The RUTHERFORD-2 trial in heterozygous FH: Results and implications

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PCSK9FORUM

The RUTHERFORD-2 Study

- **R**ed**u**ction of LDL-C with PCSK9 Inhibi**t**ion in **He**te**r**ozygous **F**amilial Hyperch**o**leste**r**olemia **D**isorder (NCT20110117)

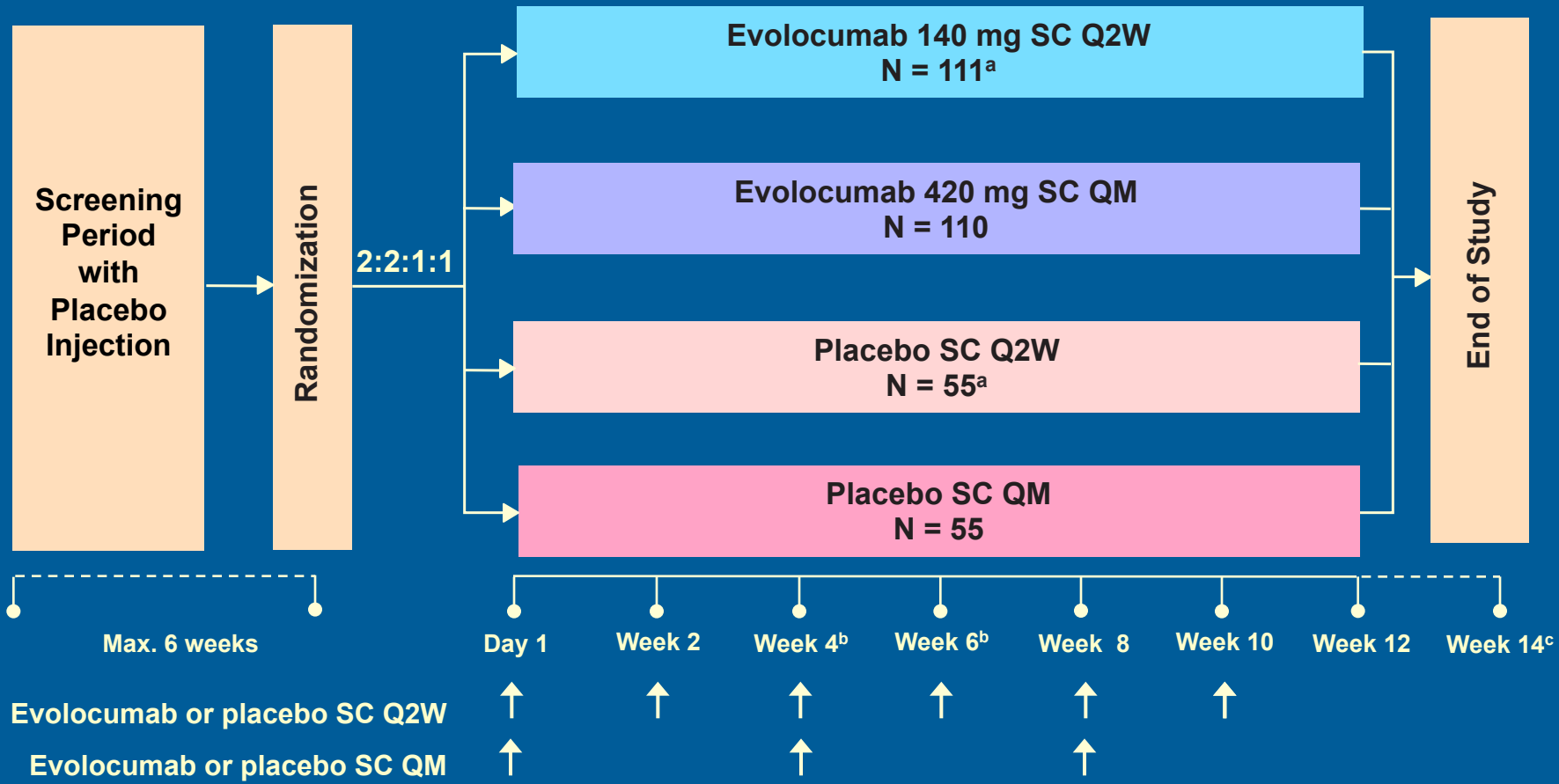
- **Design:**

A 12-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study

- **Objective:**

To evaluate the efficacy and safety of evolocumab (AMG 145) 140 mg Q2W and 420 mg QM administered subcutaneously in a large cohort of HeFH patients unable to achieve an LDL-C < 100 mg/dL despite statin therapy with or without ezetimibe

RUTHERFORD-2 Study Design



[a] N's are number of patients randomized. One patient in each of the placebo Q2W and evolocumab Q2W groups did not receive any doses of the study drug and were not included in the analyses

[b] Injections at weeks 4 and 6 were done at home

[c] Week 14 was a follow-up call for Q2W patients to capture adverse events and concomitant medications

Q2W, biweekly; QM, monthly; SC, subcutaneous

RUTHERFORD-2: Baseline Characteristics

Characteristic	Placebo Q2W (N = 54)	Evolocumab 140 mg Q2W (N = 110)	Placebo QM (N = 55)	Evolocumab 420 mg QM (N = 110)
Age (years), mean (SD)	51 (14)	53 (12)	47 (12)	52 (12)
Female, %	46	40	44	42
Race: white, %	93	90	89	89
PCSK9 (ng/mL), mean (SD)	431 (124)	458 (145)	441 (146)	436 (139)
HeFH classification[a], %				
Definite	83	77	78	76
Probable	17	23	22	24
Statin use, %	100	100	100	100
Ezetimibe use, %	61	61	66	62

[a]Based on Simon Broome criteria
HeFH, heterozygous familial hypercholesterolemia; Q2W, biweekly; QM, monthly; SD, standard deviation

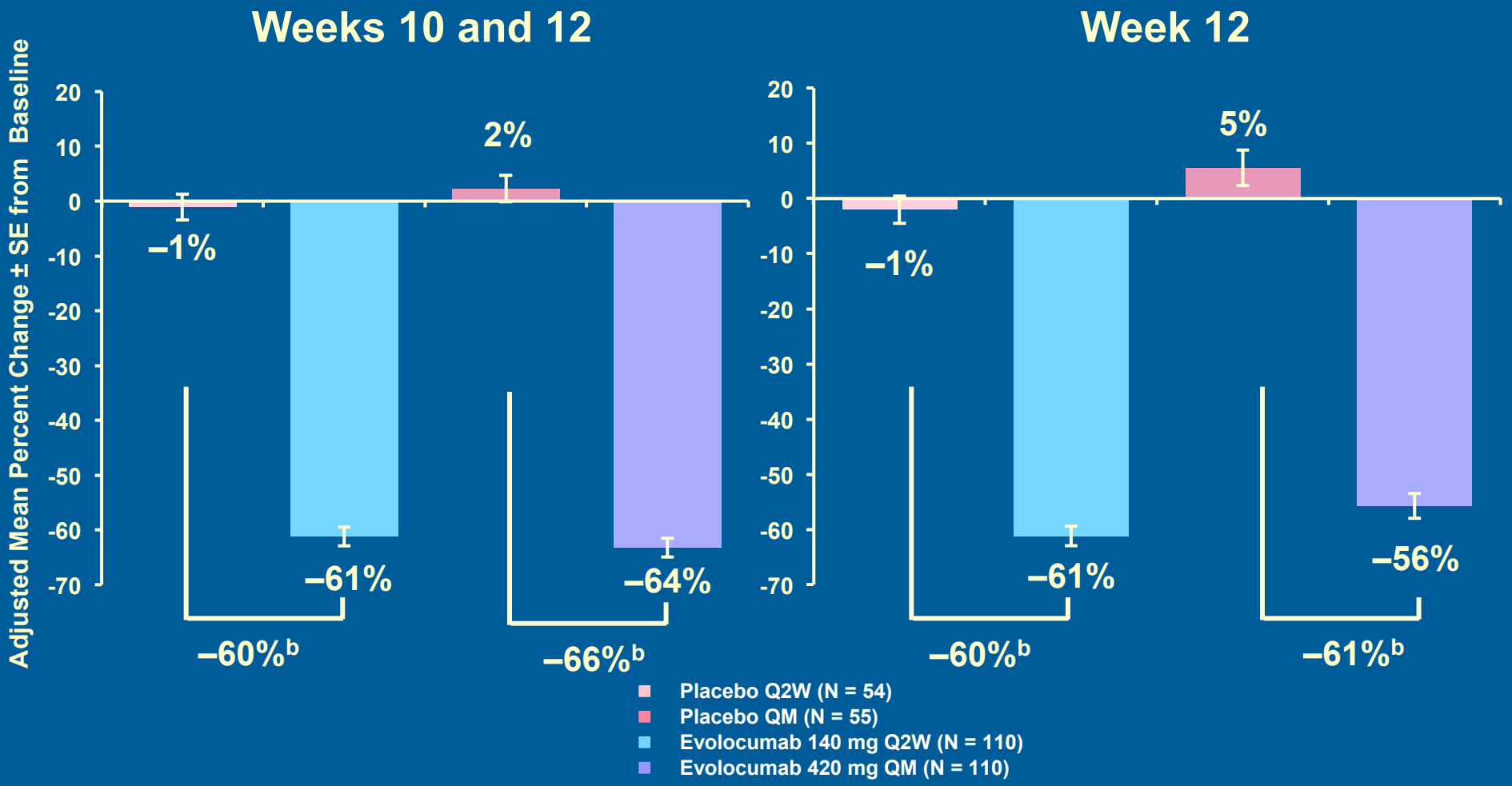
RUTHERFORD-2: Baseline Lipids

Characteristic	Placebo Q2W (N = 54)	Evolocumab 140 mg Q2W (N = 110)	Placebo QM (N = 55)	Evolocumab 420 mg QM (N = 110)
LDL-C[a] (mg/dL), mean (SD)	151 (37)	161 (51)	152 (43)	154 (43)
ApoB (mg/dL), mean (SD)	114 (30)	119 (31)	110 (22)	115 (26)
HDL-C (mg/dL), mean (SD)	53 (17)	50 (16)	49 (13)	52 (16)
ApoA1 (mg/dL), mean (SD)	145 (28)	142 (34)	135 (24)	143 (29)
Triglycerides (mg/dL), median (Q1, Q3)	96 (75, 143)	119 (87, 161)	102 (79, 151)	113 (85, 157)
Lp(a) (nmol/L), median (Q1, Q3)	44 (24, 105)	78 (29, 206)	87 (36, 219)	61 (17, 194)

[a]Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was < 40 mg/dL or triglyceride levels were > 400 mg/dL

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); Q2W, biweekly; QM, monthly; SD, standard deviation

RUTHERFORD-2: Mean % Change in LDL-C[a] from Baseline to the Mean of Weeks 10 and 12, and Week 12 Alone

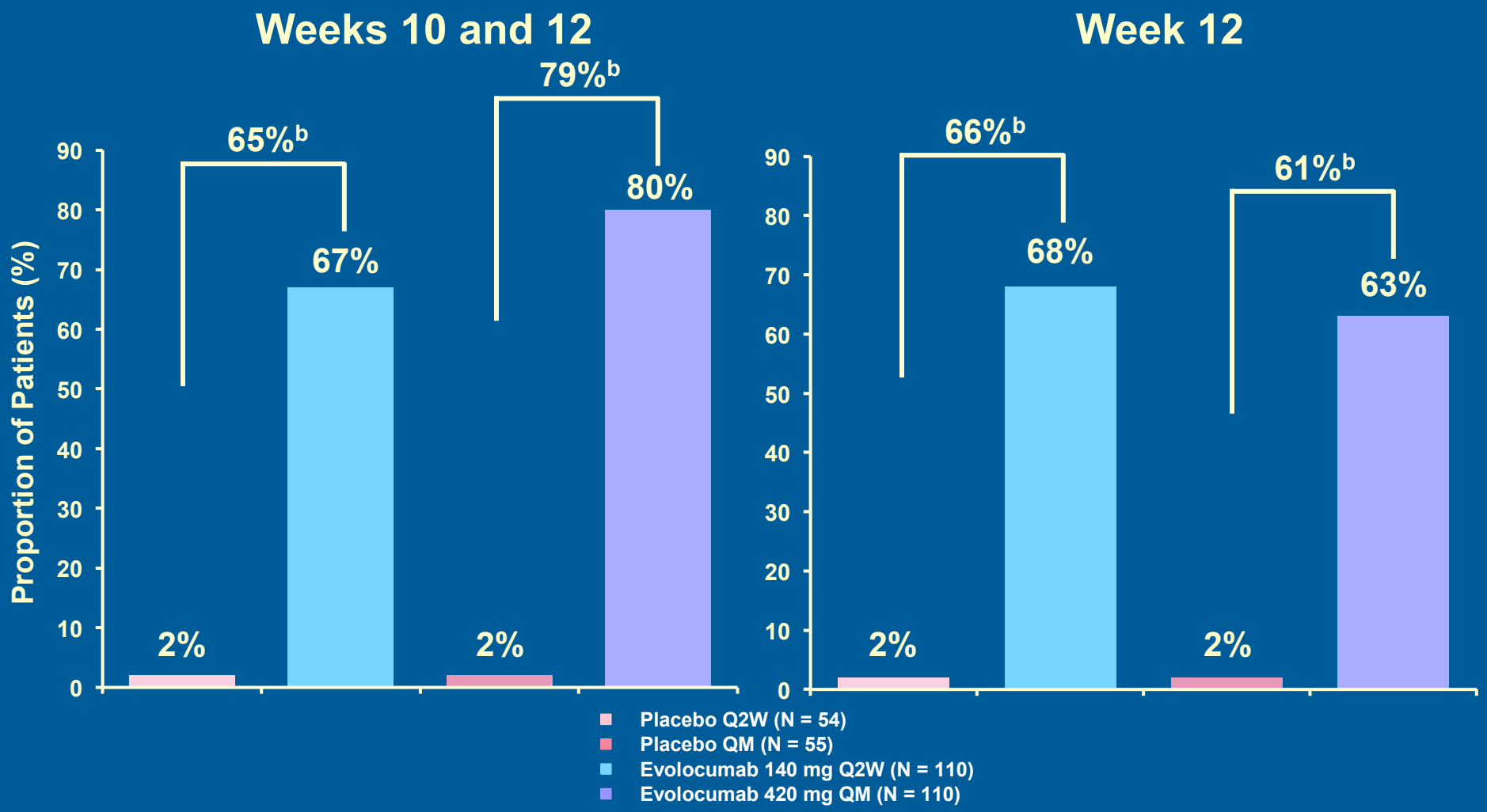


[a]Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was < 40 mg/dL or triglyceride levels were > 400 mg/dL

[b]P < 0.001; placebo-adjusted treatment difference analyzed using repeated measures model which included treatment group, stratification factors (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates

LDL-C, low-density lipoprotein cholesterol; Q2W, biweekly; QM, monthly; SE, standard error

RUTHERFORD-2: LDL-C[a] Goal Achievement < 70 mg/dL



[a]Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was < 40 mg/dL or triglyceride levels were > 400 mg/dL

[b]P < 0.001; analyzed using CMH test, stratified by the stratification factors

LDL-C, low-density lipoprotein cholesterol; Q2W, biweekly; QM, monthly

RUTHERFORD-2: Safety and Tolerability

Adverse events (AEs), n (%)	Placebo (N = 109)	Evolocumab (N = 220)
Treatment-emergent AEs	53 (48.6)	124 (56.4)
Most common AEs in Evolocumab Patients[a]		
Nasopharyngitis	5 (4.6)	19 (8.6)
Headache	4 (3.7)	9 (4.1)
Contusion	1 (0.9)	9 (4.1)
Back pain	1 (0.9)	8 (3.6)
Nausea	1 (0.9)	8 (3.6)
Arthralgia	2 (1.8)	8 (3.6)
Serious AEs	5 (4.6)	7 (3.2)
AEs leading to discontinuation of study drug	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)
Potential injection-site reactions[b]	4 (3.7)	13 (5.9)
Neurocognitive AEs[c]	0 (0.0)	0 (0.0)
Muscle-related SMQ[d]	1 (0.9)	10 (4.5)
Anti-evolocumab antibodies,[e] %	NA	0.0

[a]Occurring in ≥ 3.5% of evolocumab-treated patients
[b]Reported using high-level term grouping, which includes injection site (IS) rash, IS inflammation, IS pruritus, IS reaction, and IS urticaria
[c]Searched HLGT terms: Deliria (incl confusion); cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; mental impairment disorders.NA = not applicable
[d]Standard Medical Dictionary for Regulatory Activities (MedDRA) Queries. [e]Binding or neutralizing

RUTHERFORD-2: Key Laboratory Results

Laboratory Results	Placebo (N = 109)	Evolocumab (N = 220)
ALT or AST > 3 × ULN at any post-baseline visit, %	0.0	0.0
CK > 5 × ULN at any post-baseline visit, %	1.8	0.0
CK > 10 × ULN at any post-baseline visit, %	0.9	0.0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; ULN, upper limit of normal

RUTHERFORD-2: Conclusions

- Evolocumab administered either biweekly or monthly yielded significant reductions in LDL-C in HeFH patients on statins with or without ezetimibe.
  - The mean reduction of LDL-C at Week 12 was 61% in the 140 mg Q2W and 56% in the 420 mg QM evolocumab dose groups, respectively.
  - The mean reduction of LDL-C at the mean of Weeks 10 and 12 was 61% in the 140 mg Q2W and 63% in the 420 mg QM evolocumab dose groups, respectively.
- Evolocumab 140 mg biweekly and 420 mg monthly dosing regimens were clinically equivalent.
- The majority of patients achieved LDL-C targets.
- Evolocumab treatment resulted in favorable changes in other lipoproteins.

RUTHERFORD-2: Conclusions

- Evolocumab was well tolerated, with no notable difference in the AE profile compared with placebo.
  - The rate of nasopharyngitis and muscle-related adverse events (AEs) was higher in the evolocumab group.
    - The imbalance in the overall set of muscle-related AEs was not due to significant imbalances in any individual muscle-related event (i.e., creatine kinase).
- Evolocumab may offer a new and effective treatment option to further reduce LDL-C in HeFH patients.