Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 5, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.09.048

AMG 145, a Monoclonal Antibody Against PCSK9, Facilitates Achievement of National Cholesterol Education Program–Adult Treatment Panel III Low-Density Lipoprotein Cholesterol Goals Among High-Risk Patients

An Analysis From the LAPLACE–TIMI 57 Trial (LDL-C Assessment with PCSK9 monoclonaL Antibody Inhibition Combined With Statin thErapy–Thrombolysis In Myocardial Infarction 57)

Nihar R. Desai, MD, MPH,* Robert P. Giugliano, MD, SM,* Jing Zhou, MS,* Payal Kohli, MD,† Ransi Somaratne, MD,‡ Elaine Hoffman, PHD,* Thomas Liu, PHD,‡ Robert Scott, MD,‡ Scott M. Wasserman, MD,‡ Marc S. Sabatine, MD, MPH*

Boston, Massachusetts; and San Francisco and Thousand Oaks, California

Objectives This study sought to define the ability of AMG 145, a monoclonal antibody directed against proprotein convertase subtilisin kexin type 9 (PCSK9), to enable subjects at high risk for major adverse cardiovascular events to achieve National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATP III) parameters for low-density lipoprotein cholesterol (LDL-C) and other lipid goals.

Background Many patients at high risk for adverse cardiovascular events are unable to achieve the NCEP-ATP III LDL-C goal of <70 mg/dl, even with high-potency statin therapy.

Methods In 282 subjects from the LAPLACE–TIMI 57 (LDL-C Assessment with PCSK9 monoclonaL Antibody Inhibition Combined With Statin thErapy–Thrombolysis In Myocardial Infarction 57) trial at high risk according to NCEP-ATP III criteria, we compared the proportion of subjects achieving the NCEP-ATP III recommended LDL-C goal of <70 mg/dl across treatment arms. Other outcomes included the triple goals of LDL-C <70 mg/dl, non–high-density lipoprotein cholesterol (HDL-C) <100 mg/dl, and apolipoprotein B (ApoB) <80 mg/dl.

Results During the dosing interval, more than 90% of subjects in both of the top dose groups every 2 weeks and every 4 weeks attained this lipid target over the dosing interval, with similar success rates for the triple lipid goal.

Conclusions PCSK9 inhibition with AMG 145 enables high-risk patients to achieve established lipid goals. If this therapy demonstrates efficacy for reducing cardiovascular events with a favorable safety profile in ongoing phase 3 trials, we believe it will have major public health implications. (J Am Coll Cardiol 2014;63:430–3) © 2014 by the American College of Cardiology Foundation

From the *TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; †Division of Cardiovascular Medicine, University of California at San Francisco, San Francisco, California; and ‡Amgen, Inc., Thousand Oaks, California. The LAPLACE–TIMI 57 trial was supported by a research grant from Amgen, Inc., to the TIMI Study Group, Brigham and Women's Hospital, Boston, Massachusetts. Dr. Giugliano has received research grant support through Brigham and Women's Hospital from Daiichi Sankyo and Merck; and honoraria for consulting from Amgen, Daiichi Sankyo, and Merck. Drs. Somaratne, Liu, Scott, and Wasserman are employees of Amgen and own Amgen stock. Dr. Sabatine has received research grant support through Brigham and Women's Hospital from Abbott Laboratories, Accumetrics, Amgen, AstraZeneca, AstraZeneca/Bristol-Myers Squibb Alliance, Bristol-Myers Squibb/Sanofi-Aventis joint venture, Critical Diagnostics, Daiichi Sankyo, Eisai, Genzyme, GlaxoSmithKline, Intarcia, Merck, Nanosphere, Roche Diagnostics, Sanofi-Aventis, and Takeda; and honoraria for consulting from Aegerion, Amgen, AstraZeneca/Bristol-Myers Squibb Alliance, GlaxoSmithKline, Merck, Pfizer, Sanofi-Aventis, and Vertex. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 27, 2013; revised manuscript received August 27, 2013, accepted September 19, 2013.

The National Cholesterol Education Program (NCEP)-Adult Treatment Panel III (ATP III) recommends that low-density lipoprotein cholesterol (LDL-C) concentration be lowered to <100 mg/dl in patients with established cardiovascular (CV) disease or CV disease equivalents. In 2004, the guidelines were updated with an optional goal of <70 mg/dl (1). However, contemporary analyses demonstrate that many patients at high risk for adverse CV events are unable to achieve an LDL-C level of <70 mg/dl, even with high-potency statin therapy (2,3). Thus, additional treatment options are needed.

AMG 145, a fully human, monoclonal, immunoglobulin G2 (IgG2) antibody to proprotein convertase subtilisin kexin type 9 (PCSK9), led to significant, dose-dependent reductions in LDL-C of up to 66% in the LAPLACE–TIMI 57 (LDL-C Assessment with PCSK9 monoclonaL Antibody Inhibition Combined With Statin thErapy–Thrombolysis In Myocardial Infarction 57) trial (4). We sought to define the ability of treatment with AMG 145 to enable subjects at high risk for adverse CV events in the LAPLACE–TIMI 57 trial to achieve NCEP-ATP III LDL-C and other lipid goals.

Methods

The design and primary results of LAPLACE–TIMI 57 have been reported previously (4). Briefly, the study was a phase 2, double-blind, placebo-controlled, dose-ranging study comparing AMG 145 (in doses of 70, 105, and 140 mg every 2 weeks or 280, 350, and 420 mg every 4 weeks) versus placebo in 631 subjects with hypercholesterolemia and LDL-C concentrations >85 mg/dl on a stable dose regimen of statin therapy with or without ezetimibe. LDL-C was measured by preparative ultracentrifugation (UC-LDL-C) at baseline, day 1, and week 12 and calculated using the Friedewald equation on a fasting lipid sample at weeks 2, 4, 6, 8, and 10. This pre-specified subgroup analysis included 282 subjects at high risk as defined by NCEP-ATP III guidelines (i.e., with coronary heart disease [CHD] or CHD risk equivalents) who received the study drug and had LDL-C measurements taken at the end of the study.

The primary outcome of this analysis was the proportion of subjects who achieved the NCEP-ATP III recommended LDL-C concentration of <70 mg/dl at week 12, measured with UC-LDL-C. Secondary outcomes included the proportion of subjects who simultaneously achieved an UC-LDL-C <70 mg/dl, a non–high-density lipoprotein cholesterol (HDL-C) concentration of <100 mg/dl, and an apolipoprotein B (ApoB) concentration of <80 mg/dl and the proportion of subjects who achieved ≥50% reduction in UC-LDL-C at week 12.

A Cochrane-Armitage test for trend was used to analyze the differences among all the groups in the proportion of patients who achieved the lipid goals described above. For all analyses, p values of <0.05 were considered significant. See the Online Appendix for further details.

Results

Of the 631 randomized subjects in the LAPLACE–TIMI 57 trial, 284 (45%) were high-risk patients based on NCEP-ATP III definitions. There were no significant differences in baseline characteristics across the randomized treatment arms or among patients when pooled for placebo versus AMG 145 treatment (Online Table 1).

Of the 284 high-risk patients, 282 (99.3%) received at least 1 dose of the study drug and had LDL-C measured by UC at week 12. Among this group, each dose of AMG 145 significantly reduced UC-LDL-C from baseline to week 12 compared with placebo (Online Fig. 1) by up to 64% for the AMG 145 group treated every 2 weeks and up to 45% for the AMG 145 group treated every 4 weeks ($p < 0.001$ for each dose compared with placebo). The lowest mean ± SD of the UC-LDL-C levels achieved at week 12 were 47 ± 30 mg/dl and 59 ± 29 mg/dl, respectively. The distribution of baseline and UC-LDL-C levels achieved at 12 weeks among subjects receiving an AMG 145 dosage of 140 mg every 2 weeks is shown in Online Figure 2.

Compared with placebo, each dose of AMG 145 significantly increased the proportion of patients who achieved the NCEP-ATP III recommended LDL-C of <70 mg/dl at week 12 ($p < 0.001$ for each dose) (Fig. 1), with 90% and 70%

Abbreviations and Acronyms

ApoB = apolipoprotein B
CAD = coronary artery disease
CHD = coronary heart disease
CV = cardiovascular
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
NCEP-ATP III = National Cholesterol Education Program-Adult Treatment Panel III
NHANES = National Health and Nutrition Examination Survey
UC = ultracentrifugation
ULN = upper limit of normal

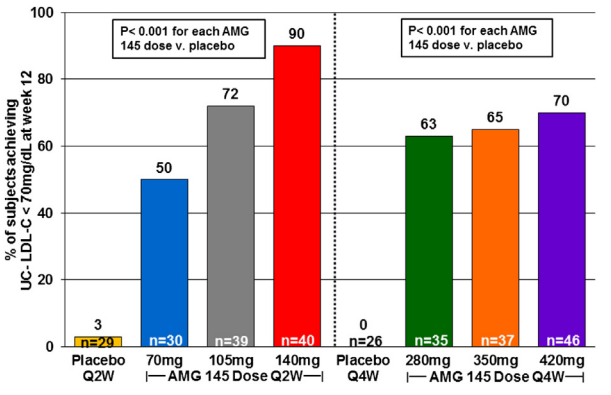

Figure 1 LDL-C Goal Attainment at Week 12

Percentages of high-risk subjects achieving NCEP-ATP III LDL-C levels <70 mg/dl at week 12 by treatment arm are shown. LDL-C at week 12 was measured using ultracentrifugation. LDL-C = low-density lipoprotein cholesterol; NCEP-ATP III = National Cholesterol Education Program–Adult Treatment Panel III; Q2W = every 2 weeks; UC = ultracentrifugation.