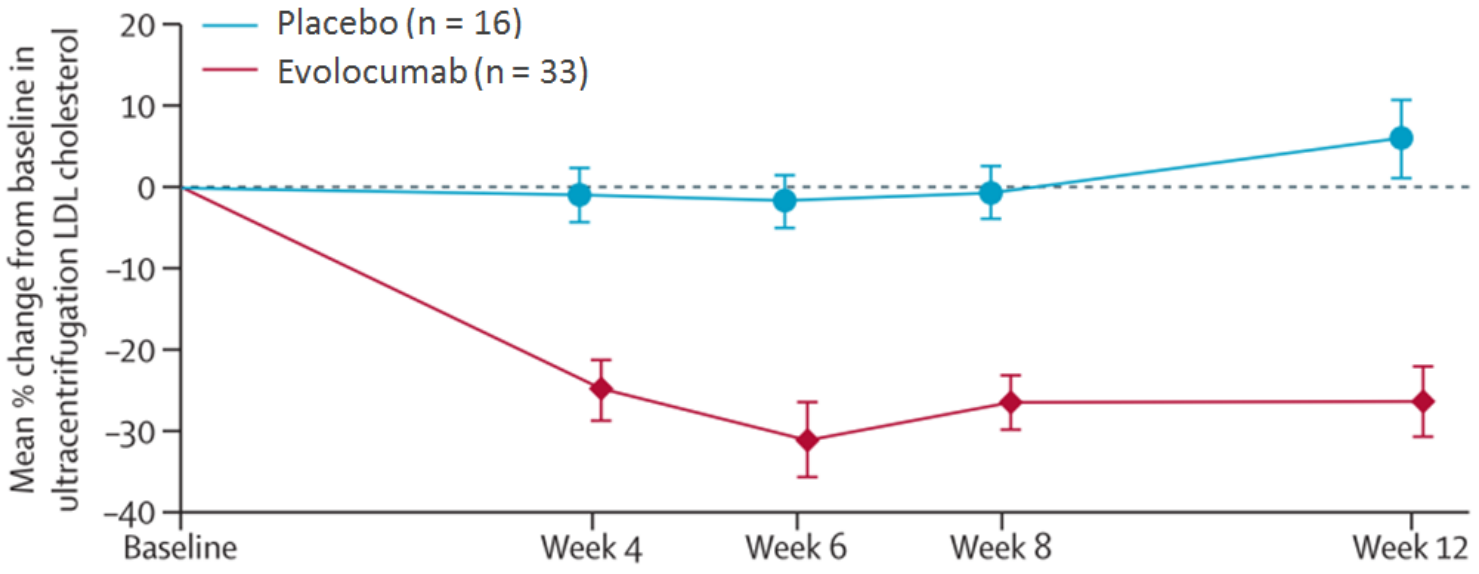
Background

- Homozygous familial hypercholesterolaemia (HoFH) is a rare and serious genetic disorder characterised by:
  - Markedly elevated LDL-C
  - Cutaneous and tendon xanthomatas in childhood
  - Premature and often fatal cardiovascular disease
- Because of minimal LDL receptor (LDLR) function, conventional lipid-lowering medication is only modestly effective and lipoprotein apheresis, if available, is frequently required.

TESLA-B

- In the TESLA part B study,[1] at Week 12, evolocumab 420 mg monthly reduced LDL-C by 23% from baseline and by 31% compared with placebo.[a]



Number of patients analysed at each visit					
Placebo	16	16	15	16	15
Evocolumab	33	32	28	32	29

[a] From a repeated measures model; the graph depicts observed data

[1] Raal et al. Lancet 2015;385:341-50

Objective

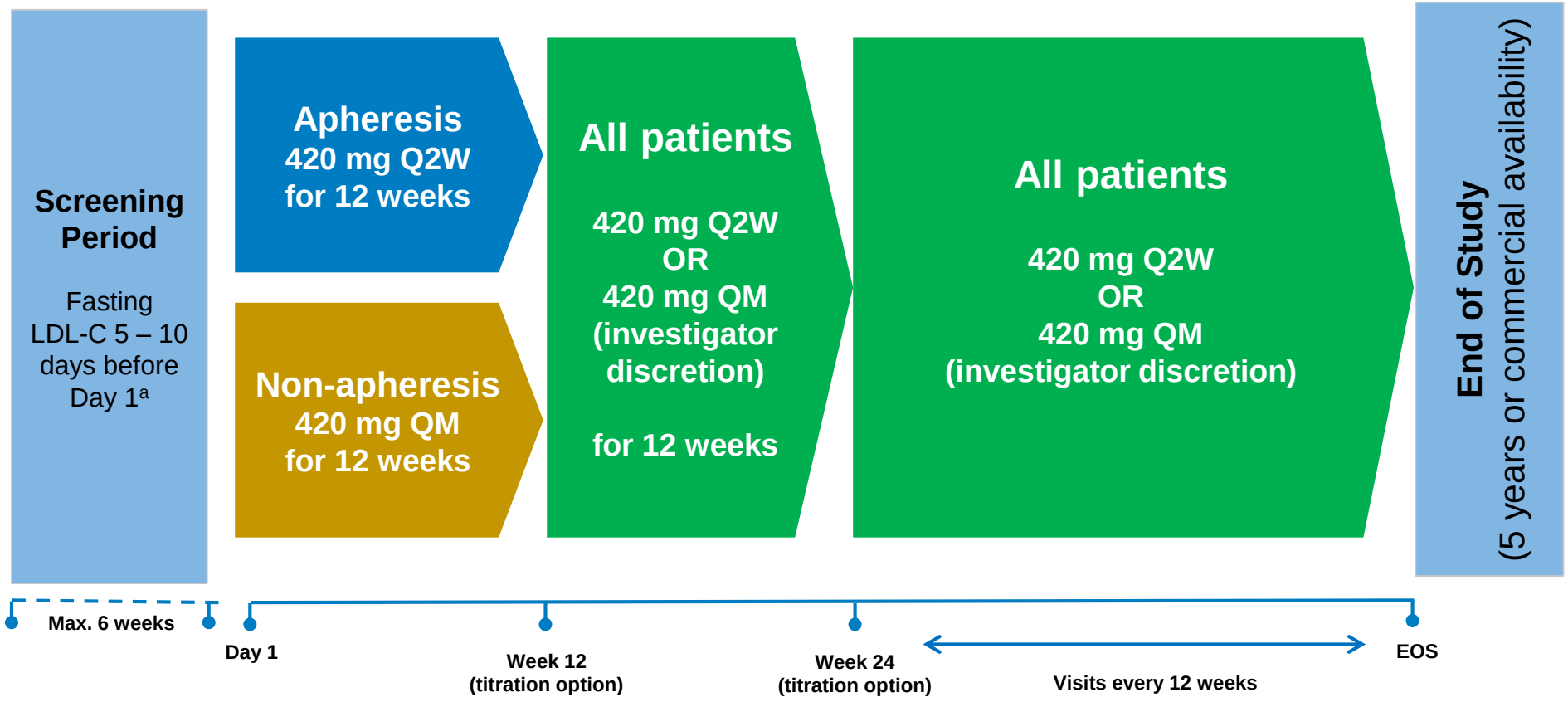
- To assess the longer-term efficacy and safety of evolocumab in a large cohort of 100 patients with HoFH

Methods

- **Patients**: Key study inclusion criteria
  - De novo or rollover patients with HoFH from TESLA-A and -B
  - Age ≥ 12 years
  - Stable low-fat diet and lipid-lowering therapy for ≥ 4 weeks
  - Apheresis schedule every two weeks (if receiving apheresis)
  - Data cutoff July 1st, 2014
- **Treatment**:
  - Apheresis patients: evolocumab 420 mg every two weeks (Q2W)
  - Non-apheresis patients: evolocumab 420 mg monthly (QM)
  - Following 12 weeks of QM dosing and at the discretion of the investigator, the dosing frequency could be increased to 420 mg Q2W in non-apheresis patients.
- In the patients receiving apheresis, lipids were measured just prior to apheresis.
- For parent study rollover patients from TESLA-A and -B, baseline was defined as parent study baseline.

TAUSSIG: HoFH Substudy

- A multicenter, single-arm, open-label, active treatment-only study evaluating the long-term efficacy and safety of evolocumab in patients with HoFH not controlled by current lipid therapy



[a] For parent study rollover patients from TESLA-A and -B, there was no screening period required before Day 1.

Baseline Patient Characteristics

	HoFH Patients (N = 100)
Age (years), mean (SD) Patients < 18 years of age (%)	34 (14) (14)
Female, %	49
Race, % White Asian American Indian or Alaska Native Other	 81 13 1 5
Apheresis, %	34
Coronary artery disease, %	46
Coronary artery bypass surgery, %	27
Cerebrovascular or peripheral arterial disease, %	16

Patient Genetic Characteristics

	HoFH Patients (N = 100)
Genetic Status, %	
Double LDLR mutation (homozygous or compound heterozygous)	88
Double LDLR mutation + ApoB heterozygous	1
ApoB homozygous	1
ApoB homozygous + LDLR heterozygous	1
LDLR heterozygous (homozygous phenotype)	1
Autosomal recessive hypercholesterolemia	4
PCSK9 gain-of-function and LDLR double heterozygous	4
Genotypes, %	
LDLR	95
PCSK9 gain-of-function	4
ApoB	3
Autosomal recessive hypercholesterolaemia	4
Mutations in both LDLR alleles, %	89

Baseline LDL-C, ApoB, Lp(a), and PCSK9

	HoFH Patients (N = 100)
LDL-C[a] (mmol/L) mean (SD)	8.3 (3.3)
ApoB (g/L) mean (SD)	2.0 (0.7)
Lp(a) (nmol/L) median (Q1, Q3)	74.0 (24.3, 154.3)
PCSK9 (nmol/L)[b] mean (SD)	9.3 (2.8)

[a] LDL-C was measured using ultracentrifugation.
[b] Mean PCSK9 levels in HeFH patients, 6.0 – 6.4 nmol/L;[2] in hypercholesterolaemia patients, 4.5 – 5.5 nmol/L[3]

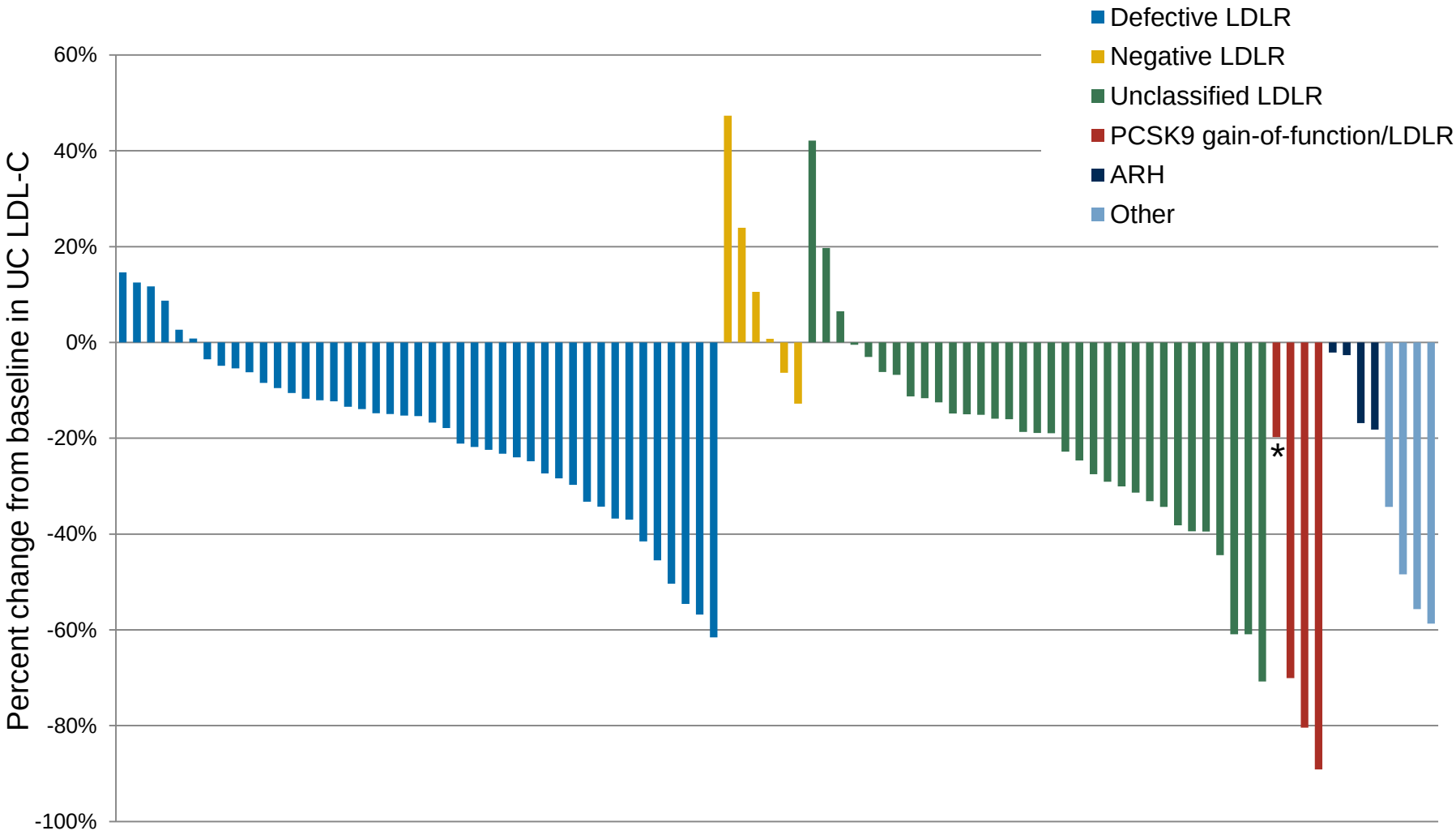
[2] Raal et al. Lancet 2015;385:331-40.
[3] Robinson et al. JAMA 2014;311:1870-82.

Results: Percent Change from Baseline to Open-label Extension Weeks 12, 24, and 48 in LDL-C, ApoB, Lp(a), and PCSK9 in HoFH Patients With and Without Apheresis[a]

	Mean (SE)[b]		
	Week 12 (N = 94)	Week 24 (N = 67)	Week 48 (N = 30)
LDL-C[c]	-20.9 (2.5)	-23.4 (3.5)	-18.6 (3.8)
ApoB	-14.8 (2.3)	-18.5 (2.8)	-17.1 (3.1)
Lp(a)	-7.6 (-21.3, 6.5)	-14.7 (-29.4, -0.5)	-14.1 (-40.6, -1.3)
PCSK9	-50.4 (4.0)	-67.1 (5.6)	-76.5 (5.9)

[a] All apheresis patients began the study on apheresis Q2W and evolocumab 420 mg Q2W to match their apheresis schedule. All non-apheresis patients began the study on evolocumab 420 mg QM; at Week 12, non-apheresis patients could uptitrate to Q2W dosing at investigator discretion.
[b] Lp(a) is presented as median (Q1, Q3).
[c] LDL-C was measured using ultracentrifugation.

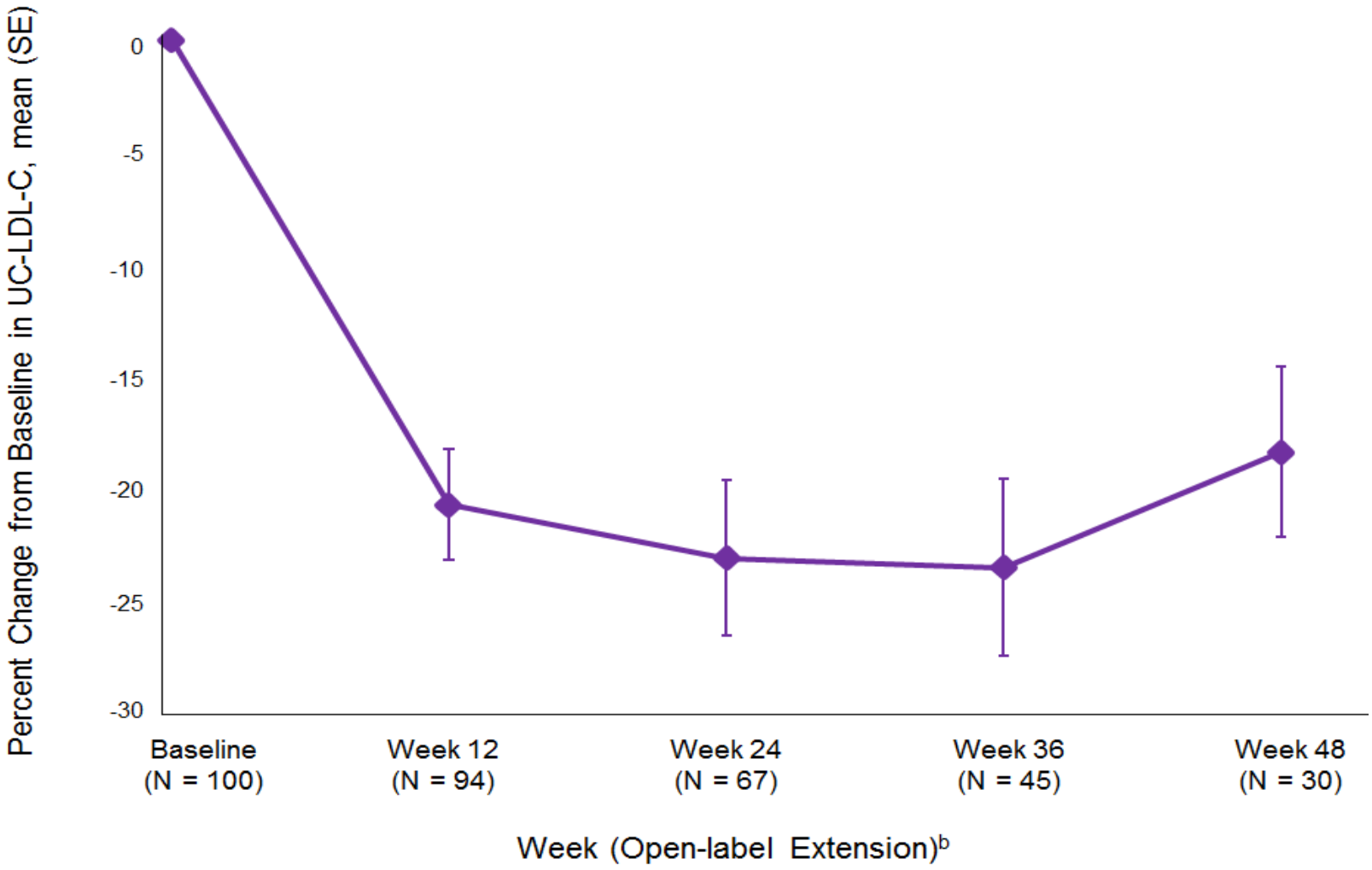
Individual Percent Change from Baseline to Week 12 in UC LDL-C (N = 94)



* Patient stopped ezetimibe and reduced rosuvastatin from 20 mg to 5 mg daily at Week 4. Because of the change in background therapy, reduction in UC LDL-C was 90% at Week 4, but only 20% at Week 12.

Abbreviations: ARH, autosomal recessive hypercholesterolaemia

Percent Change from Baseline in UC LDL-C[a]



[a] All apheresis patients began the study on apheresis Q2W and evolocumab 420 mg Q2W to match their apheresis schedule. All non-apheresis patients began the study on evolocumab 420 mg QM; at Week 12, non-apheresis patients could uptitrate to Q2W dosing at investigator discretion.

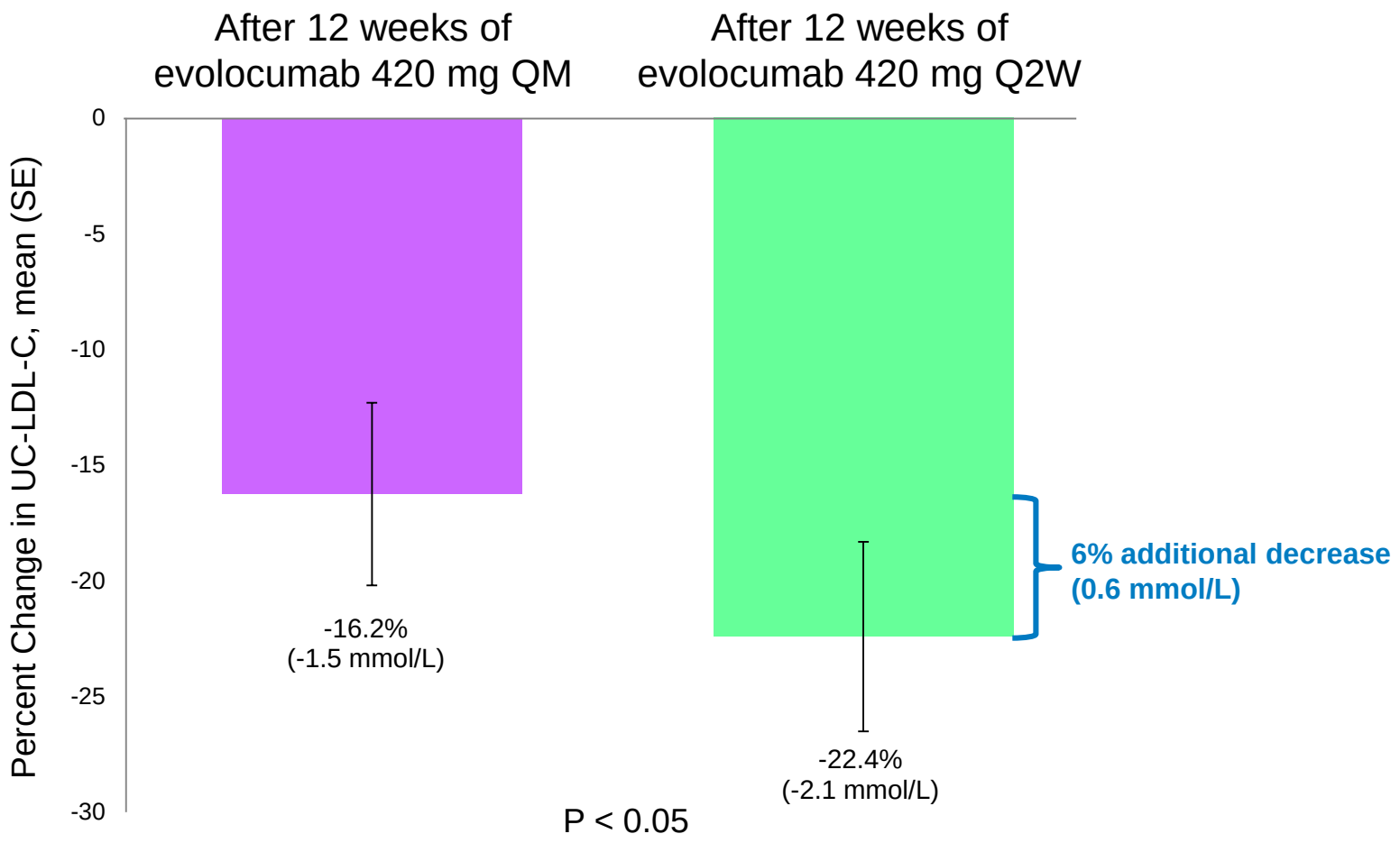
[b] For parent study rollover patients, baseline was defined as parent study baseline.

Percent Change from Baseline to Open-label Extension Week 12 in Lipids and PCSK9 by Apheresis Status[a]

	Baseline, mean (SD)		Change from baseline at Week 12 (%), mean (SE)	
	Non-apheresis (n = 66)	Apheresis (n = 34)	Non-apheresis (n = 63)	Apheresis (n = 31)
LDL-C[b]	8.7 (3.6) mmol/L	7.4 (2.6) mmol/L	-23.1 (2.8)	-16.5 (4.9)
ApoB	2.1 (0.7) g/L	1.8 (0.5) g/L	-16.1 (2.7)	-12.1 (4.3)
Lp(a)[c]	77.5 (23.0, 146.0) nmol/L	65.5 (28.0, 173.5) nmol/L	-7.5 (-17.6, 7.4)	-10.0 (-23.1, 5.0)
PCSK9	9.0 (2.6) nmol/L	9.9 (3.1) nmol/L	-31.7 (3.9)	-90.2 (2.9)

[a] All apheresis patients began the study on apheresis Q2W and evolocumab 420 mg Q2W to match their apheresis schedule. All non-apheresis patients began the study on evolocumab 420 mg QM; at Week 12, non-apheresis patients could uptitrate to Q2W dosing at investigator discretion.
[b] LDL-C was measured using ultracentrifugation.
[c] Lp(a) is presented as median (Q1, Q3).

Further Reduction in LDL-C in Non-apheresis Patients After Uptitrating Evolocumab from QM to Q2W (n = 28[a])



Data in parentheses are the absolute reduction in LDL-C.

[a] All 28 patients had 12 weeks each of evolocumab 420 mg QM and evolocumab 420 mg Q2W.

Safety and Tolerability

Adverse Events (AEs)	Patient Incidence (%)
Any AE	68
Serious AEs	10
Deaths	0
AEs leading to discontinuation of evolocumab[a]	1
Most-common AEs[b]	
Nasopharyngitis	9
Influenza	7
Anaemia[c]	5
Headache	5

[a] For rash; subsequent to this data cut, the patient was rechallenged with evolocumab.
[b] ≥ 5% of patients
[c] All non-serious, CTCAE grade 1 (n = 4) or 2 (n = 1). Evolocumab was continued in all 5 patients. Three patients were receiving apheresis (females aged 21 – 37 years); 1 had pre-existing anaemia. None of these events were deemed related to evolocumab.

Serious AEs

- All serious AEs were consistent with the natural history of HoFH.
- There were 11 events in 10 patients:
  - Complications of FH (9)
    - Aortic valve disease (2)
      - Aortic stenosis
      - Aortic valve disease
    - Atherosclerosis (6)
      - Chest pain
      - Angina pectoris
      - Coronary artery disease
      - Coronary artery occlusion
      - Myocardial ischaemia
      - Carotid artery occlusion
    - Apheresis-related (1)
      - Arteriovenous fistula thrombosis
  - Other (2)
    - Non-cardiac chest pain (known history prior to study)
    - Haematuria (while receiving heparin as part of lipid apheresis)

Conclusions

- Evolocumab 420 mg QM or Q2W reduced LDL-C in patients with HoFH on lipid-lowering therapy with or without apheresis by approximately 20% from baseline to Week 12.
- The reduction in LDL-C persisted up to Week 48.
- Increasing evolocumab 420 mg from QM to Q2W dosing resulted in an incremental 6% (0.6 mmol/L) reduction in LDL-C in non-apheresis patients.
- Evolocumab was well-tolerated; serious adverse events reflect the natural history of HoFH.