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

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Summary

Background LDL cholesterol (LDL-C) is a well established risk factor for cardiovascular disease. Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds LDL receptors, targeting them for degradation. We therefore assessed the efficacy, safety, and tolerability of AMG 145, a human monoclonal IgG2 antibody against PCSK9, in stable patients with hypercholesterolemia on a statin.

Methods In a phase 2, dose-ranging study done in 78 centres in the USA, Canada, Denmark, Hungary, and Czech Republic, patients (aged 18–80 years) with LDL-C greater than 2·2 mmol/L on a stable dose of statin (with or without ezetimibe), were randomly assigned equally, through an interactive voice response system, to subcutaneous injections of AMG 145 70 mg, 105 mg, or 140 mg, or matching placebo every 2 weeks; or subcutaneous injections of AMG 145 280 mg, 350 mg, or 420 mg, or matching placebo every 4 weeks. Everyone was masked to treatment assignment within the every 2 weeks and every 4 weeks schedules. The primary endpoint was the percentage change in LDL-C concentration from baseline after 12 weeks. Analysis was by modified intention to treat. This study is registered with ClinicalTrials.gov, number NCT01380730.

Findings 631 patients with hypercholesterolaemia were randomly assigned to AMG 145 70 mg (n=79), 105 mg (n=79), or 140 mg (n=78), or matching placebo (n=78) every 2 weeks; or AMG 145 280 mg (n=79), 350 mg (n=79), and 420 mg (n=80), and matching placebo (n=79) every 4 weeks. At the end of the dosing interval at week 12, the mean LDL-C concentrations were reduced generally dose dependently by AMG 145 every 2 weeks (ranging from 41·8% to 66·1%; p<0·0001 for each dose *vs* placebo) and AMG 145 every 4 weeks (ranging from 41·8% to 50·3%; p<0·0001). No treatment-related serious adverse events occurred. The frequencies of treatment-related adverse events were similar in the AMG 145 and placebo groups (39 [8%] of 474 *vs* 11 [7%] of 155); none of these events were severe or life-threatening.

Interpretation The results suggest that PCSK9 inhibition could be a new model in lipid management. Inhibition of PCSK9 warrants assessment in phase 3 clinical trials.

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Introduction

Reduction in LDL-cholesterol (LDL-C) concentrations has been shown to reduce subsequent cardiovascular events, both in primary and secondary prevention populations;[1] the most compelling data were from trials of statins.[2] However, many patients do not achieve their goal LDL-C concentration due to an insufficient response, intolerance to the drugs, or both,[3] and thus are at risk of subsequent events.[4]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a key part in aiding the intracellular degradation of the LDL receptor (LDL-R) within the hepatocyte lysosome.[5] Loss-of-function mutations in PCSK9 increase the number of LDL-Rs available to recycle to the hepatocyte cell surface, resulting in a reduction in LDL-C concentrations and fewer cardiovascular events.[6]

AMG 145 is a human monoclonal antibody that binds human PCSK9 with high affinity. In phase 1 studies, it reduced LDL-C concentrations up to 64% versus placebo 1 week after a single dose, and up to 81% with repeated weekly doses.[7] We therefore tested the hypothesis that, compared with placebo, 12 weeks of AMG 145 would reduce LDL-C concentrations when used in addition to a statin with or without ezetimibe in patients with hypercholesterolaemia.

Methods

Patients and study design

The design and rationale of LAPLACE-TIMI 57 has been described previously.[8] Briefly, the study was a multinational, double-blind, placebo-controlled, dose-ranging

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trial done in 78 centres in five countries (USA, Canada, Denmark, Hungary, and Czech Republic; appendix pp 3–5).

Eligible patients (aged 18–80 years) had a history of hypercholesterolaemia and fasting LDL-C concentration greater than 2·2 mmol/L while on a stable dose of statin (with or without ezetimibe) for at least 4 weeks. Patients with severe comorbidities or taking lipid-lowering drugs other than statin or ezetimibe were ineligible.[8] A complete list of inclusion and exclusion criteria is provided in the appendix p 6. After signing informed consent, patients entered a screening phase of up to 6 weeks that included fasting laboratory measurements and a one-time subcutaneous administration of three 2 mL injections of matching placebo to assess their tolerability.

The protocol and amendments were approved by the ethics committee at each centre. An independent data monitoring committee met about every 3 months to review trial conduct, data, and adverse events. Data were provided by an independent biostatistical group external to the TIMI Study Group and Amgen (Thousand Oaks, CA, USA). Treatment codes were generated and held by a statistician at Amgen who did not have access to the clinical trial database and was independent of the study team. All patients provided written informed consent.

Randomisation and masking

Investigators enrolled patients, and treatments were assigned randomly with a computer-generated list by an interactive voice response system. Eligible patients who tolerated the placebo injections were randomly assigned equally to one of eight groups: AMG 145 70 mg, 105 mg, or 140 mg every 2 weeks or matching placebo every 2 weeks; or AMG 145 280 mg, 350 mg, or 420 mg every 4 weeks or matching placebo every 4 weeks. The total volume of the every 2 week subcutaneous injections was 2 mL and that of the every 4 week subcutaneous injections was 6 mL, with a recommended volume of 2 mL per injection. Everyone involved in the conduct of the trial, including patients, investigators, the study team, monitors, and adjudicators, were masked to treatment assignment within the every 2 weeks and every 4 weeks schedules. The members of the data safety committee had access to unmasked data. Masking of the study drug was maintained by use of identical syringes with solutions for injection that were indistinguishable in appearance. During in-person follow-up visits every 2 weeks, fasting laboratory measurements, adverse events, clinical endpoints, and concomitant treatments were assessed in all patients. As part of an optional pharmacokinetic and pharmacodynamic study, fasting blood specimens were obtained at weeks 9 or 11, or both, in 158 patients. The last dose was administered on week 10 for the groups treated every 2 weeks and week 8 for the groups treated every 4 weeks, with an end of study visit 4 weeks after the last dose in each group. The fasting LDL-C concentration was calculated with the Friedewald equation for all timepoints

$$\text{LDL-C} = \text{total cholesterol} - \text{HDL} - (\text{triglycerides}/5)$$

Before randomisation and at 12 weeks, the LDL-C concentration was measured with preparative ultracentrifugation at the Lipid Core Laboratory (Cincinnati, OH, USA). Changes to the lipid-lowering regimen (statin or ezetimibe, addition of other lipid-lowering drugs) or use of other drugs that modify lipids were not permitted within the 4 weeks before screening and until the end of the study.

Endpoints

The primary efficacy endpoint was the percentage change from baseline in LDL-C concentration at week 12, measured with ultracentrifugation. Secondary efficacy endpoints were absolute change from baseline in LDL-C concentration at week 12 and the percentage changes from baseline to week 12 in concentrations of non-HDL cholesterol (non-HDL-C) and apolipoprotein B, and ratios of total cholesterol to HDL-C and apolipoprotein B to apolipoprotein A1 concentrations. We also measured the absolute and percentage changes in these parameters from baseline at each scheduled visit and the proportion of patients at 12 weeks achieving the target concentrations of LDL-C (<1·8 mmol/L), non-HDL-C (<2·6 mmol/L), and apolipoprotein B (<0·8 g/L) that are recommended in guidelines for the treatment of patients at highest risk.[9–11] Frequencies of adjudicated cardiovascular events (appendix p 45) and absolute and percentage changes from baseline at each scheduled visit in concentrations of triglycerides, HDL-C, and apolipoprotein A1 were exploratory endpoints.

Safety endpoints were the frequency of treatment-emergent adverse events, adjudicated myalgia, laboratory values, vital signs, electrocardiographic parameters, and formation of anti-AMG 145 antibody (binding and neutralising).

Statistical analysis

The analyses of efficacy and safety were done for all randomly assigned patients who were given at least one dose of study drug (modified intention to treat). Analyses of the primary and secondary efficacy endpoints were done with an ANCOVA model with covariates for treatment group and the stratification factors—screening LDL concentration (<3·4 mmol/L *vs* ≥3·4 mmol/L) and baseline use of ezetimibe (yes *vs* no). All efficacy endpoints were analysed with last observation carried forward (LOCF) imputation. A sensitivity analysis was done for patients who completed treatment and had an ultracentrifugation LDL-C concentration measured at week 12. Completion of treatment was defined as completing all the per-protocol scheduled visits up until the last visit injection.

Primary, secondary, and exploratory endpoints were evaluated independently for the groups treated every 2 weeks and every 4 weeks and compared with their respective placebo groups at a significance level of 0·05. Multiplicity adjustment of the primary analysis was based on hierarchical sequential testing within each dose frequency group (every 2 weeks and every 4 weeks), starting from the highest dose in each group and comparison of each AMG 145 dose with placebo. Analyses were done with SAS (version 9.2).

Descriptive data were used to report safety data by use of actual data without imputation. A Cochran-Armitage test for trend was used to analyse the differences between all the groups in the proportion of patients achieving the lipoprotein goals described above.

This study is registered with ClinicalTrials.gov, number NCT01380730.

Role of the funding source

The study was designed jointly by the TIMI Study Group and trial sponsor. Data were gathered by the sponsor. The raw database was provided to the TIMI Study Group and analyses were done and interpreted independently by the TIMI Study Group, who had complete access to all the data, wrote this report, and take responsibility for the data. RPG and MSS had the final responsibility for the decision to submit for publication.

Results

Of 934 patients screened, we randomly assigned 631 (67·6%) between July 18, and Dec 22, 2011 (figure 1). The most common reasons cited by patients for not wanting to be randomly assigned despite meeting entry criteria were related to family concerns or travel. None of the patients stated that intolerance to placebo injections during the run-in phase was the reason for not proceeding with randomisation. Baseline characteristics of the patients were similar between the eight groups (table 1).

Two patients (both assigned placebo every 4 weeks) were not given any study drug; 629 (99·7%) were given study drug and were included in the efficacy and safety analyses, and 623 (98·7%) had data available for the ANCOVA modeling of the primary endpoint. No patients withdrew consent after randomisation or were lost to follow-up.

13 patients stopped study drug early: six because of the patient's request, two because of adverse events (neither assessed as related to study drug by the investigator), two because of investigator's decision, and three for other reasons. A total of 603 (95·6%) patients randomly

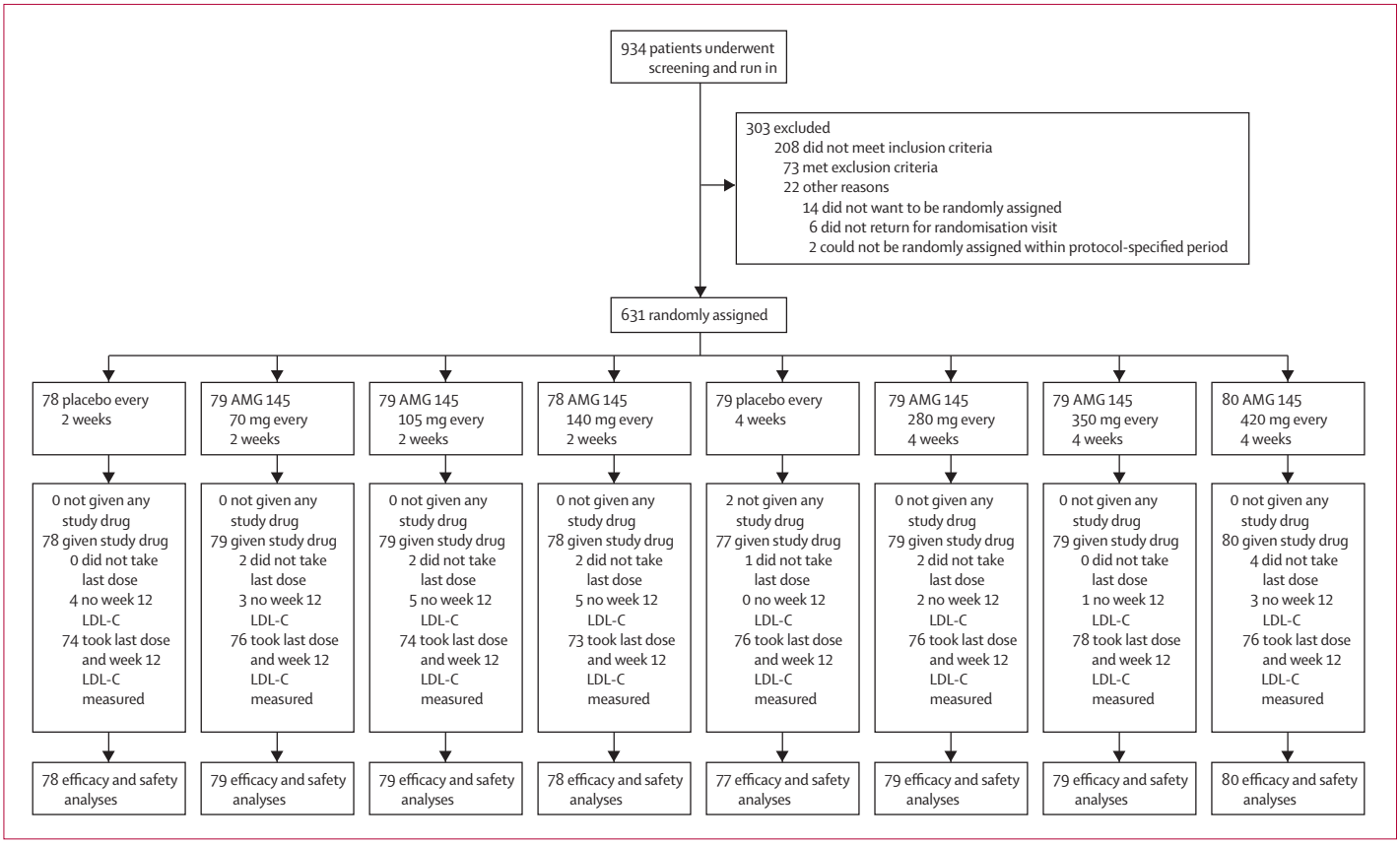


Figure 1: **Trial profile**
LDL-C=LDL cholesterol.

assigned took the last dose of study drug and had an LDL-C concentration measured with ultracentrifugation at week 12.

The mean baseline ultracentrifugation LDL-C concentration was 3·2 mmol/L (SD 0·7) in the 629 patients included in the efficacy analysis. All six doses of AMG 145

	Placebo every 2 weeks (n=78)	AMG 145 70 mg every 2 weeks (n=79)	AMG 145 105 mg every 2 weeks (n=79)	AMG 145 140 mg every 2 weeks (n=78)	Placebo every 4 weeks (n=79)	AMG 145 280 mg every 4 weeks (n=79)	AMG 145 350 mg every 4 weeks (n=79)	AMG 145 420 mg every 4 weeks (n=80)	Total (n=631)
Age (years)	61·0 (55·0–67·0)	62·0 (53·0–67·0)	59·0 (53·0–66·0)	63·5 (56·0–69·0)	63·0 (56·0–67·0)	61·0 (57·0–66·0)	64·0 (57·0–68·0)	63·0 (57·0–68·5)	62·0 (55·0–67·0)
Sex, female	42 (54%)	44 (56%)	25 (32%)	45 (58%)	42 (53%)	40 (51%)	38 (48%)	44 (55%)	320 (51%)
White	72 (92%)	72 (91%)	67 (85%)	67 (86%)	76 (96%)	64 (81%)	72 (91%)	70 (88%)	560 (89%)
Body-mass index (kg/m²)	30·1 (26·7–33·9)	28·1 (25·2–33·5)	28·4 (25·5–31·4)	29·4 (26·8–34·3)	29·2 (26·6–33·1)	29·1 (25·8–33·1)	28·9 (26·9–32·6)	28·8 (24·7–32·0)	29·0 (26·0–32·8)
Stratification criteria									
Screening LDL-C <3·4 mmol/L	51 (65%)	51 (65%)	51 (65%)	52 (67%)	52 (66%)	51 (65%)	52 (66%)	53 (66%)	413 (65%)
Baseline ezetimibe	7 (9%)	7 (9%)	7 (9%)	7 (9%)	8 (10%)	7 (9%)	7 (9%)	7 (9%)	57 (9%)
Risk factors for coronary heart disease									
Diabetes mellitus, type 2	9 (12%)	12 (15%)	16 (20%)	15 (19%)	9 (11%)	11 (14%)	12 (15%)	19 (24%)	103 (16%)
Current cigarette use	19 (24%)	12 (15%)	19 (24%)	11 (14%)	11 (14%)	7 (9%)	11 (14%)	11 (14%)	101 (16%)
Hypertension	58 (74%)	50 (63%)	52 (66%)	56 (72%)	51 (65%)	61 (77%)	54 (68%)	56 (70%)	438 (69%)
Family history of premature coronary heart disease	17 (22%)	21 (27%)	20 (25%)	23 (29%)	28 (35%)	20 (25%)	20 (25%)	31 (39%)	180 (29%)
Baseline metabolic syndrome	32 (41%)	32 (41%)	32 (41%)	37 (47%)	29 (37%)	39 (49%)	45 (57%)	30 (38%)	276 (44%)
Cardiovascular history									
Coronary artery disease	22 (28%)	20 (25%)	27 (34%)	31 (40%)	20 (25%)	18 (23%)	21 (27%)	28 (35%)	187 (30%)
Myocardial infarction	11 (14%)	7 (9%)	18 (23%)	19 (24%)	9 (11%)	6 (8%)	12 (15%)	16 (20%)	98 (16%)
Coronary artery bypass graft	8 (10%)	6 (8%)	10 (13%)	7 (9%)	5 (6%)	5 (6%)	8 (10%)	8 (10%)	57 (9%)
Percutaneous coronary intervention	12 (15%)	11 (14%)	19 (24%)	19 (24%)	9 (11%)	10 (13%)	7 (9%)	13 (16%)	100 (16%)
Cerebrovascular or peripheral arterial disease	8 (10%)	5 (6%)	10 (13%)	9 (12%)	6 (8%)	11 (14%)	8 (10%)	9 (11%)	66 (10%)
Baseline laboratory values									
Ultracentrifuge LDL-C (mmol/L)	3·2 (0·7)	3·1 (0·6)	3·3 (0·8)	3·1 (0·6)	3·2 (0·8)	3·2 (0·7)	3·2 (0·7)	3·1 (0·7)	3·2 (0·7)
Non-HDL-C (mmol/L)	3·8 (0·8)	3·8 (0·8)	3·9 (1·0)	3·8 (0·7)	3·9 (0·9)	3·8 (0·9)	3·9 (0·8)	3·7 (0·8)	3·8 (0·8)
Total cholesterol (mmol/L)	5·2 (0·9)	5·2 (0·8)	5·3 (1·0)	5·1 (0·7)	5·3 (0·9)	5·2 (0·9)	5·2 (0·8)	5·2 (0·9)	5·2 (0·9)
HDL-C (mmol/L)	1·4 (0·4)	1·4 (0·5)	1·4 (0·5)	1·4 (0·4)	1·4 (0·4)	1·4 (0·5)	1·3 (0·3)	1·4 (0·5)	1·4 (0·4)
Ratio of total cholesterol to HDL	3·94 (1·02)	4·00 (1·24)	4·13 (1·47)	3·93 (1·02)	4·06 (1·30)	4·01 (1·30)	4·12 (0·96)	3·88 (1·09)	4·01 (1·18)
Triglycerides (mmol/L)	1·5 (0·6)	1·5 (0·7)	1·5 (0·7)	1·6 (0·6)	1·6 (0·8)	1·5 (0·7)	1·7 (0·7)	1·5 (0·6)	1·5 (0·7)
VLDL-C (mmol/L)	0·6 (0·3)	0·6 (0·4)	0·6 (0·3)	0·6 (0·3)	0·7 (0·4)	0·6 (0·3)	0·7 (0·3)	0·6 (0·3)	0·6 (0·3)
Apolipoprotein B (g/L)	1·0 (0·2)	1·0 (0·2)	1·0 (0·2)	1·0 (0·2)	1·0 (0·2)	1·0 (0·2)	1·0 (0·2)	1·0 (0·2)	1·0 (0·2)
Apolipoprotein A1 (g/L)	1·6 (0·3)	1·5 (0·3)	1·6 (0·3)	1·6 (0·3)	1·6 (0·3)	1·6 (0·3)	1·5 (0·2)	1·6 (0·3)	1·6 (0·3)
Ratio of apolipoprotein B to apolipoprotein A1	0·66 (0·16)	0·67 (0·19)	0·70 (0·22)	0·65 (0·15)	0·68 (0·19)	0·66 (0·20)	0·69 (0·18)	0·65 (0·18)	0·67 (0·18)
PCSK9 (nmol/L)	6·2 (1·8)	5·7 (1·7)	6·0 (1·4)	6·1 (1·7)	6·3 (1·7)	6·3 (2·1)	6·4 (1·8)	6·4 (1·6)	6·2 (1·7)
Statin	78 (100%)	78 (99%)	78 (99%)	78 (100%)	77 (97%)	79 (100%)	79 (100%)	80 (100%)	627 (99%)
Atorvastatin	15 (19%)	16 (20%)	17 (22%)	22 (28%)	28 (35%)	17 (22%)	20 (25%)	24 (30%)	159 (25%)
Fluvastatin	0	0	0	0	0	0	1 (1%)	2 (3%)	3 (<1%)
Lovastatin	1 (1%)	0	3 (4%)	2 (3%)	3 (4%)	0	2 (3%)	3 (4%)	14 (2%)
Pitavastatin	0	1 (1%)	0	0	0	0	0	0	1 (<1%)
Pravastatin	7 (9%)	6 (8%)	6 (8%)	6 (8%)	7 (9%)	6 (8%)	2 (3%)	3 (4%)	43 (7%)
Rosuvastatin	16 (21%)	22 (28%)	17 (22%)	13 (17%)	13 (16%)	20 (25%)	16 (20%)	13 (16%)	130 (21%)
Simvastatin	39 (50%)	33 (42%)	35 (44%)	35 (45%)	26 (33%)	37 (47%)	38 (48%)	36 (45%)	279 (44%)
High-intensity statin regimen*	19 (24%)	24 (31%)	24 (31%)	25 (32%)	19 (25%)	24 (30%)	22 (28%)	29 (36%)	186 (29%)
Omega-3 fish oil	1 (1%)	1 (1%)	5 (6%)	7 (9%)	3 (4%)	1 (1%)	3 (4%)	6 (8%)	27 (4%)

Data are number (%), median (IQR), or mean (SD). LDL-C=LDL cholesterol. HDL-C=HDL cholesterol. VLDL-C=VLDL cholesterol. *Daily use of atorvastatin 40–80 mg, rosuvastatin 20–40 mg, simvastatin 80 mg, or any statin with ezetimibe. Percentages are based on non-missing results.

Table 1: **Demographics, baseline characteristics, and treatments of intention-to-treat population**

resulted in significant (p<0·0001) reductions in the primary efficacy endpoint of percentage change from baseline in LDL-C concentration measured with ultracentrifugation at week 12 (end of the dosing intervals) compared with placebo (table 2). The reductions in LDL-C concentrations versus placebo for the AMG 145 groups treated every 2 weeks ranged from 41·8% to 66·1% at 12 weeks; and for the AMG 145 groups treated every 4 weeks ranged from 41·8% to 50·3% at 12 weeks. The absolute mean reductions from baseline in LDL-C concentration measured with ultracentrifugation at week 12 with AMG 145 compared with placebo ranged from 1·3 mmol/L to 2·0 mmol/L for the groups treated every 2 weeks and ranged from 1·3 mmol/L to 1·6 mmol/L for those treated every 4 weeks. The 140 mg every 2 weeks regimen resulted in the lowest achieved mean LDL-C concentration measured with ultracentrifugation at 12 weeks of 1·1 mmol/L (SD 0·6; table 2). Analyses of patients who both completed study drug and had an ultracentrifugation LDL-C concentration measurement at week 12 were consistent with the primary results (data not shown).

Generally, the efficacy results for subgroups of age, sex, baseline LDL-C concentration, intensity of statin

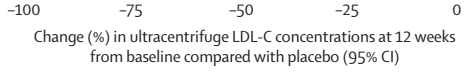
	AMG 145 70 mg every 2 weeks (n=79)	AMG 145 105 mg every 2 weeks (n=79)	AMG 145 140 mg every 2 weeks (n=78)	AMG 145 280 mg every 4 weeks (n=79)	AMG 145 350 mg every 4 weeks (n=79)	AMG 145 420 mg every 4 weeks (n=80)
Ultracentrifugation LDL-C						
Mean change in LDL-C versus placebo (SE; 95% CI); p value	−41·8% (2·7; −47·2 to −36·5); <0·0001	−60·2% (2·7; −65·6 to −54·9); <0·0001	−66·1% (2·7; −71·5 to −60·7); <0·0001	−41·8% (2·9; −47·6 to −36·1); <0·0001	−50·0% (2·9; −55·7 to −44·3); <0·0001	−50·3% (2·9; −56·0 to −44·6); <0·0001
Absolute change in LDL-C versus placebo (mmol/L; SE; 95% CI)	−1·30 (0·10; −1·50 to −1·10)	−1·96 (0·10; −2·16 to −1·76)	−2·04 (0·10; −2·24 to −1·84)	−1·31 (0·10; −1·50 to 1·12)	−1·58 (0·10; −1·77 to −1·39)	−1·58 (0·10; −1·77 to −1·39)
Achieved LDL-C (mmol/L; mean value [SD; range] at week 12)	1·88 (0·64; 0·54–3·44)	1·38 (0·55; 0·39–2·97)	1·15 (0·64; 0·28–4·84)	1·78 (0·72; 0·44–3·80)	1·54 (0·59; 0·65–3·41)	1·50 (0·67; 0·62–4·84)
LDL-C <1·0 mmol/L at week 12	5 (6%)	21 (27%)	36 (47%)	9 (12%)	10 (13%)	22 (28%)
LDL-C <0·5 mmol/L at week 12	0	2 (3%)	3 (4%)	2 (3%)	0	0
Other lipid parameters						
Mean change in total cholesterol concentration versus placebo (SE; 95% CI); p value	−26·2% (2·0; −30·2 to −22·3); <0·0001	−39·4% (2·0; −43·3 to −35·4); <0·0001	−42·5% (2·0; −46·5 to −38·5); <0·0001	−26·9% (2·0; −30·8 to −22·9); <0·0001	−32·6 (2·0; −36·5 to −28·6); <0·0001	−33·0% (2·0; −37·0 to −29·1); <0·0001
Mean change in HDL-C concentration versus placebo (SE; 95% CI); p value	6·9% (2·4; 2·3 to 11·6); 0·0034	6·6% (2·4; 2·0 to 11·2); 0·0054	8·1% (2·4; 3·5 to 12·8); 0·0007	1·6% (2·1; −2·5 to 5·8); 0·4346	5·5% (2·1; 1·4 to 9·6); 0·0086	4·5% (2·1; 0·4 to 8·7); 0·0307
Mean change in triglycerides concentration versus placebo (SE; 95% CI); p value	−18·1% (6·2; −30·2 to −6·0); 0·0035	−24·9% (6·2; −37·1 to −12·8); <0·0001	−33·7% (6·2; −45·9 to −21·5); <0·0001	−13·4% (5·7; −24·6 to −2·3); 0·0183	−13·7% (5·6; −24·8 to −2·6); 0·0156	−19·4% (5·7; −30·5 to −8·2); 0·0007
Mean change in VLDL-C concentration versus placebo (SE; 95% CI); p value	−23·4% (8·0; −39·2 to −7·6); 0·0038	−29·7% (8·1; −45·5 to −13·9); 0·0003	−44·3% (8·0; −60·1 to −28·5); <0·0001	−21·1% (7·3; −35·5 to −6·7); 0·0043	−22·2% (7·3; −36·6 to −7·8); 0·0026	−32·4% (7·3; −46·8 to −17·9); <0·0001
Mean change in non-HDL-C concentration versus placebo (SE; 95% CI); p value	−38·4% (2·5; −43·4 to −33·5); <0·0001	−55·4% (2·5; −60·4 to −50·5); <0·0001	−61·4% (2·5; −66·4 to −56·4); <0·0001	−37·8% (2·6; −42·9 to −32·7); <0·0001	−45·8% (2·6; −50·9 to −40·7); <0·0001	−47·6% (2·6; −52·7 to −42·4); <0·0001
Mean change in apolipoprotein-B concentration versus placebo (SE; 95% CI); p value	−34·7% (2·4; −39·6 to −29·9); <0·0001	−50·1% (2·4; −55·0 to −45·3); <0·0001	−56·4% (2·5; −61·3 to −51·6); <0·0001	−34·4% (2·6; −39·5 to −29·3); <0·0001	−40·8% (2·6; −45·9 to −35·7); <0·0001	−42·0% (2·6; −47·2 to −36·9); <0·0001
Mean change in apolipoprotein-A1 concentration versus placebo (SE; 95% CI); p value	2·9% (2·0; −1·0 to 6·9); 0·1451	0·55% (2·0; −3·4 to 4·5); 0·7845	0·31% (2·0; −3·7 to 4·3); 0·8789	1·25% (1·9; −2·5 to 5·0); 0·5151	4·8% (1·9; 1·0 to 8·5); 0·0137	3·6% (1·9; −0·2 to 7·4); 0·0618
Mean change in ratio of total cholesterol to HDL-C versus placebo (SE; 95% CI); p value	−31·4% (2·3; −35·8 to −27·0); <0·0001	−43·4% (2·3; −47·8 to −38·9); <0·0001	−47·7% (2·3; (−52·2 to −43·3); <0·0001	−27·7% (2·2; −32·1 to −23·4); <0·0001	−36·0% (2·2; −40·3 to −31·6); <0·0001	−35·7% (2·2; −40·0 to −31·3); <0·0001
Mean change in ratio of apolipoprotein B1 to apolipoprotein A versus placebo (SE; 95% CI); p value	−34·7% (2·4; −39·5 to −30·0); <0·0001	−47·3% (2·4; −52·1 to −42·5); <0·0001	−53·4% (2·4; (−58·2 to −48·6); <0·0001	−33·8% (2·8; −39·2 to −28·3); <0·0001	−42·4% (2·8; −47·8 to −37·0); <0·0001	−42·9% (2·8; −48·4 to −37·5); <0·0001
Mean change in PCSK9 versus placebo (SE; 95% CI); p value	−55·4% (3·9; −63·1 to −47·7); <0·0001	−65·8% (3·9; −73·4 to −58·1); <0·0001	−72·5% (3·9; −80·3 to −64·8); <0·0001	−46·3% (3·5; −53·2 to −39·3); <0·0001	−47·6% (3·5; −54·5 to −40·6); <0·0001	−56·7 (3·6; −63·7 to −49·7); <0·0001

Data are number (%), unless otherwise indicated. The treatment difference compared with placebo was calculated with least squares mean, in the same dose frequency from the ANCOVA model, which includes treatment group and stratification factors (screening LDL, baseline use of ezetimibe) as covariates. PCSK9=proprotein convertase subtilisin/kexin type 9. LDL-C=LDL cholesterol. HDL-C=HDL cholesterol. VLDL-C=VLDL cholesterol.

Table 2: **Efficacy at 12 weeks adjusted for placebo**

A

	AMG 145 140 mg every 2 weeks		Placebo every 2 weeks	
	Patients (n)	Change in LDL-C	Patients (n)	Change in LDL-C
Sex				
Male	32	−67·5%	36	1·8%
Female	45	−60·9%	42	3·4%
Age (years)				
<65	42	−64·9%	54	1·4%
≥65	35	−58·8%	24	5·8%
Body-mass index (kg/m²)				
<25	10	−68·3%	7	−12·7%
25 to <30	29	−59·0%	31	8·9%
≥30	38	−64·8%	40	1·3%
Baseline ultracentrifugation LDL-C (mmol/L)				
<2·6	12	−56·1%	15	18·0%
2·6 to <3·4	40	−61·8%	40	3·1%
≥3·4	25	−70·5%	23	−9·1%
Baseline PCSK9				
Less than median	42	−62·2%	38	2·7%
Median or greater	34	−65·4%	38	2·6%
Statin regimen				
Intensive	25	−61·5%	19	4·2%
Non-intensive	52	−65·3%	59	1·2%
Ezetimibe				
Concomitant	7	−54·5%	5	14·3%
Not concomitant	70	−63·8%	73	2·6%



B

	AMG 145 420 mg every 4 weeks		Placebo every 4 weeks	
	Patients (n)	Change in LDL-C	Patients (n)	Change in LDL-C
Sex				
Male	35	−56·5%	36	0·2%
Female	43	−45·8%	41	−1·0%
Age (years)				
<65	45	−50·5%	47	1·1%
≥65	33	−53·3%	30	−5·1%
Body-mass index (kg/m²)				
<25	21	−46·4%	11	0·7%
25 to <30	25	−50·4%	34	−0·5%
≥30	32	−55·4%	32	−3·0%
Baseline ultracentrifugation LDL-C (mmol/L)				
<2·6	17	−54·7%	12	−4·6%
2·6 to <3·4	40	−53·7%	42	−0·8%
≥3·4	21	−50·6%	23	−3·0%
Baseline PCSK9				
Less than median	33	−42·6%	36	1·1%
Median or greater	42	−54·4%	39	0·8%
Statin regimen				
Intensive	28	−50·7%	19	2·5%
Non-intensive	50	−55·7%	58	−5·7%
Ezetimibe				
Concomitant	7	−39·3%	6	−1·1%
Not concomitant	71	−56·8%	71	−5·2%

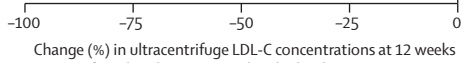


Figure 2: **Percentage change in ultracentrifugation LDL-C concentration in the main subgroups given AMG 145 140 mg every 2 weeks (A) and AMG 145 420 mg every 4 weeks (B)**
Treatment differences (95% CI) compared with placebo were calculated by use of least squares mean and treatment group and stratification factors as covariates. LDL-C=LDL-cholesterol.

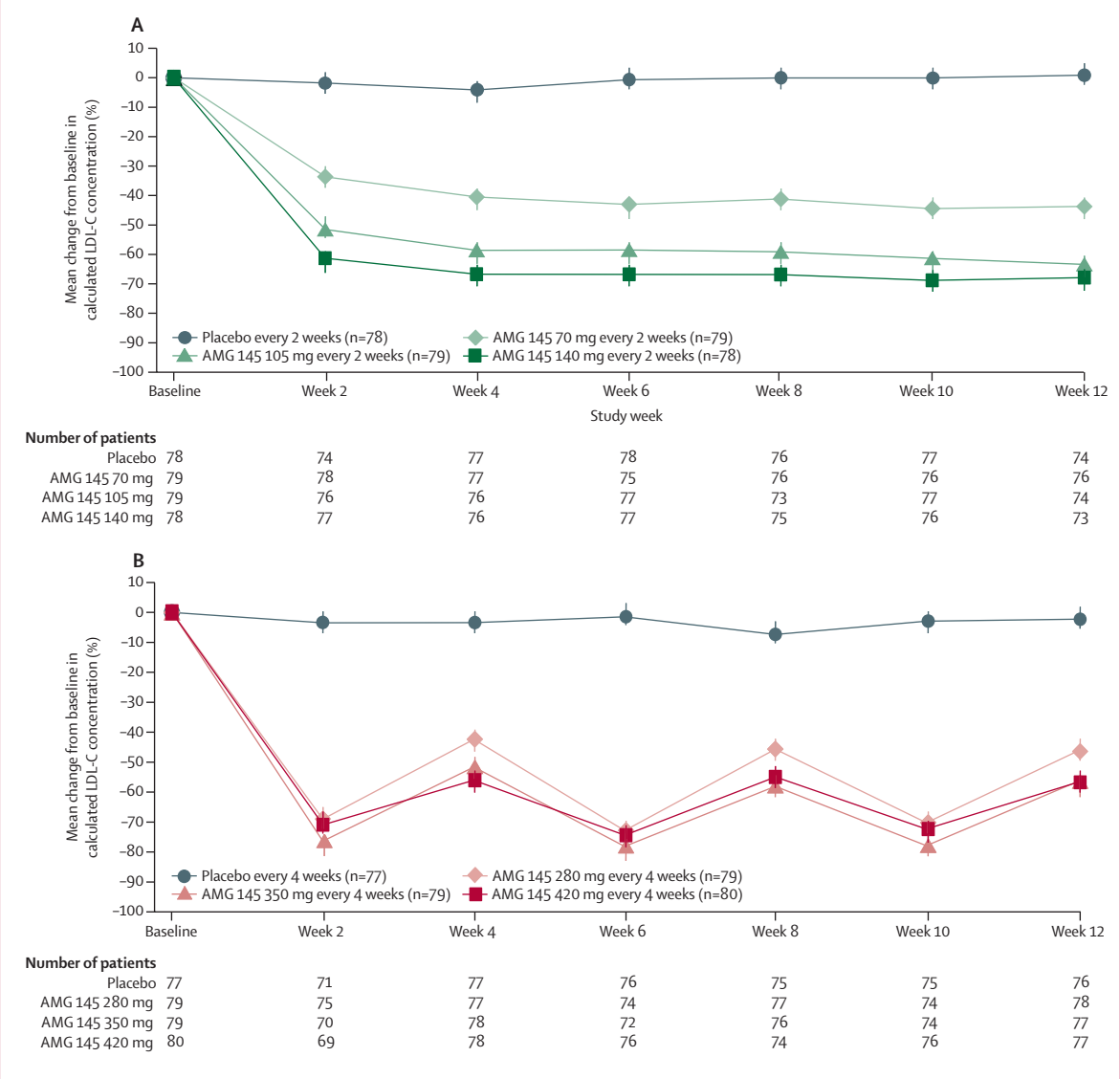


Figure 3: **Percentage change in calculated LDL-C concentration in 2 week intervals from baseline to week 12 in groups assigned to treatment every 2 weeks (A) and every 4 weeks (B)**

Data are mean (SE), with no imputation for missing data. Error bars indicate SE. The numbers of patients for whom data were available at each visit are shown. LDL-C=LDL-cholesterol.

treatment, and ezetimibe use were consistent with the primary results (figure 2). In patients in the AMG 145 420 mg every 4 weeks group with a baseline PCSK9 concentration below the median, the percentage change in ultracentrifugation LDL-C concentration adjusted for placebo was –43·7% (95% CI –52·8 to –34·6) and in those with a baseline PCSK9 concentration equal to or greater than the median the change was –55·2% (–62·8 to –47·6). The p value for the interaction was 0·0482 and this interaction was not noted in the other AMG 145 dose groups (data not shown).

Figure 3 shows the percentage change in calculated LDL-C concentration from baseline in 2 week intervals. The three dose regimens of AMG 145 every 2 weeks reduced the mean calculated LDL-C concentrations by 34–61% (absolute decrease 1·0–1·8 mmol/L) 2 weeks after the first dose (end of the dosing interval; figure 3A). At week 12, 2 weeks after the final dose was administered, the mean calculated LDL-C concentration was reduced by 44–68% (figure 3A). The three dose regimens of AMG 145 every 4 weeks reduced the mean calculated LDL-C concentration by 69–76% (absolute reduction 2·1–2·3 mmol/L) 2 weeks after the initial administration (midpoint of the scheduled dosing interval), which was nearly identical to that achieved 2 weeks after the third dose (week 10; figure 3B). At 4 weeks after the initial dose (end of the dosing interval), the three groups treated every 4 weeks had mean reductions in calculated

LDL-C concentrations of 42–56% (absolute reduction 1·3–1·7 mmol/L), which were similar to those 4 weeks after the second and third doses (weeks 8 and 12, respectively; figure 3B).

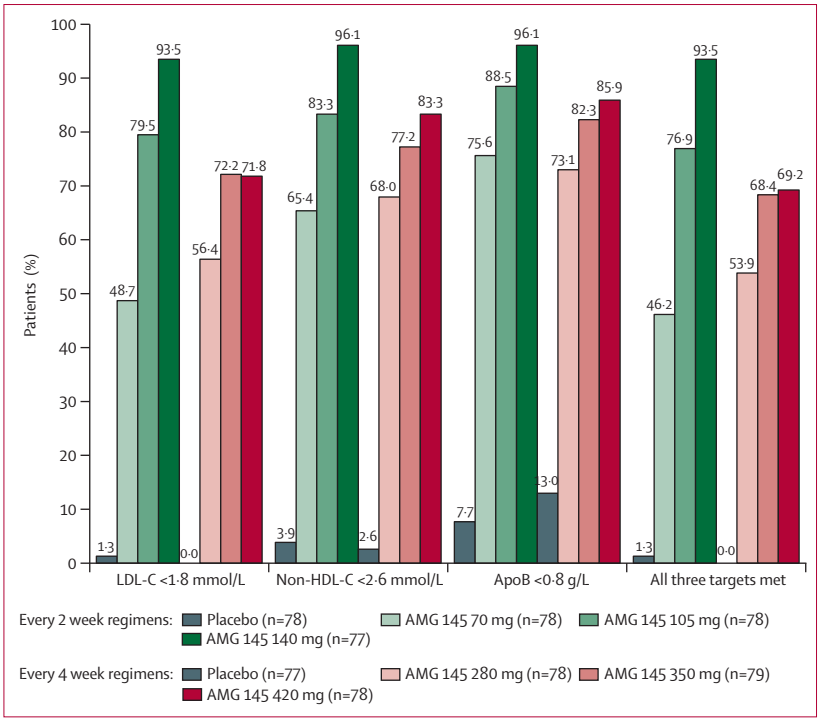


Figure 4: **Frequency of attainment of lipoprotein targets at week 12**
The percentage of patients who achieved concentrations of LDL-C of less than 1·8 mmol/L by ultracentrifuge, non-HDL-C of less than 2·6 mmol/L, ApoB of less than 0·8 g/L, and all three of these lipoprotein targets are shown for each of the eight groups after 12 weeks of treatment. Trend p<0·0001 for every 2 weeks and every 4 weeks groups for each of the four measures. LDL-C=LDL cholesterol. Non-HDL-C=non-HDL cholesterol. ApoB=apolipoprotein B.

In the subset of patients who had additional measurements of LDL-C concentrations during the dosing intervals, AMG 145 140 mg every 2 weeks resulted in a mean reduction versus placebo at week 9 (1 week after dosing) of 85·0% (SE 7·5) and AMG 145 420 mg every 4 weeks in a fall of 70·4% (6·7) at week 9 (1 week after dosing; appendix pp 18–19). The mean absolute calculated LDL-C concentrations in the two groups at week 9 were 0·49 mmol/L (SD 0·32) and 0·67 mmol/L (0·37).

There were significant reductions from baseline at week 12 compared with placebo in the secondary endpoints of absolute change in LDL-C concentration with ultracentrifugation and the percentage change in non-HDL-C and apolipoprotein B concentrations, and ratios of total cholesterol to HDL-C and apolipoprotein B to apolipoprotein A1 (p<0·0001 for each dose *vs* placebo for each parameter; table 2). All dose regimens of AMG 145 also significantly reduced total cholesterol, triglycerides, VLDL-cholesterol (VLDL-C), and PCSK9 concentrations compared with placebo (table 2). PCSK9 concentrations were reduced by 46·3–72·5% compared with placebo (p<0·0001; table 2). Five of the AMG 145 dose regimens increased HDL-C concentration by 4·5–8·1% compared with placebo (table 2).

All AMG 145 dose regimens were more likely than was placebo at week 12 to reduce the ultracentrifugation LDL-C concentration to less than 1·8 mmol/L (ranging from 49% to 94% with AMG 145 regimens administered every 2 weeks *vs* 1% with placebo; ranging from 56% to 72% with AMG 145 regimens every 4 weeks *vs* 0 with placebo; p<0·0001 for each pairwise comparison *vs* placebo; figure 4). Additionally, the frequency of achievement of target concentrations of non-HDL-C (<2·6 mmol/L), apolipoprotein B (<0·8 g/L), and all three lipid parameters

	Placebo every 2 weeks (n=78)	AMG 145 70 mg every 2 weeks (n=79)	AMG 145 105 mg every 2 weeks (n=79)	AMG 145 140 mg every 2 weeks (n=78)	Placebo every 4 weeks (n=77)	AMG 145 280 mg every 4 weeks (n=79)	AMG 145 350 mg every 4 weeks (n=79)	AMG 145 420 mg every 4 weeks (n=80)
All adverse events	33 (42%)	41 (52%)	52 (66%)	43 (55%)	38 (49%)	45 (57%)	48 (61%)	48 (60%)
Serious adverse events	4 (5%)	0	1 (1%)	4 (5%)	0	2 (3%)	2 (3%)	2 (3%)
Leading to drug discontinuation	0	0	0	2* (3%)	0	0	0	0
Treatment-related adverse events†	7 (9%)	4 (5%)	9 (11%)	4 (5%)	4 (5%)	6 (8%)	7 (9%)	9 (11%)
Leading to drug discontinuation	0	0	0	0	0	0	0	0
Injection-site reactions	2 (3%)	1 (1%)	1 (1%)	0	1 (1%)	2 (3%)	3 (4%)	1 (1%)
AST or ALT greater than three times ULN	1 (1%)	0	0	0	0	0	0	0
Creatine phosphokinase greater than five times ULN‡	0	1 (1%)	1 (1%)	1 (1%)	0	0	0	1 (1%)
Positively adjudicated clinical cardiovascular events§	1 (1%)	1 (1%)	0	4 (5%)	0	1 (1%)	1 (1%)	0
All-cause mortality	0	0	0	1 (1%)	0	0	0	0

Data are number (%). AST=aspartamine aminotransferase. ALT=alanine aminotransferase. ULN=upper limit of normal. *Both events were reported as non-serious by the investigators; one patient developed an asymptomatic creatine phosphokinase greater than ten times ULN that on repeat testing 1 week later was normal, and one patient stopped study drug because of fatigue that began the day after the first dose. †All 50 treatment-related adverse events were reported as non-serious by the investigator and none led to discontinuation of drug. ‡All were asymptomatic. §Acute coronary syndrome, coronary revascularisation, transient ischaemic attack, congestive heart failure requiring hospital admission, or death.

Table 3: **Adverse events**

(LDL-C, non-HDL-C, and apolipoprotein B) simultaneously were significantly higher with AMG 145 than with placebo (figure 4). AMG 145 140 mg every 2 weeks simultaneously achieved an LDL-C concentration of less than 1·8 mmol/L, non-HDL-C of less than 2·6 mmol/L, and apolipoprotein B of less than 0·8 g/L in 72 (94%) of 77 patients.

Adverse events were reported in 348 (55%) of 629 patients given the study drug, with a higher frequency in those given AMG 145 (277 [58%] of 474) than in those given placebo (71 [46%] of 155; table 3). The most commonly reported adverse events (appendix pp 20–44) in the AMG 145 group were nasopharyngitis (48 [10%] *vs* 11 [7%] in placebo group), cough (16 [3%] *vs* three [2%], respectively), and nausea (15 [3%] *vs* one [0·6%], respectively)—none of which were significantly different between AMG 145 and placebo. There was no evidence of an association between the dose or frequency of AMG 145, ultracentrifugation LDL-C concentration achieved at week 12, and the frequency of adverse events (data not shown). The incidence of adverse events that the investigator judged as related to study drug were similar in patients treated with AMG 145 (39 [8%] of 474) and placebo (11 [7%] of 155). None of the 474 patients given AMG 145 had severe (grade 3) or life-threatening (grade 4) adverse events that the investigator judged as related to the drug.

Overall 11 (2%) of 629 patients reported injection-site reactions (eg, pruritis, erythema, haematoma, or pain), of which three (2%) of 155 were in the placebo group and eight (2%) of 474 were in the AMG 145 groups (p=0·81), with no differences in frequencies between the groups. The rates of missed doses were infrequent and similar for the every 2 weeks (33 [2%] of 1884) and every 4 weeks (19 [2%] of 945) dose groups. No patients developed anti-AMG 145 antibodies, neutropenia, or vasculitis. There were no changes in laboratory or electrocardiographic parameters from baseline in the different dose groups or compared with placebo.

11 adjudicated clinical cardiovascular events were reported in eight patients—three percutaneous coronary interventions, two non-fatal myocardial infarctions and two coronary bypass graft surgeries, and one each of cardiovascular death (sudden death leading to a motor vehicle accident), congestive heart failure leading to hospital admission, unstable angina requiring hospital admission, and transient ischaemic attack (table 3; appendix p 45). There were no imbalances in cardiovascular events between groups.

Discussion

AMG 145 significantly reduced the LDL-C concentration from baseline compared with placebo by up to 66% at the end of the dosing interval in stable patients with hypercholesterolaemia already treated with a statin. The addition of AMG 145 to background treatment with statin, with or without ezetimibe, helped most patients achieve an LDL-C concentration of 1·8 mmol/L; 94% achieved this concentration with AMG 140 mg every 2 weeks (panel). Additionally, all regimens of AMG 145 significantly reduced concentrations of non-HDL-C, apolipoprotein B, VLDL-C, and triglycerides, and ratios of total cholesterol to HDL-C, and apolipoprotein B to apolipoprotein A1 compared with placebo, thus helping most patients achieve the most stringent targets of several lipid subfractions recommended in current guidelines.[9–11] Although an increase in HDL-C concentration was noted with most of the AMG 145 regimens, the effect was small, and only one group had a significant increase in apolipoprotein A1 concentration. We speculate that the changes in HDL-C concentrations are mediated by a reduced ability for cholesterol to be transferred from HDL-C to LDL-C, rather than a direct effect on HDL-C production or clearance.

As expected, the reductions in LDL-C concentrations in between the administration of doses were greater than those at the end of the dosing interval; the highest doses of every 2 weeks and every 4 weeks of AMG 145 reduced calculated LDL-C concentration by 85·0% and 70·4%, respectively, 1 week after the dose. The numbers of patients in these analyses were smaller than the number in the full cohort and thus the exact magnitude of this effect will benefit from further validation. Comprehensive analyses of serial AMG 145, PCSK9, and LDL-C concentrations in patients in the pharmacokinetic and pharmacodynamic substudy are in progress and should provide additional information about the dose-response relation. Nonetheless, for the every 2 weeks, and particularly the every 4 weeks regimens, the returns at the higher end of the dose range seemed to diminish. In terms of an every 2 weeks versus an every 4 weeks regimen, whether the maximum transient effect on LDL-C concentration or area under the curve is more important is not known; however, both daily administration of statins and fortnightly LDL-C apheresis[12] (which has a maximum effect in the first 2 weeks, after which there is a rapid return towards baseline) are effective

Panel: Research in context

Systematic review

We searched PubMed for all articles published in the past 10 years with titles or abstracts containing the MeSH terms "PCSK9" or "proprotein convertase subtilisin/kexin" in the title or abstract. We found only one other PCSK9 inhibitor (SAR236553/REGN727) for which results in people have been reported.

Interpretation

Subcutaneous administration of the human PCSK9 antibody AMG 145 70–140 mg every 2 weeks or 280–420 mg every 4 weeks greatly reduced the concentrations of LDL-cholesterol and other apolipoprotein-B-containing atherogenic lipoproteins compared with placebo. AMG 145 was well tolerated with no adverse safety signals during this 12 week study. The clinical benefit and long-term safety of AMG 145 needs to be assessed in further trials.

in reducing the occurrence of cardiovascular events. Because the effect on LDL-C concentration varies over time with periodic dosing of a monoclonal antibody inhibitor of PCSK9, measurement of LDL-C concentrations both during and at the end of a dosing interval might be helpful. In view of the substantial reductions in LDL-C concentrations in our study, both every 2 weeks and every 4 weeks regimens would seem to be options to offer patients with a trade off between volume and frequency of injections.

AMG 145 was well tolerated, with no dose-related or dose-frequency-related increase in the reported adverse events. However, over 12 weeks, few patients had a serious adverse event, reducing our statistical power to detect imbalances. Additional information about the safety of long-term administration in terms of clinical, laboratory, and immune reactions is being gathered in two studies with a planned total enrolment of about 2000 patients (NCT01439880 and NCT01516879). Although the patients had high risk of cardiovascular disease, this trial was not powered to detect a difference in the rates of clinical cardiovascular events, which were, as expected, infrequent during the 12 weeks of follow-up.

Our results extend the findings reported with another PCSK9 antibody,[13–15] thus providing further evidence for the important part that this protease plays in the disposition of circulating LDL-C. In the absence of direct comparisons between AMG 145 and SAR236553/REGN727, an indirect comparison (with different methods for measurement of LDL-C concentrations) seems to show similar percentage changes in LDL-C concentrations adjusted for placebo at 12 weeks with the highest doses of AMG 145 (140 mg) every 2 weeks compared with SAR236553/REN727 (150 mg) as reported in a phase 2 trial of patients with hypercholesterolaemia on atorvastatin (66% and 67%, respectively).[14] In a similar comparison of the highest doses every 4 weeks tested in these two studies, the percentage reductions in LDL-C concentration at 12 weeks adjusted for placebo with AMG 145 420 mg and SAR236553/REGN727 300 mg were 50% and 43%, respectively.

Our study differs from the other trials of PCSK9 inhibitors in several important ways. The substantially (greater than three times) larger size of LAPLACE-TIMI 57 (631 enrolled, 474 given AMG 145) provides increased precision in terms of the lipid-lowering efficacy and tolerability of PCSK9 inhibition in patients with hypercholesterolaemia, and important insights into the dosing interval. Patients were broadly representative of those with hypercholesterolaemia, although as is common practice in phase 2 studies of lipid lowering, patients with serious comorbidities and those taking lipid-lowering drugs other than statin or ezetimibe were excluded. Whereas in previous studies with other members of this class of drug,[13–15] patients with a baseline LDL-C concentration of less than 2·6 mmol/L were excluded, we included 115 patients with LDL-C concentrations of less than 2·6 mmol/L, which is clinically relevant because 2·6 mmol/L is greater than the optimum targets recommended in current guidelines[9–11] for patients at highest risk of future cardiovascular events. To better represent clinical practice, we encouraged physicians to use intensive regimens of any statin at any dose to achieve the ideal LDL-C concentration for their patients. By contrast with previous studies of patients without familial hypercholesterolaemia, we permitted the use of ezetimibe in addition to statin. Importantly, we noted that there was a consistent reduction in LDL-C concentration irrespective of the potency of statin or the use of ezetimibe (although the low proportion of patients on ezetimibe reduces our ability to draw definitive conclusions), as might be expected on the basis of the different mechanisms of actions of these drugs. However, bile-acid sequestrants, nicotinic acid (>200 mg/day), and fibrates were not permitted, and thus the effect of AMG 145 in patients also taking these drugs is not known.

Because statins upregulate PCSK9,[16] the addition of a PCSK9 inhibitor to high-dose statin (with or without ezetimibe) might provide an effective option for patients who cannot achieve their target LDL-C concentration despite available oral treatments, including patients with or without familial hypercholesterolaemia. Of note, with the AMG 145 140 mg every 2 weeks regimen, 94% of patients achieved an LDL-C concentration of less than 1·8 mmol/L, with a mean of 1·1 mmol/L (SD 0·6). Similar low concentrations of cholesterol occurring naturally in selected populations have been associated with very low rates of coronary heart disease,[17] suggesting that intense pharmacological inhibition of PCSK9 could further reduce the occurrence of cardiovascular events substantially for many patients.

In conclusion, our findings support the idea that PCSK9 inhibition could offer a new model for lipid management that next requires a large phase 3 clinical trial with several years of follow-up to investigate the long-term clinical efficacy and safety of AMG 145 in patients at increased risk of cardiovascular events.

Contributors

RPG, NRD, PK, MSS, TL, SMW, and RSc jointly conceived and designed the study. RPG, NRD, PK, RSo, STM, TEA, SMW, RSc, and MSS supervised the trial. RSo, SMW, and RSc acquired the data. RPG, NRD, PK, WJR, RSo, FH, TL, SM, EBH, SMW, RSc, and MSS analysed and interpreted the data. SM and EBH did the statistical analyses. RPG and MSS supervised the analyses. RPG drafted the initial report and all coauthors revised the report and approved the final version.

Conflicts of interest

RPG, NRD, PK, SM, EBH, STM, TEA, and MSS received research grant support through Brigham and Women's Hospital for this trial from Amgen. RPG and MSS also have served as consultants for Amgen. WJR received research grant support for participation in this trial from Amgen. RSo, FH, TL, SMW, and RSc are employees of Amgen and own Amgen stock. MSS also received research grant support through Brigham and Women's Hospital from AstraZeneca, AstraZeneca/Bristol-Myers Squibb Alliance, Bristol-Myers Squibb/Sanofi-Aventis Joint Venture, Daiichi-Sankyo, Genzyme, Sanofi-Aventis, Merck, and Pfizer, and received honoraria for consulting from Aegerion, Sanofi-Aventis, GlazoSmithKline, Merck, and Pfizer.

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References

1 O'Keefe JH Jr, Cordain L, Harris WH, Moe RM, Vogel R. Optimal low-density lipoprotein is 50 to 70 mg/dl: lower is better and physiologically normal. *J Am Coll Cardiol* 2004; **43:** 2142–46.

2 Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010; **376:** 1670–81.

3 Waters DD, Brotons C, Chiang CW, et al. Lipid treatment assessment project 2: a multinational survey to evaluate the proportion of patients achieving low-density lipoprotein cholesterol goals. *Circulation* 2009; **120:** 28–34.

4 Murphy SA, Cannon CP, Wiviott SD, McCabe CH, Braunwald E. Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compared with moderate lipid-lowering statin therapy after acute coronary syndromes from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) trial. *J Am Coll Cardiol* 2009; **54:** 2358–62.

5 Artenstein AW, Opal SM. Proprotein convertases in health and disease. *N Engl J Med* 2011; **365:** 2507–18.

6 Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006; **354:** 1264–72.

7 Dias CS, Shaywitz AJ, Wasserman SM, et al. Effects of AMG145 on low-density lipoprotein cholesterol levels: Results from 2 randomized, double-blind, placebo-controlled, ascending-dose phase 1 studies in healthy volunteers and hypercholesterolemic subjects on statins. *J Am Coll Cardiol* 2012; published online Oct 17. http://dx.doi.org/10.1016/j.jacc.2012.08.986.

8 Kohli P, Desai NR, Giugliano RP, et al. Design and rationale of the LAPLACE-TIMI 57 Trial: a phase II, double-blind, placebo-controlled study of the efficacy and tolerability of a monoclonal antibody inhibitor of PCSK9 in subjects with hypercholesterolemia on background statin therapy. *Clin Cardiol* 2012; **35:** 385–91.

9 Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; **110:** 227–39.

10 Genest J, McPherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult—2009 recommendations. *Can J Cardiol* 2009; **25:** 567–79.

11 Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011; **32:** 1769–818.

12 Mabuchi H, Koizumi J, Shimizu M, et al. Long-term efficacy of low-density lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia. Hokuriku-FH-LDL-Apheresis Study Group. *Am J Cardiol* 1998; **82:** 1489–95.

13 Stein EA, Mellis S, Yancopoulos GD, et al. Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. *N Engl J Med* 2012; **366:** 1108–18.

14 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:** 2344–53.

15 Stein EA, Gipe D, Bergeron J, et al. 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.

16 Dubuc G, Chamberland A, Wassef H, et al. Statins upregulate PCSK9, the gene encoding the proprotein convertase neural apoptosis-regulated convertase-1 implicated in familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol* 2004; **24:** 1454–59.

17 Chen Z, Peto R, Collins R, MacMahon S, Lu J, Li W. Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. *BMJ* 1991; **303:** 276–82.