Efficacy and Safety of Alirocumab Versus Ezetimibe Over 2 Years (from ODYSSEY COMBO II)

Mahfouz El Shahawy, MD\(^a\,\,b\), Christopher P. Cannon, MD\(^b\), Dirk J. Blom, MMed, PhD\(^c\), James M. McKenney, PharmD\(^d\), Bertrand Cariou, MD, PhD\(^e\), Guillaume Lecorps, MSc\(^f\), Robert Pordy, MD\(^g\), Umesh Chaudhari, and Helen M. Colhoun, MD\(^h\)

The proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab has been shown to substantially reduce low-density lipoprotein cholesterol (LDL-C). Demonstrating whether efficacy and safety are maintained over a long duration of exposure is vital for clinical decision-making. The COMBO II trial compared the efficacy and safety of alirocumab versus ezetimibe over 2 years. A prespecified first analysis was reported at 52 weeks. Here we report the final end-of-study data (on-treatment) and evaluate post hoc the safety profile with longer versus shorter duration of alirocumab exposure. Patients (n = 720) on maximally tolerated statin dose were treated with alirocumab (75/150 mg every 2 weeks) or ezetimibe (10 mg/day). Overall mean adherence for both treatment groups during the first and second year was >97%. At 2 years, LDL-C was reduced by 49% (alirocumab) versus 17% (ezetimibe; p < 0.0001), and LDL-C <70 mg/dl was achieved by 73% of alirocumab-treated versus 40% of ezetimibe-treated patients. Overall safety was similar in both treatment groups at 2 years and during the first versus the second year. Local injection-site reactions were reported by 2.5% (alirocumab) versus 0.8% (ezetimibe) during the first year, and 0.2% versus 0.5% during the second year, indicating early occurrence during prolonged alirocumab exposure. Two consecutive calculated LDL-C values <25 mg/dl were observed in 28% of alirocumab-treated patients (vs 0.4% with ezetimibe). Persistent anti-drug antibody responses were observed in 1.3% (6 of 454) of alirocumab-treated versus 0.4% (1 of 231) of ezetimibe-treated patients. Neutralizing antibodies (that inhibit binding in vitro) were observed in 1.5% (7 of 454) of alirocumab-treated patients (0 with ezetimibe), mostly at isolated time points. Alirocumab sustained substantial LDL-C reductions and was well tolerated up to 2 years in the COMBO II trial. © 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). (Am J Cardiol 2017;**;****;****).

Alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, reduces low-density lipoprotein cholesterol (LDL-C) levels by up to 61% in addition to statins ± lipid-lowering therapies.\(^1\)\(^-\)\(^3\) The ODYSSEY Phase 3 COMBO II (NCT01644188) trial evaluated the efficacy and safety of alirocumab versus ezetimibe in reducing LDL-C in patients at high risk of cardiovascular (CV) events on maximally tolerated statin dose (MTD, defined in the supplement) who were not at pre-specified LDL-C target levels.\(^4\)\(^,\)\(^5\) At 24 weeks, alirocumab reduced LDL-C by 51% (vs 21% with ezetimibe), corresponding to achieved LDL-C levels of 52 mg/dl and 83 mg/dl, respectively.\(^5\) An important consideration is whether the number and nature of adverse events (AEs) change following long-term alirocumab exposure, considering the recent data on the variability in efficacy and AEs related to immunogenicity seen on treatment with bococizumab, another PCSK9 antibody.\(^6\)\(^,\)\(^7\) Here we report the final end-of-study efficacy and safety data from the COMBO II trial to evaluate whether the effect of alirocumab versus ezetimibe is sustained for up to 2 years. We also compared post hoc the treatment adherence, safety, and the incidence of AEs in the first year versus the second year of the study.

Methods

Detailed methods and patient disposition have been reported previously (Figure 1).\(^4,\)\(^5\) Briefly, the multinational, multicenter, double-blind, active controlled, parallel-group study included patients with hypercholesterolemia and established coronary heart disease (CHD; defined in the Supplement) or CHD risk equivalents (ischemic stroke, peripheral artery disease, moderate chronic kidney disease, or diabetes mellitus plus ≥2 additional risk factors) not at National Cholesterol Education Program, Adult Treatment Panel III goal despite stable MTD for ≥4 weeks before the screening visit. The goal for patients with documented CV disease was LDL-C <70 mg/dl, or <100 mg/dl for patients without

\(^{\ast}\)Corresponding author: Tel: (941)366-9800; fax: (941)366-2781.
E-mail address: mshahawy@cardiologycenter.net (M. El Shahawy).

\(^{\ast\ast}\)See page ** for disclosure information.
Patients (n = 720) were randomized 2:1 to receive double-blind treatment for 2 years with either subcutaneous alirocumab 75 mg (in 1-ml volume) every 2 weeks (Q2W) (plus oral placebo for ezetimibe daily) or 10 mg oral ezetimibe daily (plus placebo subcutaneous Q2W for alirocumab) and continued to receive their background statin therapy. At week 12, the alirocumab dose was automatically increased to 150 mg Q2W (1-ml volume) if the week 8 LDL-C value was ≥70 mg/dl, while maintaining subject and investigator blinding. There was an 8-week posttreatment observation period following the 2-year (104-week) double-blind period. The protocol was approved by the institutional review boards of participating centers. All participants gave written informed consent. Race was self-reported in this study.

The overall treatment adherence for injections was defined during the treatment period for each patient as follows: 100% − (percentage of days with below-planned dosing + percentage of days with above-planned dosing). Overall treatment adherence rates were analyzed in the first (weeks 0 to 52) and second (weeks 52 to 104) years of treatment (further details in the Supplement). Safety was assessed by analyzing AE reports and laboratory analyses from the time of signed informed consent until the end of the study. AEs were defined as treatment-emergent if they developed, worsened, or became serious during the period between first and last dose of study treatment (planned at week 102) plus 10 weeks (further details in the Supplement).

In addition to overall AE rates up to the end of the study, we also compared (post hoc) the rates of AEs in the first year (weeks 0 to 56) versus the second year (weeks 56 to 112) of the study. If a patient had an event once during weeks 0 to 56 and once during weeks 56 to 112, the 2 events were analyzed separately in the respective time period in which they occurred. Although the last treatment dose was at week 102,
residual effect of alirocumab is expected until 10 weeks after the last injection. The AE follow-up period is 8 weeks following the end-of-treatment visit at week 104; hence, the overall study period was up to 112 weeks. A comparison between weeks 0 to 56 and weeks 56 to 112 was used to allow for equal periods of treatment duration.

The presence of anti-drug antibodies (ADAs) was evaluated at weeks 0, 12, 24, 52, and 104 using a validated, titer-based immunoassay (sensitivity ~5 ng/ml; Regeneron Pharmaceuticals, Inc., Tarrytown, NY; assay details in the Supplement and as reported previously). A persistent ADA response was defined as 2 consecutive positive postbaseline responses separated by a minimum of 12 weeks. Samples positive for ADAs were further examined for neutralizing antibodies (NAbs), which are ADAs that inhibit the binding of alirocumab to PCSK9 in vitro (assay details in the Supplement and previously reported).

All statistical analyses were performed by Sanofi at the direction of the independent investigators, who had access to any relevant data analysis on request in this study. Statistical analyses have been described previously. A mixed-effect model with repeated measures was used to compare changes in LDL-C and other lipoproteins assumed to be normally distributed between alirocumab and ezetimibe patient groups over 2 years. Lipoproteins assumed to be non-normally distributed (i.e., triglycerides and Lp[a]) were analyzed using multiple imputation to handle missing data followed by robust regression model.

Results

Demographic characteristics, disease characteristics, and lipid parameters at baseline were generally similar in the alirocumab group compared with the ezetimibe group, and have been reported previously. Mean (standard deviation [SD]) age at screening was 62 (9.3) years, 74% were male, and 85% were white. Mean (SD) baseline LDL-C levels were 109 (37) and 105 (34) mg/dl in the alirocumab (n = 479) and ezetimibe (n = 241) groups, respectively (Table S1 in the Supplement).

Atherosclerotic cardiovascular disease (ASCVD), which included CHD, ischemic stroke, and peripheral arterial disease, was documented in 95% of patients. Of the total population, 81% had hypertension and 31% had investigator-reported type 2 diabetes mellitus (defined by medical history, Table S1 in the Supplement).

Exposure to investigational medical product injections with ≥102 weeks’ duration was observed in 79% (378 of 479) and 78% (187 of 241) of alirocumab- and ezetimibe-treated patients, respectively. Exposure to investigational medical product capsules with ≥102 weeks’ duration was observed in 81% (381 of 472) and 79% (187 of 237) of alirocumab- and ezetimibe-treated patients, respectively.

The overall mean (SD) treatment adherence over 2 years was high in both groups: 98% (5.1) for the alirocumab-treated and 98% (3.5) for the ezetimibe-treated group. The majority of patients in the alirocumab (98%) and ezetimibe (99%) groups had at least 80% adherence for injections (i.e., patients received ≥80% of their injections on schedule). Similarly, 96% of alirocumab-treated and 98% of ezetimibe-treated patients had at least 80% adherence for capsules. There was no difference in treatment adherence between the first year and the second year of treatment. The overall mean (SD) treatment adherence for both treatment groups during the first and second year of treatment was >97%. The percentage of patients with ≥80% adherence for injections was 99% for both the alirocumab and the ezetimibe groups during the first year and 99% and 98%, respectively, during the second year. Similarly, the percentage of alirocumab-treated patients with ≥80% adherence for capsules was 97% (vs 99% ezetimibe-treated) during the first year and 97% (vs 98% ezetimibe-treated) during the second year.

In the on-treatment analysis, LDL-C was reduced from baseline to week 24 by 52% with alirocumab versus 22% with ezetimibe (least squares [LS] mean difference of −31%, 95% confidence interval [CI] −35 to −26; p < 0.0001; Figure 2). A sustained effect of alirocumab was observed on calculated LDL-C over 2 years with reductions of 49% versus 17% with ezetimibe at 2 years (LS mean difference of −32%, 95% CI −38 to −26; p < 0.0001; Figure 1, Table S2 in the Supplement). Alirocumab treatment for 2 years resulted in mean (standard error) calculated LDL-C values of 54 (1.8) mg/dl versus 87 (2.6) mg/dl on ezetimibe treatment (p < 0.0001). LDL-C <70 mg/dl was achieved by 73% of alirocumab-treated versus 40% of ezetimibe-treated patients at 2 years. Significant (p < 0.0001) reductions from baseline up to 2 years were observed in Lp(a), Apo B, and non−HDL-C levels, whereas HDL-C levels significantly (p < 0.0001) increased with alirocumab versus ezetimibe treatment (LS mean difference of +7.4% for percent change from baseline at 2 years, Figures 2). Triglycerides were reduced from baseline to 2 years by 8.2% in the alirocumab group and by 11.4% in the ezetimibe group, but the difference between treatment arms was not statistically significant (Figure 2).

Over the course of the whole study period, AEs were reported by 391 (82%) alirocumab-treated versus 198 (82%) ezetimibe-treated patients, and serious AEs were reported by 124 (26%) versus 60 (25%) patients, respectively. AEs leading to death occurred in 6 (1.3%) alirocumab-treated versus 6 (2.5%) ezetimibe-treated patients, and AEs leading to discontinuation of study treatment occurred in 44 (9.2%) versus 19 (7.9%) patients, respectively (Table 1).

In AEs of interest, higher rates were observed with alirocumab versus ezetimibe for injection-site reactions and allergic reactions (Table 1). Cataract conditions were observed in 10 (2.1%) alirocumab-treated and 6 (2.5%) ezetimibe-treated patients. Single elevations of alanine and aspartate aminotransferase were observed at higher frequencies with alirocumab versus ezetimibe, whereas creatinine kinase levels were comparable between the 2 groups (Table 1).

A comparison of AE rates between the first year and the second year of the study period identified local injection-site reactions in 12 (2.5%) alirocumab-treated versus 2 (0.8%) ezetimibe-treated patients during the first year, compared with 1 (0.2%) alirocumab-treated versus 1 (0.5%) ezetimibe-treated patient during the second year (Table 2). Of the 12 injection-site reactions reported by alirocumab-treated patients during the first year, 11 (92%) were of mild intensity (vs 2 [100%] in the ezetimibe group) and 1 (8.3%) was of moderate intensity (Table S3 in the Supplement). During the second year, the single (100%) injection-site reaction reported in the alirocumab group was of mild intensity (vs 1 [100%] of severe intensity in the ezetimibe group, Table S3 in the Supplement).
Over the complete 2 years of follow-up, there was no meaningful difference between treatment groups over the study period for ophthalmological events, neurological or neurocognitive disorders, hepatic disorders, or AEs related to diabetes or diabetic complications (Table 1, Table S4 in the Supplement). Overall rates of specific AEs were similar in the alirocumab and ezetimibe groups for the first and the second year (Table 2). In other AEs of interest, rates were similar in the first and the second year of the study (Table 2).

At least 2 consecutive LDL-C values <25 mg/dl were observed in 128 (28%) patients in the alirocumab group (including 45 [9.8%] patients with 2 consecutive LDL-C values <15 mg/dl), of whom 91 (71%) reported at least 1 AE after the first LDL-C <25 mg/dl value (Table 3). The median time to the first calculated LDL-C value <25 mg/dl and <15 mg/dl was 12 and 16 weeks, respectively. Most patients were on 75 mg Q2W alirocumab at the time of the first LDL-C value <25 mg/dl (90%) and <15 mg/dl (88%). Of the 351 alirocumab-treated patients with LDL-C ≥25 mg/dl, 288 (82%) reported any AE (Table 3). The AE profile in patients with 2 consecutive LDL-C values <25 mg/dl was not notably different from the overall population or from patients with LDL-C ≥25 mg/dl, and no safety concerns were reported (Table 3). There were no injection-site reactions reported in these patients: 2 (1.6%) patients with 2 consecutive values of LDL-C <25 mg/dl versus 7 (2.0%) patients with LDL-C ≥25 mg/dl who reported cataracts. One ezetimibe-treated patient had 2 consecutive LDL-C <25 mg/dl values (time to the first value

Figure 2. On-treatment analysis of (A) mean change in calculated LDL-C, and mean percent change from baseline in (B) Lp(a), (C) Apo B, (D) non–HDL-C, (E) HDL-C, and (F) triglycerides over 2 years. *p < 0.0001 vs ezetimibe. Changes in lipoproteins versus study time points on treatment with alirocumab and ezetimibe. Values above and below the data points indicate the percentage reduction from baseline, with percentage differences indicated by the values next to the arrows. Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); LS = least squares; SE = standard error.
of LDL-C < 25 mg/dl was 52 weeks); this patient did not report any AEs.

Persistent ADA responses were observed in 1.3% (6 of 454) of patients administered alirocumab versus 0.4% (1 of 231) of patients administered ezetimibe, with median time of onset being 12 and 52 weeks, respectively (Table S5). The first ADA response was observed in the first year (weeks 0 to 56) of treatment for all patients. ADA responses exhibited low titers, resolved over time, and had no clinical impact on either pharmacokinetics or safety of alirocumab. At least 1 NAb response was observed in 1.5% (7 of 454) of alirocumab-treated patients (mostly at single, isolated time points); no NAb responses were observed in ezetimibe-treated patients (Table S5). NAbs detected by immunoassays were transient and at isolated time points.

Discussion

These data indicate that the efficacy and safety of alirocumab are maintained through 2 years in high-risk patients when administered in addition to MTD at 75 mg Q2W, with potential increase to 150 mg Q2W based on individual LDL-C responses at week 8.

Overall treatment adherence was high in both treatment groups and did not vary between the first and the second year of the treatment period. In the on-treatment analysis, alirocumab resulted in sustained LDL-C reductions and goal achievement compared with ezetimibe, demonstrating superiority of treatment in patients at high CV risk not at LDL-C treatment goal. The slight decrease observed in efficacy at 2 years compared with efficacy at 24 weeks in the alirocumab-treated group was also observed in the ezetimibe-treated group.

The changes in atherogenic lipid levels observed in this study are consistent with those in the overall ODYSSEY trials.
An increase in HDL-C observed

Median
24 (5.0%) 13 (3.2%) 10 (4.1%) 9 (4.3%)

The slightly increased rate of injection-
AEs of special interest

AEs occurring in ≥5% of patients in any of the groups

Infections and infestations
128 (26.7%) 75 (18.2%) 61 (25.3%) 67 (32.1%)

Upper respiratory tract infection
31 (6.5%) 14 (3.4%) 13 (5.4%) 6 (2.9%)

Musculoskeletal and connective tissue disorders
93 (19.4%) 64 (15.6%) 41 (17.0%) 25 (12.0%)

Myalgia
21 (4.4%) 6 (1.5%) 13 (5.4%) 0

Nervous system disorders
78 (16.3%) 39 (9.5%) 38 (15.8%) 24 (11.5%)

Dizziness
21 (4.4%) 9 (2.2%) 13 (5.4%) 6 (2.9%)

Gastrointestinal disorders
76 (15.9%) 37 (9.0%) 30 (12.4%) 31 (14.8%)

Injury, poisoning, and procedural complications
58 (12.1%) 46 (11.2%) 34 (14.1%) 20 (9.6%)

Accidental overdose
29 (6.1%) 22 (5.4%) 17 (7.1%) 5 (2.4%)

Cardiac disorders
58 (12.1%) 26 (6.3%) 28 (11.6%) 21 (10.0%)

General disorders and administration site conditions
56 (11.7%) 24 (5.8%) 25 (10.4%) 13 (6.2%)

Respiratory, thoracic, and mediastinal disorders
43 (9.0%) 20 (4.9%) 21 (8.7%) 16 (7.7%)

Investigations
38 (7.9%) 20 (4.9%) 23 (9.5%) 7 (3.3%)

Skin and subcutaneous tissue disorders
34 (7.1%) 19 (4.6%) 15 (6.2%) 4 (1.9%)

Vascular disorders
34 (7.1%) 27 (6.6%) 21 (8.7%) 14 (6.7%)

Metabolism and nutrition disorders
32 (6.7%) 19 (4.6%) 18 (7.5%) 10 (4.8%)

Psychiatric disorders
21 (4.4%) 9 (2.2%) 12 (5.0%) 4 (1.9%)

Eye disorders
21 (4.4%) 10 (2.4%) 6 (2.5%) 11 (5.3%)

Renal and urinary disorders
20 (4.2%) 17 (4.1%) 12 (5.0%) 8 (3.8%)

AEs of special interest

General allergic reaction
29 (6.1%) 13 (3.2%) 12 (5.0%) 5 (2.4%)

AEs related to diabetes mellitus or diabetic complications
24 (5.0%) 13 (3.2%) 10 (4.1%) 9 (4.3%)

Neurological
13 (2.7%) 7 (1.7%) 6 (2.5%) 5 (2.4%)

Local injection-site reactions
12 (2.5%) 1 (0.2%) 2 (0.8%) 1 (0.5%)

Hepatic disorders
11 (2.3%) 9 (2.2%) 7 (2.9%) 6 (2.9%)

Ophthalmological
7 (1.5%) 2 (0.5%) 1 (0.4%) 3 (1.4%)

Neurocognitive disorder
3 (0.6%) 4 (1.0%) 4 (1.7%) 1 (0.5%)

weeks 0 to 56 versus weeks 56 to 112 included double-blind treatment up to week 104 plus an 8-week follow-up. To have equal time periods for comparison, AEs were analyzed for weeks 0 to 56 and weeks 56 to 112. If a patient had an event once in weeks 0 to 56 and once in weeks 56 to 112, the 2 events were recorded separately in the respective time period they occurred. Certain AEs were grouped as AEs of special interest (prespecified in the phase 3 study protocols), based on identified, potential, and theoretical risks for the new drug class collected during the clinical trial program. These included local injection-site reactions, general allergic events, neurological events, hepatic disorders, and ophthalmological events. Other predefined categories, including AEs related to neurocognitive disorders and diabetes mellitus, were analyzed in the same way as the other AEs of interest, but not specifically defined as AEs of special interest in the protocols. AEs related to diabetes mellitus or diabetic complications are regardless of baseline status. Based on standard or custom Medical Dictionary of Regulatory Activities queries.

COMBO II has been analyzed in a separate study. Median fasting glucose and glycated hemoglobin values up to 2 years in those with and without diabetes were comparable between treatment groups. The slightly increased rate of injection-site reactions in alirocumab-treated patients was seen only in the first year of the study, indicating that these reactions occur early during exposure. The decreased rate of injection-site reactions in the second compared with the first year was unlikely to be due to treatment discontinuation. The AE rates seen in patients with 2 consecutive calculated LDL-C values of <25 mg/dl were similar to the overall alirocumab-treated population.

Administration of alirocumab 75 mg Q2W or 75 mg increased to 150 mg Q2W as an add-on therapy over 2 years...
was associated with low levels of immunogenicity. NAb re-
sponses identified by immunoassays were transient and
observed in 7 alirocumab-treated patients. These responses
do not necessarily impact clinical efficacy; however, a robust
analysis of the efficacy of alirocumab by ADA status in this
study was not possible because of the low patient numbers.

In a pooled analysis of 10 ODYSSEY Phase 3 trials with 4747
patients, including the COMBO II study, ADA and NAb re-
sponses occurred at a low rate and were transient, occurring
at single time points. In the overall ODYSSEY program, mean
reductions in LDL-C were maintained over time in patients
with persistent and NAb responses. Overall, the results of
the post hoc safety analysis up to 2 years reported here are
comparable with those reported previously up to 1.5 years
(78 weeks) in the ODYSSEY LONG TERM study. The
similar safety profile of alirocumab- and ezetimibe-treated pa-
tients in the later time period of the study should be interpreted
cautiously, as patients with AEs reported in the first year may
discontinue treatment. This study was not powered for
analysis of CV events. Pooled post hoc analysis from the
ODYSSEY program indicated a 24% risk reduction in major
adverse CV events per 39 mg/dl lower LDL-C level (hazard
ratio 0.79, 95% CI 0.63 to 0.91). In this study, LDL-C was
reduced by 53 mg/dl with alirocumab at 2 years. Recent clinical
outcomes results with other PCSK9 inhibitors have yielded
promising results.

The ongoing ODYSSEY OUTCOMES study has randomized approximately 18,000 patients to
alirocumab or placebo to evaluate the effect of treatment on
major adverse CV events. These end-of-study data from
COMBO II provide important information for clinicians and
patients on the efficacy and safety of alirocumab co-
administered with MTD.

Disclosures

Dr. El Shahawy reports research support from AstraZeneca,
Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Eli
Lilly & Company, Pfizer, Regeneron Pharmaceuticals, Inc.,
Sanofi, Talsy, and the National Institutes of Health; and has
participated in speaker’s bureau for Amgen, Bristol-Myers
Squibb, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc.,
and Sanofi.

Dr. Cannon has received grant support from Accumedics,
Arisaph, AstraZeneca, Boehringer Ingelheim, CSL Behring,
Essentials, GlaxoSmithKline, Janssen, Merck, Regeneron Pharmaceuticals, Inc., Sanofi, and Takeda; and consultant/advisory board fees from Bristol-Myers Squibb, LipoMedix, and Pfizer.

Dr. Blom has received grants for conducting clinical trials from Sanofi-Aventis, Regeneron Pharmaceuticals, Inc., Novartis, Eli Lilly & Company, Amgen, and Aegerion; honoraria for lectures from Sanofi-Aventis, Regeneron Pharmaceuticals, Inc., Aegerion, Amgen, AstraZeneca, MSD, Pfizer, Servier, and Unilever; advisory board fees from Sanofi-Aventis, Aegerion, Amgen, AstraZeneca, and MSD; travel assistance from Amgen and Aegerion; a fee for chairing a steering committee from Aegerion; a consultancy fee from Gumphire; and nonfinancial support (editorial assistance and statistical analysis) from Sanofi-Aventis and Regeneron Pharmaceuticals, Inc.

Dr. McKenney reports no disclosures.

Dr. Cario reports personal fees from Sanofi, during the conduct of the study; and personal fees from Amgen, Eli Lilly & Company, Genfit, MSD, Novo Nordisk, Pierre Fabre, AstraZeneca, Sanofi, and Regeneron Pharmaceuticals, Inc., outside the submitted work.

Mr. Lecorps and Dr. Chaudhari report they are employees and stockholders of Sanofi.

Dr. Pordy reports he is an employee and stockholder of Regeneron Pharmaceuticals, Inc.

Dr. Colhoun has received research support from Pfizer and Sanofi, and reports grants, personal fees, and nonfinancial support from Sanofi and Regeneron Pharmaceuticals, Inc., during the conduct of the study: grants, personal fees, and nonfinancial support from Eli Lilly & Company, grants and other support from Roche Pharmaceuticals, grants from Pfizer, Boehringer Ingelheim, and AstraZeneca LP; and other support from Bayer, outside the submitted work.

Acknowledgments: The authors would like to thank the patients, their families, and all investigators involved in this study. The following people from the study sponsors provided editorial comments on the manuscript: Jay Edelberg, Tu Nyugen, Michael Howard, and L. Veronica Lee (Sanofi), and William J. Sasiela, Rita Samuel, and Carol Hudson (Regeneron Pharmaceuticals, Inc.). Statistical analyses were performed by Guillaume Lecorps, Sanofi. Dr. El Shahawy MD had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Medical writing support under the direction of the authors was provided by Rob Campbell, PhD, and Aparna Shetty, PhD, of Prime (Knutsford, UK), supported by Sanofi and Regeneron Pharmaceuticals, Inc., according to Good Publication Practice guidelines (Link). The sponsors were involved in the study design, collection, analysis and interpretation of data, as well as data checking of information provided in the article. The authors were responsible for all content and editorial decisions and received no honoraria related to the development of this publication.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, http://dx.doi.org/10.1016/j.amjcard.2017.06.023.
