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.