European Heart Journal (2016) **37**, 1360–1369
doi:10.1093/eurheartj/ehv707

Safety and efficacy of LY3015014, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9): a randomized, placebo-controlled Phase 2 study

John J.P. Kastelein[1]*, Steven E. Nissen[2], Daniel J. Rader[3], G. Kees Hovingh[1], Ming-Dauh Wang[4], Tong Shen[4], and Kathryn A. Krueger[4]

[1]Department of Vascular Medicine, Academic Medical Center of the University of Amsterdam, Meibergdreef 9, Room F4-159.2, 1105 AZ Amsterdam, The Netherlands; [2]Cleveland Clinic Heart and Vascular Institute, Cleveland, OH, USA; [3]University of Pennsylvania, Philadelphia, PA, USA; and [4]Eli Lilly and Company, Indianapolis, IN, USA

Received 12 August 2015; revised 11 November 2015; accepted 2 December 2015; online publish-ahead-of-print 12 January 2016

See page 1370 for the editorial comment on this article (doi:10.1093/eurheartj/ehw023)

Aims The objective of this study was to evaluate the efficacy, safety, and tolerability of LY3015014 (LY), a neutralizing antibody of proprotein convertase subtilisin/kexin type 9 (PCSK9), administered every 4 or 8 weeks in patients with primary hypercholesterolaemia, when added to a background of standard-of-care lipid-lowering therapy, including statins.

Methods and results Double-blind, placebo-controlled trial randomized 527 patients with primary hypercholesterolaemia from June 2013 to January 2014 at 61 community and academic centres in North America, Europe, and Japan. Patients were randomized to subcutaneous injections of LY 20, 120, or 300 mg every 4 weeks (Q4W); 100 or 300 mg every 8 weeks (Q8W) alternating with placebo Q4W; or placebo Q4W. The primary endpoint was percentage change from baseline in low-density lipoprotein cholesterol (LDL-C) by beta quantification at Week 16. The mean baseline LDL-C by beta quantification was 136.3 (SD, 45.0) mg/dL. LY3015014 dose-dependently decreased LDL-C, with a maximal reduction of 50.5% with 300 mg LY Q4W and 37.1% with 300 mg LY Q8W compared with a 7.6% increase with placebo maintained at the end of the dosing interval. There were no treatment-related serious adverse events (AEs). The most common AE terms (>10% of any treatment group) reported more frequently with LY compared with placebo were injection site (IS) pain and IS erythema. No liver or muscle safety issues emerged.

Conclusions LY3015014 dosed every 4 or 8 weeks, resulted in robust and durable reductions in LDL-C. No clinically relevant safety issues emerged with the administration of LY. The long-term effects on cardiovascular outcomes require further investigation.

Keywords Low-density lipoprotein cholesterol • Hypercholesterolaemia • Lipid-lowering therapy

Introduction

Reduction in plasma levels of low-density lipoprotein cholesterol (LDL-C) remains the cornerstone of strategies to reduce the risk of cardiovascular disease (CVD) in both primary and secondary prevention patients. Statins have been shown to lower LDL-C levels and reduce the risk of CVD in virtually all types of patients. However, despite treatment with statins according to current guidelines, considerable residual risk for CVD remains. Accordingly, research efforts have focused on identification of additional LDL-C-lowering strategies.

In recent years, clinical studies have addressed the safety and efficacy of inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), which plays a pivotal role in LDL-C metabolism by virtue of its inhibitory effect on recycling of the LDL receptor.

* Corresponding author. Tel: +31 20 566 6612, Fax: +31 20 566 9343, Email: J.J.Kastelein@amc.uva.nl; juliesherman@lilly.com

Antibody neutralization of PCSK9, through subcutaneous injection of anti-PCSK9 antibodies, appears safe and effective for reducing LDL-C in patients on standard-of-care lipid-lowering therapies, including statins. Several PCSK9 antibodies have reached late-stage development, typically demonstrating LDL-C reductions of 60% or greater when administered every 2 or 4 weeks.[1–3] Notably, however, large dosages are required to sustain LDL-C reductions when administered at monthly intervals. For chronic administration, less frequent subcutaneous dosing would clearly be preferable.

LY3015014 (LY) is a humanized immunoglobulin G4 (IgG4) monoclonal antibody characterized by a comparatively long duration of action demonstrated in preclinical studies.[4,5] The durability in LDL-C reduction may result from LY binding to a site that permits normal proteolytic cleavage of PCSK9, which may result in a reduction of target-mediated drug disposition. Based on these data, we hypothesized that administration of LY every 8 weeks might be sufficient for LDL-C reduction and offer a significant dosing advantage over other anti-PCSK9 antibodies that require dosing every 2 or 4 weeks.

Thus, the aim of our current study was to evaluate the LDL-C reduction following subcutaneous administration of LY every 4 or 8 weeks in patients with primary hypercholesterolaemia, when added to a background of standard-of-care lipid-lowering therapy.

Methods

Patients

This was a multicentre, randomized, double-blind, parallel, placebo-controlled clinical study that enrolled patients aged 18–80 (≥20 years age lower limit in Japan; ≤65 years age upper limit in Czech Republic) with primary hypercholesterolaemia, defined as LDL-C ≥80 mg/dL (subset between 80 and 100 mg/dL capped at 20% of patients) and triglycerides (TG) ≤450 mg/dL (see Supplementary material online, *Figure S1* for study diagram). Patients with probable or definite diagnosis of heterozygous familial hypercholesterolaemia based on clinical criteria (US MedPed Program, Simon Broome Register Group or Dutch Lipid Clinic Network) or genotype (LDL receptor, ApoB or PCSK9 mutation) (at least 20%) and with polygenic hypercholesterolaemia were included. Patients were required to be on a stable diet and with or without stable use of ezetimibe or statin for at least 6 weeks. Subset not on a statin with an unconfirmed 'history of statin intolerance' was capped at 20%. See supplementary information for key inclusion/exclusion criteria.

The trial was approved by Independent Ethics Committees, and each patient provided written informed consent. The trial was conducted in accordance with the principles of The Declaration of Helsinki and Good Clinical Practice Guidelines and was registered on Clinicaltrials.gov (NCT01890967).

Study design

All patients underwent a Screening and Run-in Phase up to 8 weeks to stabilize diet and statin and/or ezetimibe dose and to adequately wash out of other lipid-modifying therapies. The study evaluated 16 weeks of treatment with LY, and patients were randomly assigned, in a 1 : 1 : 1 : 1 : 1 : 1 ratio, to receive subcutaneous injections of LY into an abdominal wall skinfold, at the doses of 20, 120, or 300 mg every 4 weeks (Q4W); 100 or 300 mg every 8 weeks (Q8W) (alternating with placebo Q4W); or placebo Q4W. Efficacy assessments included LDL-C, non-HDL-C, ApoB, TG, HDL-C, Lp(a), free PCSK9, and high-sensitivity C-reactive protein (hsCRP). Safety was assessed throughout the study by monitoring adverse events (AEs), laboratory assessments, vital signs, as well as physical examination.

Randomization

Randomization was performed by an interactive web response system. The dynamic allocation (minimization) method was used to stratify based on HeFH or polygenic hypercholesterolaemia, geographic region, history of diabetes, statin dose [none, low/mid-dose, or high dose (atorvastatin 40–80 mg; rosuvastatin 20–40 mg)], ezetimibe use, baseline LDL-C (≥80 to <100 mg/dL; ≥100 mg/dL), and prior possible exposure to PCSK9 antibody.

Clinic visits and laboratory tests

Patients were examined during scheduled visits every 2 weeks during the 16-week treatment phase and at follow-up visits 4 and 8 weeks after completion of the treatment phase. Lipoprotein levels, including calculated LDL-C, and safety laboratory measurements were obtained at all visits. Low-density lipoprotein cholesterol by beta quantification was measured at baseline (after the screening and run-in phase) and Week 16. A central laboratory (QLabs) performed all biochemical determinations. Low-density lipoprotein cholesterol was performed by beta quantification (ultracentrifugation followed by enzymatic determination) at Pacific Biometrics. See supplementary information for additional assay methodologies. All reported deaths, myocardial infarctions, strokes, hospitalization for unstable angina, and coronary revascularization procedures were adjudicated by a blinded clinical endpoint committee. Safety data were also subject to periodic review by the Data and Safety Monitoring Board.

Statistical analysis

Randomized patients who took at least one dose of study treatment were included in the safety analyses. The efficacy analyses were performed for dosed patients with a baseline measurement and at least one post-baseline measurement of the analysed parameter. Between-treatment comparisons were made at a two-sided significance level of 0.05.

Demographic and baseline characteristics were summarized using frequencies for categorical variables, and means with standard deviations or medians with inter-quartile ranges (IQR) for continuous variables. Frequencies of AEs are summarized by treatment group.

The primary efficacy endpoint, per cent change in LDL-C measured by beta quantification from baseline to end of treatment or early discontinuation, was analysed using analysis of covariance (ANCOVA), with baseline LDL-C measured by beta quantification, disease state, and statin dose as covariates and treatment as a fixed effect. Secondary efficacy endpoints, including changes and per cent changes in calculated LDL-C, HDL-C, TG, non-HDL-C, ApoB, CRP, Lp(a), and free PCSK9 level, were analysed by mixed effects model repeated measures (MMRM), with baseline analysed efficacy measurement, disease state, and statin dose as covariates and treatment, visit, and treatment by visit interaction as fixed effects. See supplementary information for additional statistical methodology.

Results

Participants

Between 27 June 2013 and 2 January 2014, 807 patients were screened at 61 sites, and 527 patients were randomized to treatment (*Figure 1*); see Supplementary material online, *Table S1* for sites

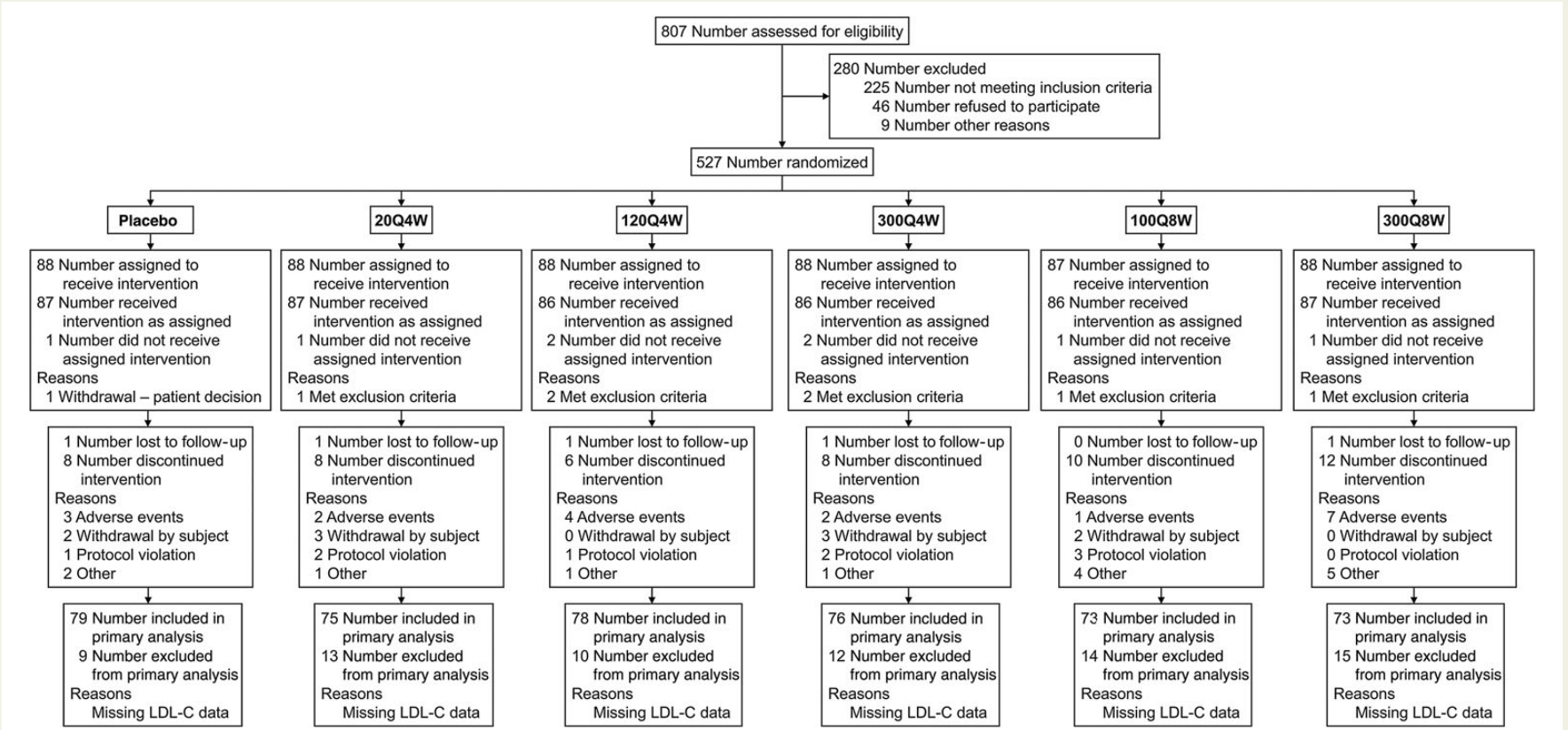

Figure 1 Study flow. 20Q4W, 20 mg every 4 weeks; 120Q4W, 120 mg every 4 weeks; 300Q4W, 300 mg every 4 weeks: 100Q8W, 100 mg every 8 weeks; 300Q8W, 300 mg every 8 weeks.

and enrolment by country. Baseline characteristics were similar for all treatment groups (*Table 1*).

Overall, the majority of patients were male (53.6%) and white (68.6%). Mean age was 58.4 years (22–81 years). Of all patients, 10.0% were on atorvastatin 40–80 mg or rosuvastatin 20–40 mg, 69.7% were on other statin types or doses, and 20.2% were not using a statin. Ezetimibe use was reported in 13.9% of patients. Baseline lipid profiles were as follows: LDL-C (beta quantification),

Table 1 Baseline patient characteristics

	20 mg Q4W (*n* = 87)	120 mg Q4W (*n* = 86)	300 mg Q4W (*n* = 86)	100 mg Q8W (*n* = 86)	300 mg Q8W (*n* = 87)	Placebo Q4W (*n* = 87)
Gender (% male)	51.7	52.3	54.7	58.1	50.6	54.0
Mean age (years)	57.2 (9.4)	57.1 (12.4)	59.7 (9.4)	59.6 (8.1)	58.7 (10.1)	57.9 (11.2)
Mean BMI (kg/m^2)	27.4 (5.2)	29.0 (5.0)	28.3 (4.7)	28.5 (6.3)	28.0 (5.2)	29.0 (5.9)
Race (*n*, %)						
White	61 (70.1)	59 (68.6)	60 (69.8)	58 (67.4)	58 (66.7)	60 (69.0)
Asian	22 (25.3)	21 (24.4)	25 (29.1)	21 (24.4)	23 (26.4)	25 (28.7)
Black	4 (4.6)	6 (7.0)	1 (1.2)	6 (7.0)	5 (5.7)	1 (1.1)
Region (*n*, %)						
Europe	29 (33.3)	28 (32.6)	27 (31.4)	29 (33.7)	28 (32.2)	30 (34.5)
North America	40 (46.0)	40 (46.5)	42 (48.8)	39 (45.3)	41 (47.1)	40 (46.0)
Japan	18 (20.7)	18 (20.9)	17 (19.8)	18 (20.9)	18 (20.7)	17 (19.5)
Lipid profile (mg/dL)						
LDL-C (beta quantification)	134.1 (42.4)	134.0 (40.7)	132.1 (42.3)	135.2 (41.2)	146.0 (60.5)	136.5 (39.6)
LDL-C (calculated)	128.6 (40.2)	130.8 (43.8)	126.0 (39.9)	127.9 (40.6)	139.1 (56.3)	130.1 (40.6)
Non-HDL-C	156.8 (42.8)	160.5 (46.9)	157.8 (45.3)	159.0 (44.6)	170.3 (60.6)	160.7 (45.8)
Apo B	111.4 (27.9)	112.8 (31.3)	111.1 (29.4)	112.2 (27.3)	120.2 (38.8)	114.4 (28.6)
TG, median (IQR)	126.0 (96.0, 171.0)	136.0 (96.0, 186.0)	141.5 (105.5, 193.0)	135.5 (106.0, 182.0)	151.0 (105.0, 190.0)	142.0 (105.0, 188.0)
HDL-C	57.4 (13.9)	54.4 (13.1)	54.8 (14.7)	57.8 (13.8)	54.8 (15.7)	54.9 (13.0)
Lp(a), median (IQR)	20.65 (8.1, 54.9)	25.55 (9.8, 69.0)	13.70 (7.6, 37.1)	31.00 (10.3, 64.3)	17.25 (9.9, 69.7)	26.10 (14.3, 74.9)
Total cholesterol	214.2 (44.7)	215.0 (47.6)	212.6 (47.5)	216.7 (44.5)	225.2 (60.0)	215.7 (46.2)
Free PCSK9 (ng/mL)	535.55 (164.87)	513.36 (175.71)	530.87 (214.68)	553.90 (163.98)	526.00 (183.35)	588.77 (207.05)
hsCRP, median (IQR), (mg/L)	1.030 (0.6, 2.5)	1.335 (0.7, 2.2)	1.630 (0.5, 2.9)	1.385 (0.7, 3.0)	1.100 (0.6, 2.8)	1.350 (0.6, 2.6)
HeFH (clinical criteria) (*n*, %)	23 (26.4)	23 (26.7)	24 (27.9)	25 (29.1)	24 (27.6)	23 (26.7)
Low LDL-C (<100 mg/dL) (%)	21.8	15.1	26.7	15.1	16.1	14.9
Statin use at baseline (*n*, %)						
No statin	19 (21.8)	17 (19.8)	17 (19.8)	17 (19.8)	17 (19.5)	18 (20.7)
Low-/mid-dose statin	65 (74.7)	60 (69.8)	61 (70.9)	57 (66.3)	62 (71.3)	57 (65.5)
high-dose statin	3 (3.4)	9 (10.5)	8 (9.3)	12 (14.0)	8 (9.2)	12 (13.8)
Ezetimibe use at baseline (*n*, %)	12 (13.8)	11 (12.8)	13 (15.1)	12 (14.0)	12 (13.8)	12 (13.8)
Diabetes mellitus (*n*, %)	19 (21.8)	18 (20.9)	16 (18.6)	16 (18.6)	17 (19.5)	18 (20.7)
Metabolic syndrome (*n*, %)	23 (26.4)	34 (39.5)	32 (37.2)	35 (40.7)	34 (39.1)	33 (37.9)
Prior possible PCSK9 Ab exposure (*n*, %)	2 (2.3)	2 (2.3)	2 (2.3)	3 (3.5)	3 (3.4)	1 (1.1)

Data include all values from randomized patients who received at least one dose of study treatment. Values are mean (SD) unless otherwise noted. To convert LDL-C and HDL-C to millimoles per litre, multiply by 0.0259. To convert TG to millimoles per litre, multiply by 0.0113.

Ab, antibody; Apo B, apolipoprotein B; BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; IQR, inter-quartile range; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; PCSK9, proprotein convertase subtilisin/kexin type 9;TG, triglycerides.

Table 2 **Change in laboratory measures**

	20 mg Q4W (*n* = 87)	120 mg Q4W (*n* = 86)	300 mg Q4W (*n* = 86)	100 mg Q8W (*n* = 86)	300 mg Q8W (*n* = 87)	Placebo Q4W (*n* = 87)
LDL-C, mg/dL						
End of treatment	109.5 (34.6)	73.7 (30.1)	64.0 (30.3)	112.5 (36.8)	87.9 (46.8)	142.2 (39.6)
Absolute change	−23.2 (−29.3, −17.1)	−55.2 (−61.1, −49.3)	−67.9 (−73.8, −62.0)	−21.3 (−27.4, −15.3)	−50.5 (−56.7, −44.3)	8.8 (2.94, 14.57)
Percentage change	−14.9 (−19.6, −10.2)	−40.5 (−45.0, −36.0)	−50.5 (−55.0, −46.0)	−14.9 (−19.5, −10.2)	−37.1 (−41.9, −32.3)	7.6 (3.2, 12.1)
Relative % change	−22.6 (−28.5, −16.6)[a]	−48.1 (−54.0, −42.3)[a]	−58.2 (−64.1, −52.3)[a]	−22.5 (−28.5, −16.5)[a]	−44.8 (−50.7, −38.8)[a]	
Non-HDL-C, mg/dL						
End of treatment	127.1 (37.5)	92.5 (34.3)	78.9 (32.4)	131.9 (34.9)	107.2 (51.7)	163.9 (40.8)
Absolute change	−28.2 (−34.0, −22.4)	−64.9 (−70.5, −59.2)	−78.3 (−83.9, −72.6)	−27.7 (−33.5, −22.0)	−57.2 (−63.0, −51.3)	6.5 (0.8, 12.1)
Percentage change	−16.1 (−19.8, −12.5)	−39.3 (−42.9, −35.7)	−48.9 (−52.5, −45.3)	−16.1 (−19.8, −12.5)	−35.8 (−39.5, −32.1)	4.9 (1.3, 8.5)
Relative % change	−21.0 (−25.9, −16.1)[a]	−44.2 (−49.1, −39.3)[a]	−53.8 (−58.7, −48.9)[a]	−21.0 (−26.0, −16.1)[a]	−40.7 (−45.6, −35.7)[a]	
Apo B, mg/dL						
End of treatment	90.9 (24.0)	67.2 (20.3)	59.2 (21.3)	94.7 (23.3)	80.1 (32.5)	116.4 (25.2)
Absolute change	−19.9 (−23.6, −16.2)	−43.8 (−47.5, −40.1)	−52.5 (−56.1, −48.8)	−18.6 (−22.2, −14.9)	−36.7 (−40.5, −32.9)	4.4 (0.8, 8.0)
Percentage change	−16.6 (−21.2, −12.1)	−34.9 (−39.3, −30.4)	−46.8 (−51.2, −42.4)	−16.0 (−20.4, −11.6)	−31.9 (−36.5, −27.4)	4.2 (−0.2, 8.6)
Relative % change	−20.8 (−26.7, −14.9)[a]	−39.0 (−44.9, −33.2)[a]	−51.0 (−56.8, −45.1)[a]	−20.2 (−26.0, −14.3)[a]	−36.1 (−42.0, −30.2)[a]	
TG, mg/dL						
End of treatment, median (IQR)	111.0 (79.0, 164.0)	119.5 (91.0, 160.0)	108.0 (84.0, 162.0)	123.5 (92.5, 166.5)	113.0 (81.0, 159.0)	136.0 (98.0, 191.0)
Absolute change	−10.2 (−21.3, 0.9)	−17.9 (−28.7, −7.1)	−31.0 (−41.9, −20.2)	−19.8 (−30.7, −8.8)	−20.2 (−31.4, −9.1)	−1.1 (−12.0, 9.7)
Percentage change	−6.1 (−12.7, 0.5)	−7.2 (−13.6, −0.9)	−15.1 (−21.5, −8.7)	−7.2 (−13.6, −0.7)	−10.6 (−17.2, −4.0)	3.5 (−2.8, 9.9)
Relative % change	−9.7 (−18.5, −0.8)[b]	−10.8 (−19.5, −2.0)[b]	−18.6 (−27.4, −9.8)[a]	−10.7 (−19.6, −1.9)[b]	−14.1 (−23.0, −5.3)[b]	
HDL-C, mg/dL						
End of treatment	61.0 (17.1)	57.7 (13.5)	59.0 (15.9)	60.6 (14.0)	57.8 (15.6)	56.1 (13.0)
Absolute change	2.6 (0.9, 4.3)	3.5 (1.9, 5.2)	4.5 (2.8, 6.2)	1.9 (0.2, 3.6)	4.5 (2.8, 6.3)	0.6 (−1.0, 2.3)
Percentage change	4.5 (1.4, 7.6)	7.3 (4.2, 10.4)	8.8 (5.7, 11.9)	4.5 (1.3, 7.6)	8.4 (5.3, 11.6)	1.6 (−1.4, 4.7)
Relative % change	2.9 (−1.4, 7.2)	5.6 (1.4, 9.9)[b]	7.2 (2.9, 11.4)[b]	2.8 (−1.5, 7.1)	6.8 (2.5, 11.1)[b]	
Lp(a), mg/L						
End of treatment, median (IQR)	20.1 (7.5, 43.1)	26.1 (7.0, 61.2)	10.5 (5.6, 28.6)	26.9 (9.9, 61.5)	13.9 (8.0, 69.0)	27.6 (14.0, 74.9)
Percentage change[c]	−16.6 (−23.6, −9.1)[b]	−19.0 (−25.5, −11.9)[a]	−37.3 (−42.3, −31.9)[a]	−7.5 (−15.0, 0.5)	−21.0 (−27.5, −13.9)[a]	−0.3 (−8.5, 8.6)
Free PCSK9, ng/mL						
End of treatment	438.7 (141.8)	275.0 (129.6)	135.6 (107.2)	470.6 (208.0)	326.1 (157.7)	583.2 (217.1)
Absolute change	−99.9 (−134.3, −65.4)	−257.7 (−291.1, −224.2)	−397.5 (−431.1, −364.0)	−68.8 (−103.2, −34.3)	−205.7 (−239.8, −171.6)	31.4 (−1.6, 64.4)
Percentage change	−16.3 (−27.7, −4.9)	−36.6 (−47.7, −25.4)	−68.0 (−79.2, −56.8)	−4.4 (−15.7, 7.0)	−35.2 (−46.4, −24.0)	9.9 (−1.1, 20.8)

Relative % change	−26.2 (−41.7, −10.7)[b]	−46.4 (−61.8, −31.1)[a]	−77.9 (−93.3, −62.5)[a]	−14.2 (−29.8, 1.3)	−45.0 (−60.5, −29.6)[a]	
hsCRP, mg/L						
End of treatment, median (IQR)	0.950 (0.6, 1.6)	1.365 (0.7, 3.3)	1.145 (0.6, 2.6)	1.015 (0.6, 2.9)	1.200 (0.5, 2.1)	1.440 (0.7, 3.0)
Absolute change	−0.2 (−1.6, 1.2)	1.6 (0.3, 3.0)	−0.3 (−1.6, 1.1)	−0.3 (−1.7, 1.1)	−0.7 (−2.1, 0.7)	0.5 (−0.8, 1.9)
Percentage change	80.7 (−12.1, 173.5)	93.7 (4.5, 182.9)	3.4 (−86.8, 93.7)	18.6 (−72.4, 109.7)	−6.3 (−99.6, 87.0)	64.0 (−26.0, 154.0)
Relative % change	16.6 (−110.8, 144.1)	29.6 (−95.6, 154.8)	−60.6 (−186.6, 65.4)	−45.4 (−172.2, 81.4)	−70.3 (−198.5, 57.8)	

End of treatment values are mean (SD) unless otherwise noted. Absolute changes are least-squares mean changes from baseline until Visit 10 from mixed model repeated measures (95% CI) unless otherwise noted. Percentage changes are least-squares mean percentage changes from baseline until Visit 10 from mixed model repeated measures (95% CI) unless otherwise noted. Relative changes are differences in percentage changes between placebo and LY3015014 counterpart. To convert LDL-C and HDL-C to millimoles per litre, multiply by 0.0259. To convert TG to millimoles per litre, multiply by 0.0113. SI conversions: To convert HDL-C and LDL-C to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113.

Apo B, apolipoprotein B; hsCRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; IQR, inter-quartile range; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; TG, triglycerides.

[a] $P < 0.001$ relative to placebo.

[b] $P < 0.05$ relative to placebo.

[c] LS geometric mean per log-transformed analysis.

mean, 136.3 (SD, 45.0) mg/dL; HDL-C, mean 55.7 (SD, 14.1) mg/dL; TG, median, 139.0 (IQR, 101–186) mg/dL.

Overall, 93.3% of patients were compliant with study drug (missed no more than one full or partial dose of study drug) with no difference in compliance between LY and placebo treatment groups (93.1 vs. 94.3%, respectively).

Efficacy

The effects of placebo and LY administration on lipoprotein and apolipoprotein levels are summarized in *Table 2*. LY3015014 administration produced a significant and dose-dependent decrease in LDL-C. Least squares (LS) mean (95% CI) per cent reductions in LDL-C by beta quantification compared with placebo, from baseline to the end of the dosing interval (Week 16), were −14.9% (−19.6, −10.2) with LY20 Q4W, −40.5% (−45.0, −36.0) with LY120 Q4W, −50.5% (−55.0, −46.0) with LY300 Q4W, −14.9% (−19.5, −10.2) with LY100 Q8W, and −37.1% (−41.9, −32.3) with LY300 Q8W, and 7.6% (3.2, 12.1) with placebo.

Significant reductions in percentage change in calculated LDL-C were evident at all visits during the treatment phase beginning 2 weeks following the initial dose for each treatment group (*Figure 2*). The maximum LDL-C per cent reductions compared with placebo [LS mean difference (95% CI)] were −35.9% (−40.8, −30.9), LY20 Q4W; −58.1% (−63.0, −53.2), LY120 Q4W; −62.8% (−68.3, −57.3), LY300 Q4W; −55.9% (−60.9, −51.0), LY100 Q8W; and −62.3% (−67.3, −57.4), LY300 Q8W (at Week 14, 300Q4 vs. PBO; at Week 10, all other LY dose groups vs. PBO). For patients who completed the treatment phase in the LY120 Q4W, LY300 Q4W, and LY300 Q8W dose groups, 53.8, 71.8, and 35.6% had LDL-C decreases of ≥50% measured 4 and 8 weeks, respectively, after the final Q4W and Q8W dose.

There were greater percentage reductions from baseline to trough LDL-C by beta quantification across all LY doses, except 20Q4, in patients taking statins compared with patients not taking statins (main effect, $P=0.006$). Greater efficacy also was observed in patients with baseline LDL-C at or above the median compared with below the median (main effect, $P < 0.001$). A significant treatment interaction was observed with gender ($P = 0.028$). Greater per cent reductions in LDL-C were observed among male patients vs. female patients with all LY doses, except 100Q8. Subgroup analyses are available in Supplementary material online, *Figure S2*.

Decreases in LDL-C were accompanied by dose-dependent reductions in non-HDL-C ranging from 21.0 to 53.8% ($P < 0.001$), ApoB by 20.2 to 51.0% ($P < 0.001$), and TG by 9.7 to 18.6% ($P < 0.05$), for all pairwise comparisons with placebo. Increases in HDL-C from 5.6 to 7.2% were observed with the LY120 Q4W, LY300 Q4W, and LY300 Q8W dose groups ($P < 0.05$ compared with placebo). Reductions in Lp(a) ranging from 16.6 to 37.3% were observed with all Q4W dose groups and LY300 Q8W, compared with 0.31% reduction with placebo ($P < 0.05$ by log-transformed analysis).

Consistent with the mechanism of action, LY decreased free PCSK9 levels in a dose-dependent fashion with a maximum 77.9% reduction from baseline with LY300 Q4W compared with placebo. Total PCSK9 levels increased by up to 132.5% with LY300 Q4W compared with placebo. There were no significant changes from baseline in hsCRP with LY.

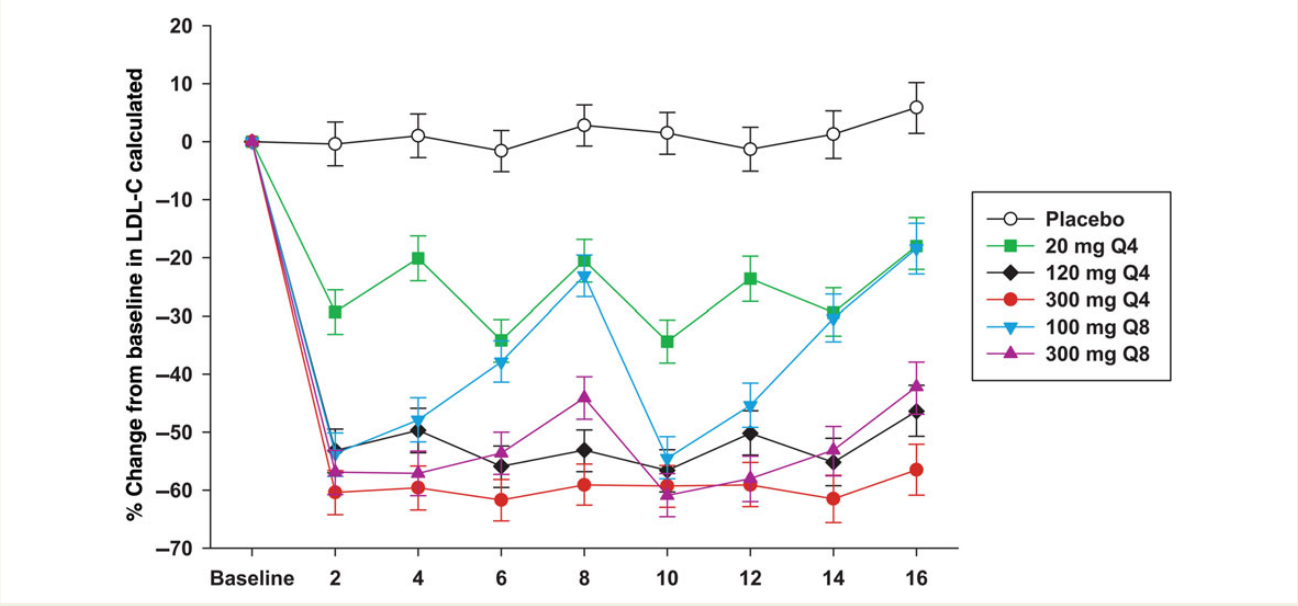

Figure 2 Percentage change in calculated LDL-C at 2-week intervals from baseline to Week 16. Data are LS Mean (SE) with no imputation for missing data. 20Q4W, 20 mg every 4 weeks; 120Q4W, 120 mg every 4 weeks; 300Q4W, 300 mg every 4 weeks; 100Q8W, 100 mg every 8 weeks; 300Q8W, 300 mg every 8 weeks.

Table 3 Safety data

	LY3015014					Placebo Q4W (*n* = 87)
	20 mg Q4W (*n* = 87)	120 mg Q4W (*n* = 86)	300 mg Q4W (*n* = 86)	100 mg Q8W (*n* = 86)	300 mg Q8W (*n* = 87)	
Serious adverse events (%)	3.4	7.0	2.3	2.3	4.6	5.7
Deaths (*n*)	0	0	0	0	0	1
Drug-related adverse events (%)	32.2	37.2	36.0	30.2	28.7	24.1
Discontinuation due to adverse events (%)	3.4	4.7	3.5	1.2	8.0	3.4
CK > 5X ULN (%)	1.2	4.7	0	2.3	1.1	3.5
CK > 10X ULN (%)	0	1.2	0	0	1.1	2.3
ALT or AST > 3X ULN (%)	0	1.2	0	0	1.1	0
Most frequent adverse events (>10%)						
Nasopharyngitis	23.0	25.6	16.3	12.8	17.2	17.2
Injection site pain	17.2	12.8	9.3	8.1	10.3	3.4
Headache	6.9	12.8	9.3	9.3	2.3	6.9
Injection site erythema	1.1	10.5	8.1	2.3	3.4	0
Back pain	4.6	10.5	3.5	2.3	2.3	3.4
Anti-drug antibodies (>4X titre increase) (%)[a]	5.8	10.5	3.5	3.5	3.4	0
Neurocognitive-related adverse events (%)[b]	1.1	2.3	3.5	1.2	1.1	3.4

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; ULN, upper limit of normal.
[a]Increase in ADA titre assessed from baseline to end of follow-up phase.
[b]Neurocognitive-related adverse events include adverse event preferred terms within the dementia and non-infectious encephalopathy/delirium standardized MedDRA queries.

Safety assessments

No treatment-related serious AEs were reported (*Table 3*, Safety Data). Overall, 21 (4.0%) of patients discontinued study drug or study due to an AE, without a difference among treatment groups.

Mild injection site (IS) reactions, including IS pain and IS erythema, were the most common AEs reported more frequently with LY compared with placebo. Three patients discontinued study drug due to IS-related AEs, including IS reaction (LY120 Q4W),

IS erythema (LY300 Q4W), and IS urticaria (LY300 Q8W). Ninety-two per cent of IS-related AEs were mild; there were no severe IS AEs.

Positive anti-drug antibodies (ADA) were detected post-baseline in 6.5% of LY-treated patients and 4.7% of placebo patients. Twenty-three LY patients and no placebo patients demonstrated greater than four-fold increase in titre from baseline to the final follow-up visit. The ADA assay was not drug tolerant and was able to detect ADAs when LY levels were below 0.1 μg/mL, which occurred at the final follow-up visit in 96, 48, and 14% of patients in the LY20 Q4W, LY120 Q4W, and LY300 Q4W groups and in 95 and 60% of patients in the LY100 Q8W and LY300 Q8W groups.

Two patients (0.5% of LY-treated patients) with greater than four-fold increases in ADA titre had a >80% reduction in peak LY level following their last drug administration compared with their first one, associated with a more rapid return of LDL-C levels to baseline compared with group means. None of the 132 patients with LY levels >0.1 μg/mL at the final follow-up visit, precluding sensitive detection of ADAs, had a >80% reduction in peak LY levels from the first to last drug administration, indicating a low likelihood of undetected, neutralizing ADAs. Ten patients (2.3% of LY-treated patients) with a greater than four-fold ADA titre increase reported an IS AE (mild severity in 9; moderate severity in 1). No severe or serious hypersensitivity reaction-related AEs were reported.

One death occurred in a patient receiving placebo; the precipitating event was adjudicated to be a sudden cardiac death. Five other adjudicated cardiovascular events occurred in four patients without a relationship to LY dose. Treatment with LY did not increase mean systolic or diastolic blood pressure or proportion of patients with increase in systolic blood pressure >20 mmHg or diastolic blood pressure >10 mmHg.

Creatine kinase elevations >5 times the upper limit of normal occurred in a comparable proportion of LY and placebo-treated patients. Elevations in aspartate aminotransferase or alanine aminotransferase levels >3 times the upper limit of normal were uncommon and not observed with the highest LY dosage group. Neurocognitive-related AEs were reported in 1.9% of LY patients and 3.4% of placebo patients. There was no significant correlation between the minimum calculated LDL-C achieved post-baseline and the proportion of patients reporting any AEs (odds ratio 1.02; 95% CI 0.97, 1.07; $P = 0.376$ via logistic regression).

Discussion

In the current Phase 2 study, the subcutaneous administration of LY, a monoclonal antibody against PCSK9, dosed every 4 or 8 weeks, resulted in significant and durable reductions of LDL-C, non-HDL-C, Apo-B, and Lp(a).

The LS means reductions in LDL-C by beta quantification from baseline to end of treatment phase ranged from −14.9 to −50.5% with 20–300 mg every 4 weeks and from −14.9 to −37.1% with 100–300 mg every 8 weeks, compared with 7.6% increase with placebo. Maximal reductions in calculated LDL-C by Friedewald equation were −62.8 and −62.3% with 300 mg LY dosed every 4 and 8 weeks, compared with placebo. The LDL-C reductions were maintained over the dosing interval for all three Q4W dose groups. Approximately two-thirds of the maximal effect was maintained at the end of the dosing interval for the LY300 Q8W group.

In the current trial, LDL-C reductions had greater durability than seen with previously studied PCSK9 antibodies.[1,6–8] Maximal reductions of LDL-C do not fundamentally differ between these PCSK9 antibodies, but there are notable efficacy differences based on the dose and administration interval. Alirocumab at 150 mg every 2 weeks, evolocumab 140 mg every 2 weeks, and bococicumab 150 mg every 2 weeks maintained their LDL-C-lowering effects throughout their respective dosing intervals. Less frequent dosing at 4-week intervals for alirocumab 300 mg, evolocumab 350 mg, and bococicumab 300 mg resulted in inconsistent suppression of LDL-C levels. Although the clinical relevance of a more consistent reduction of LDL-C with Q4W dosing of LY is not known, it may offer the potential for enhanced cardiovascular benefits.[9]

Additionally, reductions in other atherogenic lipoproteins, including non-HDL-cholesterol, ApoB, and Lp(a), were substantial. Similar to other monoclonal antibodies against PCSK9 in development, only modest improvements in the levels of TG and HDL-cholesterol were observed. The LDL-C lowering efficacy of LY was evident across multiple patient populations, including HeFH, polygenic hypercholesterolaemia, with and without diabetes, on statins or off statins, and at high or low BMI. A significant treatment interaction was observed for gender, with greater LDL-C reduction among male patients.

Compared with the >500% increase in total PCSK9 observed with alirocumab,[10] total PCSK9 increase was substantially less with LY (maximum 132.5% increase with LY300 Q4W compared with placebo) in this study. This reduced accumulation of LY may reflect a difference in LY binding to PCSK9 compared with other PCSK9 antibodies in development.[4,5] As the LY-binding epitope does not include the furin cleavage site, the antibody may bind while allowing normal proteolytic degradation of PCSK9, minimizing accumulation of PCSK9.[11]

No clinically relevant safety issues emerged with the administration of LY. Serious treatment-related AEs were not reported and common AEs, other than IS-related erythema or pain, did not differ between LY and placebo. Most importantly, there was no effect of LY on mean plasma levels of parameters of liver toxicity (ALT, AST, and total bilirubin). LY3015014 also did not affect skeletal muscle AE reporting, mean changes in serum CK, or incidence of CK outliers. Similar to alirocumab and evolocumab,[12,13] nasopharyngitis was the most commonly reported AE; however, there was no dose-related increase with LY.

As seen with alirocumab, evolocumab, and bococizumab, the adverse effect profile of LY, in terms of liver and muscle, is distinctly different from that of statins, fibric acid derivatives, or nicotinic acid. However, IS reactions did occur more frequently with LY administration. These reactions were generally mild and only 3 out of 527 randomized patients stopped treatment for this reason. The presence of neutralizing antibodies cannot be excluded in two patients with a post-baseline increase in ADA titre who demonstrated reductions in LY level and LDL-C response. The clinical relevance of potentially undetected ADAs with long-term treatment is unknown. However, over the duration of this Phase 2 study, they were of doubtful clinical relevance, considering the robust LDL-C reductions observed.

Long-term safety data for PCSK9 antibodies are eagerly awaited from ongoing large cardiovascular outcomes trials (ODYSSEY Outcomes, NCT01663402; OSLER-2, NCT01854918; FOURIER, NCT01764633; SPIRE-1, NCT01975376; and SPIRE-2, NCT01975389) in which overall >50 000 patients will be recruited.

In conclusion, this study showed that LY, a monoclonal antibody against PCSK9, resulted in robust and durable reductions in LDL-C when dosed every 4 or 8 weeks. The short-term safety profile of LY was comparable to that described for other antibodies against PCSK9. Evaluating the long-term safety profile and effects on cardiovascular outcomes require further investigation.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

J.J.P.K. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: J.J.P.K., S.E.N., D.J.R., M.D.W., T.S., K.A.K.; Collection, management, analysis, and interpretation of the data: J.J.P.K., S.E.N., D.J.R., G.K.H., M.D.W., T.S., K.A.K. Drafting of the work or revising it critically for important intellectual content: J.J.P.K., S.E.N., D.J.R., G.K.H., M.D.W., T.S., K.A.K. Preparation, review, and approval of the manuscript: J.J.P.K., S.E.N., D.J.R., G.K.H., M.D.W., T.S., K.A.K. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: J.J.P.K., S.E.N., D.J.R., G.K.H., M.D.W., T.S., K.A.K.

Study investigators: Ronnie Aronson, LMC Endocrinology Centres Ltd, Toronto, CA; Benjamin Lasko, Manna Research, Inc., Toronto, CA; Lawrence Leiter, St Michaels Hospital, Toronto, CA; Jean-Claude Tardif, Montreal Heart Institute, Montreal, CA; Robert Williams, The Medical Arts Health Research Group, Kelowna, CA; Vincent Woo, University of Manitoba Health Sciences Center, Winnipeg, CA; Eric St-Amour, Q&T Research, Gatineau, CA; Naresh Aggarwal, Aggarwal and Associates Ltd, Brampton, CA; Miranda DuPreez, The Medical Arts Health Research Group, Kamloops, CA; Robert Hegele, Robarts Research Institute, London, CA; Pierre Filteau, Centre Medical des Carrieres, St Marc des Carrieres, CA; Jacques Genest, McGill University, Montreal, CA; Vera Adamkova, Institute klinicke a experimentalni mediciny – IKEM, Praha 4, CZ; Jiri Kuchar, Kardiologie a vnitrni lekarstvi, Cesky Krumlov, CZ; Jana Cepova, Fakultni Nemocnice Motol, Praha 5, CZ; Ivana Kellnerova, Svitavska nemocnice, a.s., Svitavy, CZ; Richard Ceska, III. Interni klinika VFN a LF UK,Centrum preventivni kardiol, Praha 2, CZ; Jiri Matuska, Interni a cevni ambulance, Hodonin, CZ; Lia Bang, Rigshospitalet, Copenhagen, DK; Henrik Nielsen, Bispebjerg Hospital, Kobenhavn NV, DK; Albert Marni Joensen, Aalborg Sygehus, Aalborg, DK; Jens Dahlgaard Hove, Hvidovre Hospital, Hvidovre, DK; Kristian Korsgaard Thomsen, Sydvestjysk Sygehus Esbjerg, Esbjerg, DK; Soren Galatius, Gentofte Hospital, Hellerup, DK; Arihiro Kiyosue, Tokyo-Eki Center-building Clinic, Chuo-ku, JP; Katsuji Hashimoto, AMC nishi-umeda clinic, Osaka, JP; Yumiko Ide, Tokyo Center Clinic, Chuo-ku, JP; Takayuki Azuma, Yaesu Sakura-dori Clinic, Chuo-ku, JP; Masahiro Endo, Tokyo Heart Center, Shinagawa, JP; Masayoshi Sone, Sone Clinic, Shinjuku, JP; Takeshi Yamato, Kouwa Clinic, Toshima-ku, JP; Hikaru Ishii, Shin Nihonbashi Ishii Clinic, Chuo, JP; Yuya Tanaka, Tanaka naika, Osaka-shi, JP; Hiroaki Yamamoto, Gakkentoshi Clinic, Fukuoka-shi, JP; Tsuyoshi Yamaguchi, Yamaguchi Clinic, Ota-ku, JP; Masae Banno, Banno Clinic, Ota-ku, JP; Vicdan Köse, Andromed Medical Research Center, Breda, NL; Kees Hovingh, Academisch Medisch Centrum, Amsterdam, NL; Ben Imholz, TweeSteden Ziekenhuis, Waalwijk, NL; Christine Voors-Pette, Andromed Medical Research Center, Groningen, NL; Wouter Van Kempen, Andromed Medical Research Center, Rotterdam, NL; Cihal Gürlek, Admiraal de Ruyter Ziekenhuis, Goes, NL; Frank Visseren, Universitair Medisch Centrum Utrecht, Utrecht, NL; Jacqueline De Graaf, Universitair Medisch Centrum St Radboud Nijmegen, Nijmegen, NL; Abraham Kroon, Academisch Ziekenhuis Maastricht, Maastricht, NL; VRN-Vascular Research Network, VRN B.V. The Vascular Research Network, Amsterdam, NL; Monika Lukaszewicz, Centrum Badan Kllinicznych PI House Sp.z.o.o, Gdansk, PL; Malgorzata Timler, Centrum Terapii Wspolczesnej, Lodz, PL; Jerzy Supronik, Zdrowie Osteo-Medic s.c. L i A Racewicz, A i J Supronik, Bialystok, PL; Katarzyna Landa, LANDA Specjalistyczne Gabinety Lekarskie, Krakow, PL; Marcin Mazurek, NZOZ ReuMed, Lublin, PL; Harold Bays, L-Marc Research Center, Louisville, USA; Anthony Dulgeroff, High Desert Medical Group, Lancaster, USA; Charles Lambert, Research Institute at Pepin Heart Hospital, Tampa, USA; Robert Lipetz, Encompass Clinical Research, Spring Valley, USA; Stephen Crowley, Aurora Denver Cardiology Associates, PC, Aurora, USA; William Eaves, Grace Research, Bossier, USA; Mark Hepp, Clearwater Cardiovascular & Interventional Consultants, Safety Harbor, USA; Jennifer Robinson, University of Iowa Hospital & Clinic, Iowa City, USA; John Rubino, PMG Research of Raleigh, LLC, Raleigh, USA; William Smith, Volunteer Research Group, Knoxville, USA; Kasi Ramanathan, Northwest Ohio Cardiology Consultants, Toledo, USA; James Trippi, The Care Group, Indianapolis, USA; John Pasquini, Novant Health-Mid Carolina Cardiology, Charlotte, USA; Tooraj Raoof, Tooraj Joseph Raoof M.D., Inc., Encino, USA; Traci Turner, Metabolic & Atherosclerosis Center, Cincinnati, USA; Jose Vazquez-Tanus, Research and Cardiovascular Corp., Ponce, PR.

Additional contributions: Jozef Milata, BSN, RN, of Eli Lilly and Company for operational support; Zachary P. Neeb, PhD, of Eli Lilly and Company for procedural and editorial support; Mingyuan Shao, MS, of C5Research at Cleveland Clinic for statistical support.

Funding

This work was supported by Eli Lilly and Company, which was responsible for the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication. Funding to pay the Open Access publication charges for this article was provided by Eli Lilly and Company.

Conflict of interest: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. J.J.P.K. has reported receiving consulting fee and/or honoraria of Eli Lilly, Cerenis, The Medicines Company, CSL Behring, Amgen, Sanofi, Regeneron, Genzyme, Aegerion, Esperion, AstraZeneca, Omthera, Pronova, Vascular Biogenics, Boehringer Ingelheim, Catabasis, AtheroNova, UniQure, Novartis, Merck, Isis, Kowa, Dezima Pharmaceuticals. S.E.N. has

reported grants from Eli Lilly, grants from Amgen, and grants from Pfizer during the conduct of the study. D.J.R. has reported personal fees from Eli Lilly during the conduct of the study. G.K.H. has reported that his institution has received funding from Dezima, Amgen, Pfizer, Sanofi, Regeneron, AstraZeneca, Genzyme, Cerenis, Synageva, Roche, ISIS pharmaceuticals, Kowa, and Merck for performing clinical trials related to various forms of lipid-lowering medication and consulting fees from Amgen, Pfizer, Roche, and Sanofi. M.D.W., T.S., and K.A.K. are each Eli Lilly employees and reported owning Eli Lilly and Company stock/stock options.

References

1. Giugliano RP, Desai NR, Kohli P, Rogers WJ, Somaratne R, Huang F, Liu T, Mohanavelu S, Hoffman EB, McDonald ST, Abrahamsen TE, Wasserman SM, Scott R, Sabatine MS; LAPLACE-TIMI 57 Investigators. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. *Lancet* 2012;**380**:2007–2017.
2. Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, Langslet G, Scott R, Olsson AG, Sullivan D, Hovingh GK, Cariou B, Gouni-Berthold I, Somaratne R, Bridges I, Scott R, Wasserman SM, Gaudet D; RUTHERFORD-2 Investigators. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;**385**:331–340.
3. Robinson JG, Nedergaard BS, Rogers WJ, Fialkow J, Neutel JM, Ramstad D, Somaratne R, Legg JC, Nelson P, Scott R, Wasseman SM, Weiss R, for the LAPLACE-2 Investigators. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomised clinical trial. *JAMA* 2014;**311**:1870–1882.
4. Beyer TP, Eacho PI, Schroeder KM, Hansen RJ, Wroblewski VJ, Han B, Pickard RT, Kowala MC. A PCSK9 antibody that blocks binding to LDLR while allowing normal PCSK9 inactivation by furin is afforded a reduced clearance rate and a longer duration of effect in mice. *ATVB* 2015;**35**:A538. Abstract 538.
5. Schroeder KM, Beyer TP, Hansen RJ, Han B, Pickard RT, Wroblewski VJ, Kowala MC, Eacho PI. Proteolytic cleavage of antigen extends the durability of an anti-PCSK9 monoclonal antibody. *J Lipid Res* 2015;**56**:2124–2132.
6. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand AC, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. *J Am Coll Cardiol* 2012;**59**:2344–2353.
7. Ballantyne CM, Neutel J, Cropp A, Duggan W, Wang EQ, Plowchalk D, Sweeney K, Kaila N, Vincent J, Bays H. Results of bococizumab, a monoclonal antibody against proprotein convertase subtilisin/kexin type 9, from a randomised, placebo-controlled, dose-ranging study in statin-treated subjects with hypercholesterolemia. *Am J Cardiol* 2015;**115**:1212–1221.
8. Stein EA, Gipe D, Bergeron J, Gaudet D, Weiss R, Dufour R, Wu R, Pordy R. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. *Lancet* 2012;**380**:29–36.
9. Bangalore S, Breazna A, DeMicco DA, Wun CC, Messerli FH; TNT Steering Committee and Investigators. Visit-to-visit low-density lipoprotein cholesterol variability and risk of cardiovascular outcomes: insights from the TNT trial. *J Am Coll Cardiol* 2015;**65**:1539–1548.
10. Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. *N Engl J Med* 2012;**367**:1891–1900.
11. Benjannet S, Rhainds D, Hamelin J, Nassoury N, Seidah NG. The proprotein convertase (PC) PCSK9 is inactivated by furin and/or PC5/6A: functional consequences of natural mutations and post-translational modifications. *J Biol Chem* 2006;**281**:30561–30572.
12. Praluent [package insert]. Bridgewater, NJ: Regeneron Pharmaceuticals, Inc. / sanofi-aventis U.S. LLC; 2015.
13. Repatha [package insert]. Thousand Oaks, CA: Amgen, Inc; 2015.