Original article

Effect of alirocumab on coronary atheroma volume in Japanese patients with acute coronary syndromes and hypercholesterolemia not adequately controlled with statins: ODYSSEY J-IVUS rationale and design

Junya Ako (MD, PhD, FJCC)*, Kiyoshi Hibi (MD, PhD, FJCC), Ken Kozuma (MD, PhD), Katsumi Miyauchi (MD, PhD, FJCC), Yoshihiro Morino (MD, PhD, FJCC), Toshiro Shinke (MD, PhD, FJCC), Kenichi Tsujita (MD, PhD), Kiyoko Uno (MD, PhD), Yumiko Kawabata (MS), Takaumi Hiro (MD, PhD, FJCC)

*Department of Cardiovascular Medicine, Kitasato University Hospital, Sagamihara-City, Kanagawa, Japan
Division of Cardiology, Yokohama City University Medical Center, Yokohama-City, Kanagawa, Japan
Division of Cardiology, Tokyo University Hospital, Itabashi-ku, Tokyo, Japan
Division of Cardiovascular Medicine, Department of Internal Medicine, Juntendo University Hospital, Bunkyo-ku, Tokyo, Japan
Division of Cardiology, Department of Internal Medicine, Iwate Medical University, Morioka-city, Iwate, Japan
Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe-city, Hyogo, Japan
Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto-City, Kumamoto, Japan
Cardiovascular Medical, Sanofi, Shinjuku-ku, Tokyo, Japan
Clinical Sciences and Operations, R&D, Sanofi, Shinjuku-ku, Tokyo, Japan
Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Itabashi-ku, Tokyo, Japan

A R T I C L E   I N F O

Article history:
Received 10 October 2017
Received in revised form 10 October 2017
Accepted 17 November 2017
Available online 30 March 2018

Keywords:
Alirocumab
Low-density lipoprotein cholesterol
Coronary artery disease
Monoclonal antibody

A B S T R A C T

Background: Serial intravascular ultrasound (IVUS) imaging can be used to evaluate the effect of cholesterol-lowering on coronary atheroma progression and plaque volume, with evidence of potential incremental effects with more aggressive lipid-lowering treatments. Alirocumab is a highly specific, fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9). This study will investigate the effect of alirocumab on coronary artery plaque volume in Japanese patients with a recent acute coronary syndrome (ACS) and hypercholesterolemia while on stable statin therapy.

Methods: ODYSSEY J-IVUS is a phase IV, open-label, randomized, blinded IVUS analysis, parallel-group, multicenter study in Japanese adults recently hospitalized for an ACS and who have elevated low-density lipoprotein cholesterol (LDL-C) values (>100 mg/dl [2.6 mmol/L]) at ACS diagnosis and suboptimal LDL-C control on stable statin therapy. Patients will be randomized (1:1) to receive alirocumab or standard-of-care (SOC). The alirocumab arm will receive alirocumab 75 mg every 2 weeks (Q2W) added to statin therapy (atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day), with a dose increase to 150 mg Q2W in patients whose LDL-C value remains ≥100 mg/dl at week 12. The SOC arm will receive atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day, with dose adjustment to achieve LDL-C <100 mg/dl. Post-treatment IVUS imaging will be done at week 36 ± 2. The primary objective is to compare the effect of alirocumab versus SOC on coronary atheroma progression (percent change in normalized total atheroma volume) after 9 months of treatment.

Conclusion: ODYSSEY J-IVUS will provide insights into the effect of alirocumab on coronary atherosclerotic plaque volume in patients with a recent ACS and hypercholesterolemia while on stable statin therapy.

ClinicalTrials.gov number: NCT02984982.

© 2018 The Authors. ISDN. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Introduction

Patients with an acute coronary syndrome (ACS) are at high risk of cardiovascular death or recurrent ischemic events [1], and are recommended an early intensive statin therapy to reduce this risk based on evidence from multiple randomized controlled studies [2–4]. High-dose statins are generally safe and well-tolerated in predominantly Western populations [5]. They are efficacious in lowering low-density lipoprotein cholesterol (LDL-C), by 30–50% from pretreatment levels [6–8], and slow the progression of coronary atherosclerosis [9]. The incremental benefit of adding a non-statin lipid-lowering therapy to standard statin therapy in reducing the risk of cardiovascular events in ACS patients was first demonstrated in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [10]. Recently, the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial reported a cardiovascular benefit of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor on top of statin therapy in patients with atherosclerotic cardiovascular disease and LDL-C ≥70 mg/dL [11]. In the Heart Institute of Japan PROper lipid lower- ing with Pitavastatin and Ezetimibe in acute coronary syndrome (HI-PROPER) trial in ACS patients with dyslipidemia, intensive lowering with pitavastatin plus ezetimibe demonstrated no greater cardiovascular benefit than pitavastatin monotherapy, except in the subgroup of patients with higher cholesterol absorption [12]. Guidelines published by the Japan Atherosclerosis Society (JAS) recommend lowering LDL-C to <100 mg/dL (2.6 mmol/L) in patients with established cardiovascular disease [13].

Epidemiological studies report lower cardiovascular and higher cerebrovascular event rates in Japanese versus Western populations [14,15]. The Reduction of atherothrombosis for Continued Health (REACH) investigators, in an analysis involving stable outpatients with or at risk of atherothrombosis, reported a correlation between Japanese ethnicity and lower cardiovascular risk compared with non-Japanese populations [16]. These Japanese-specific characteristics indicate the need for a specific outcome, or outcome surrogate marker, to establish the benefit of intensive LDL-C lowering in the Japanese population.

Intravascular ultrasound (IVUS) generates high-resolution images of the full thickness of the artery wall, providing the most accurate quantitation of plaque burden available currently [17]. Serial IVUS imaging has been employed to evaluate the effect of LDL-C-lowering strategies [9,18–22]. These studies demonstrated benefit in terms of reducing progression of coronary atherosclerosis and plaque volume, with evidence of potential incremental effects with more aggressive LDL-C-lowering regimens. Furthermore, a meta-analysis of six trials that used serial IVUS reported a direct relation between the burden of coronary atherosclerosis, its progression, and adverse cardiovascular events [23]. In Japan, IVUS forms part of the standard intervention procedure, and has been used in clinical trials to evaluate the effect of medical therapies on coronary atheroma progression [24,25]. The widespread use of IVUS in Japan is a unique characteristic of cardiovascular intervention practice in the country, and offers the opportunity for an effective imaging study involving country-wide samples.

Alirocumab is a highly specific, fully human monoclonal antibody to PCSK9. As monotherapy or on a background of other lipid-lowering treatment, alirocumab reduced LDL-C by 44–72% in patients with hypercholesterolemia [28–30]. In Japan, alirocumab is indicated for the treatment of patients with familial hypercholesterolemia or hypercholesterolemia who are at high cardiovascular risk and in whom statins are not sufficient to reduce serum LDL-C levels. The standard treatment dose is 75 mg every 2 weeks (Q2W), with a dose increase to 150 mg Q2W if the LDL-C reduction is insufficient. The ODYSSEY-J-IVUS study will investigate the effect of alirocumab on progression of coronary atheroma volume in Japanese patients recently hospitalized for an ACS who have not achieved the recommended LDL-C level of <100 mg/dL at ACS diagnosis, as defined by the JAS [13]. The primary objective is to compare the effect of alirocumab versus standard of care on coronary atheroma progression (defined as percent change in normalized total atheroma volume (TAV)) after 9 months of treatment. The secondary objectives are to compare the efficacy of alirocumab versus the standard of care on secondary endpoints, including absolute change in percent atheroma volume (PAV) and in normalized TAV after 9 months of treatment; to evaluate the effect of alirocumab on LDL-C, apolipoprotein B, triglycerides, non-high-density lipoprotein cholesterol (non-HDL-C), lipoprotein(a), and HDL-C after 9 months of treatment; and to evaluate the safety and tolerability of alirocumab.

Methods

ODYSSEY-J-IVUS is a phase IV, open-label, randomized, blinded IVUS analysis, parallel group, multicenter study in Japanese patients recently hospitalized for an ACS and who have elevated LDL-C values despite stable statin therapy. Approximately 200 patients from 40 study sites were to be randomized. The first patient was enrolled on November 15, 2016, and the last patient on 02 November, 2017 (n = 206 patients).

The study is being performed according to the principles derived from the Declaration of Helsinki and the International Conference on Harmonization guidelines for good clinical practice, and to all applicable laws, rules, and regulations. The protocol was approved by the institutional review boards of participating centers. All patients who agreed to participate were required to provide written informed consent. The study is registered at http://clinicaltrials.gov/NCT02984982.

Study population

Eligible patients are those aged ≥20 years who have been hospitalized for any ACS (ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina); have LDL-C ≥100 mg/dL (2.6 mmol/L) at ACS diagnosis; have undergone IVUS imaging with at least 50% angiographic stenosis of the culprit vessel, within 1-week of ACS onset; and are negative to serum hepatitis B surface antigen, to total hepatitis B core antibody (or positive to hepatitis B core antibody and negative to hepatitis B DNA), and to hepatitis C antibody tests. Study exclusion criteria are listed in Table 1.

ACS patients who have already been on any statin therapy and whose LDL-C value is ≥100 mg/dL (2.6 mmol/L) at diagnosis will switch to atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day (if not already on either of these), based on the investigators’ judgment. Patients not previously taking a statin whose LDL-C is ≥100 mg/dL (2.6 mmol/L) at the time of ACS diagnosis, who start treatment with atorvastatin 10 mg/day or rosuvastatin 5 mg/day immediately after the diagnosis, and whose LDL-C value remains ≥100 mg/dL (2.6 mmol/L) (or ≥70 mg/dL, if the physician determines appropriate) 2–4 weeks later, will also be eligible to participate.

STEMI is defined as symptoms suggesting ischemia (e.g. chest pain or shortness of breath), with ≥1 mm of ST elevation in ≥2 consecutive chest leads or ≥2 consecutive limb leads on an electrocardiogram, or a newly occurring left bundle branch block, and elevated cardiac markers (troponin T ≥0.1 ng/mL or troponin I ≥0.04 ng/mL or creatine phosphokinase ≥2 times the upper limit or normal). NSTEMI is defined as symptoms suggesting ischemia,
with ST depression $>0.5$ mm (0.05 mV), negative T-wave ($\geq 3$ mm: dynamic T-wave inversion), or transient ST elevation $<0.5$ mm; and elevated cardiac markers (as described for STEMI). Unstable angina is defined as symptoms suggesting ischemia plus one of the following: ST depression $>0.5$ mm or negative T-wave ($\geq 3$ mm: dynamic T-wave inversion); elevated troponin T ($\geq 0.014 - 0.1$ ng/mL); confirmation of the coronary lesion responsible for ACS by diagnostic imaging (e.g. coronary angiography, multidetector computed tomography); new decrease in wall motion by cardiac ultrasoundography; and evidence of reversible decrease in myocardial blood flow induced by pharmacological or exercise stress.

Study design

The study consists of a 36-week open-label treatment period (including post-treatment IVUS imaging), starting within 4 weeks of ACS diagnosis (Fig. 1). During the open-label treatment period, patients will be randomized by permuted-block design to receive either alirocumab or standard-of-care (1:1). Randomization will be stratified according to previous use of statin therapy at ACS diagnosis. The last dose of alirocumab will be given at week 34.

Patients in the alirocumab arm will receive alirocumab 75 mg Q2W added to statin therapy (atorvastatin $\geq 10$ mg/day or rosvastatin $\geq 5$ mg/day). At week 14, patients whose LDL-C value at week 12 remains $\geq 100$ mg/dL (2.6 mmol/L) will have their alirocumab dose increased to 150 mg Q2W. Patients in the standard-of-care arm will receive atorvastatin $\geq 10$ mg/day or rosvastatin $\geq 5$ mg/day, with dose adjustment (within the range approved by the health authority) to achieve an LDL-C target $<100$ mg/dL; any non-statin lipid-lowering therapy will be continued at the same doses determined after ACS diagnosis and percutaneous coronary intervention (PCI), unless modifications are required by the investigator. For patients on statin monotherapy, concomitant non-statin lipid-lowering therapy will be considered by investigators if the LDL-C target of $<100$ mg/dL (2.6 mmol/L) cannot be achieved.

Post-treatment IVUS imaging of the same vessels at ACS diagnosis will be carried out at the end of treatment period (at week 36 $\pm 2$ weeks, depending on patient availability) in both study arms, and will be conducted according to the relevant instruction manual. The image analyzed will be one taken $\geq 5$ mm from the proximal or distal edges of the stent, with priority given to images proximal to the first lesion with PCI followed by distal to the first lesion with PCI.

Study treatments

Injections of alirocumab 75 mg or 150 mg (given in a 1-ml volume) will be administered subcutaneously by autoinjector into the abdomen, thigh, or outer area of upper arm by site staff, the patient, or another designated person. Patients can self-administer the study drug at home if the investigator feels the patient can carry out the injection correctly. Patients who subsequently choose not to continue self-injecting, or who are unable to do so, may return to the sites for injection of study drug. All patients are required to visit the study site at least every 4 weeks, and at weeks 0, 4, 12, 14, 24, and 36, regardless of the means of administration. Alirocumab 75 mg Q2W administration will be carried out from the randomization visit (week 0) to week 34. However, if the evaluation IVUS imaging cannot be performed by week 36, alirocumab will be administered at week 36 and the evaluation IVUS can be performed up to week 38. At week 14, a dose increase to 150 mg Q2W will be conducted in patients whose LDL-C values remain $\geq 100$ mg/dL (2.6 mmol/L) at week 12.

Non-investigational oral products include atorvastatin, rosuvastatin, ezetimibe, fibrates (fenofibrate or bezafibrate), antiplatelets (e.g. aspirin, clopidogrel), and warfarin or non-vitamin K antagonist oral anticoagulants (dabigatran, edoxaban, rivaroxaban, or apixaban). Other drug medications or medical products maybe considered, if necessary, but should be kept to a minimum and taken at a stable dose, when possible.

This study is an open-label design and thus no attempt will be made to blind study drug administration. Assessment for the primary and key secondary efficacy endpoints will, however, be conducted in the central laboratory based on objectively collected imaging data blinded to study treatment groups.

Key study endpoints

The primary efficacy endpoint is the percent change in normalized TAV from baseline to week 36, defined as:

$$\frac{\text{NormalizedTAV(week36)} - \text{NormalizedTAV(baseline)}}{\text{NormalizedTAV(baseline)}} \times 100$$

The baseline normalized TAV value will be that obtained before randomization. The normalized TAV at week 36 will be the normalized TAV obtained after the $\geq 24$ weeks of treatment after randomization. The normalized TAV will be calculated as the

Table 1
Study exclusion criteria.

<table>
<thead>
<tr>
<th>Exclusion criteria related to study methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients who have been treated previously with at least one dose of any anti-PCSK9 monoclonal antibody.</td>
</tr>
<tr>
<td>2. Uncontrolled hypertension (multiple reading with systolic blood pressure $&gt;180$ mmHg or diastolic blood pressure $&gt;110$ mmHg) between the acute coronary syndrome diagnosis and randomization visit.</td>
</tr>
<tr>
<td>4. Currently under treatment for cancer.</td>
</tr>
<tr>
<td>5. Patients on lipoprotein apheresis.</td>
</tr>
<tr>
<td>6. Conditions/situations such as:</td>
</tr>
<tr>
<td>• Any clinically significant abnormality identified that in the judgment of the investigator or any sub-investigator would preclude safe completion of the study or constrain endpoint assessment such as major systemic diseases, patients with short life expectancy.</td>
</tr>
<tr>
<td>• Considered by the investigator or any sub-investigator as inappropriate for this study for any reason, for example:</td>
</tr>
<tr>
<td>» Those deemed unable to meet specific protocol requirements, such as scheduled visits.</td>
</tr>
<tr>
<td>» Investigator or any sub-investigator, pharmacist, study coordinator, other staff, or relative thereof directly involved in the conduct of the protocol, etc.;</td>
</tr>
<tr>
<td>» Presence of any other condition (e.g. geographic, social, etc.) actual or anticipated, that the investigator feels would restrict or limit the patient’s participation for the duration of the study.</td>
</tr>
<tr>
<td>7. Laboratory findings measured within 2 weeks after the acute coronary syndrome diagnosis (positive serum or urine pregnancy test in women of childbearing potential).</td>
</tr>
</tbody>
</table>

Exclusion criteria related to background therapies

8. All contraindications to statin or other lipid-modifying therapies or warning/precaution of use (when appropriate) as displayed in the respective national product labeling for these treatments.

Exclusion criteria related to the current knowledge of alirocumab

9. All contraindications to alirocumab as displayed in the respective national product labeling for these treatments.

10. Known hypersensitivity to monoclonal antibody including alirocumab or any component of the drug product used in the current study.

11. Pregnant or breast-feeding women.

12. Women of childbearing potential not protected by highly effective method (s) of birth control (as defined for contraception in the informed consent form and/or in a local protocol addendum) and/or who are unwilling or unable to be tested for pregnancy.

Additional exclusion criteria before randomization

13. Patient who has withdrawn consent before enrollment/randomization (starting from signed informed consent form).
summation of plaque area in each measured image taken at predetermined intervals between each image (δ = 0.5 mm), normalized to account for differences in segment length between different subjects:

\[ TAV(\text{mm}^2) = \sum (EEM_{CSA} - \text{Lumen}_{CSA}) \delta \]

NormalizedTAV(\text{mm}^2) = \frac{TAV \times C}{n}

where \( n \) is the number of analyzed frames, \( C \) is the median of the number of analyzed frames in the cohort, external elastic membrane (EEMCSA) is the cross-sectional area of the EEM border, and LumenCSA is the cross-sectional area of the lumen border, both of which are directly measured by the central reading laboratory, blinded to study treatment groups.

The key secondary efficacy endpoint is absolute change in PAV from baseline to week 36, defined as PAV at week 36 − PAV at baseline. The PAV will be calculated as the proportion of the entire vessel volume occupied by atherosclerotic plaque throughout the segment of interest:

\[ \text{PAV} = \left( \frac{\sum (EEM_{CSA} - \text{Lumen}_{CSA})}{\sum_{\text{CSA}}} \right) \times 100 \]

Other secondary efficacy endpoints, in hierarchical order, are absolute change in normalized TAV from baseline to week 36; absolute and percent changes in EEM volume and in lumen volume from baseline to week 36; absolute and percent changes in calculated LDL-C from baseline to week 12, and week 36; and absolute and percent changes in apolipoprotein-B, non-HDL-C, total cholesterol, lipoprotein(a), HDL-C, triglycerides, and apolipoprotein A1 from baseline to week 36.

The primary efficacy endpoint will be analyzed in the modified intent-to-treat (mITT) population (the randomized population that takes at least one dose or partial dose of study drug and has an available value of normalized TAV before randomization and at
≥24 weeks of treatment) using an analysis of covariance (ANCOVA) model; treatment group and randomization strata will be fixed effects and the baseline normalized TAV will be the covariate. Throughout the ANCOVA model, running using a SAS mixed procedure, the alirocumab arm will be compared with the standard-of-care arm at the 2-sided 0.05 level for superiority and providing baseline adjusted least squares mean estimates at week 36 for each treatment group, with their corresponding standard errors and the 95% confidence interval of the difference. A hierarchical procedure will be used for each pairwise comparison to control type I error and to handle multiple endpoints. If the primary endpoint analysis is significant at the 0.05 alpha level, the key secondary efficacy endpoints will be tested sequentially at the 0.05 level.

Safety analysis

The safety population is the randomized population that received at least one dose or partial dose of study drug. The safety summary will be descriptive in nature.

Discussion

Vascular imaging has been used for over three decades to examine the progression of atherosclerotic disease and the effect of interventions that aim to slow this process [38,39]. Advances in arterial wall imaging have enhanced the ability to directly visualize atherosclerotic plaque. Whereas angiography has been widely used to quantify the extent of obstructive disease, it does not image the artery wall, the site at which plaque accumulates. Accordingly, use of wall-based imaging approaches, such as IVUS, provides the potential for more precise assessments of atherosclerotic plaque. Nicholls et al. [23], in a meta-analysis of six IVUS trials involving 4137 patients, demonstrated a direct relation between coronary atherosclerosis burden, progression of atherosclerosis, and adverse cardiovascular events, and thus supports the use of atherosclerosis imaging with IVUS in the evaluation of new antiatherosclerotic therapies. IVUS can also be used to detect vasa vasorum neovascularization of the coronary arteries, which is involved in the progression and vulnerability of coronary atherosclerotic plaque, with more enhanced neovascularization in ACS than stable angina pectoris [40].

The multinational Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN) compared the effects of the highest doses of atorvastatin (80 mg/day) and rosuvastatin (40 mg/day) on the progression of coronary atherosclerosis in 1039 patients with coronary disease [20]. The rosuvastatin group achieved lower LDL-C levels than the atorvastatin group (62.6 mg/dL vs. 70.2 mg/dL, \( p < 0.001 \)) and higher HDL-C levels (50.4 mg/dL vs. 48.6 mg/dL, \( p = 0.01 \)). The primary endpoint, PAV, decreased in both groups consistent with plaque regression, but the between-group difference did not achieve statistical significance (\( p = 0.17 \)). In contrast, the secondary endpoint – change in normalized TAV – demonstrated greater regression in rosuvastatin-treated patients (\( p = 0.01 \)). Approximately two-thirds of the patients demonstrated regression, reinforcing the theory that aggressively lowering LDL-C to ≤70 mg/dL offers significant plaque reduction. The PRECISE-IVUS trial [27] demonstrated greater plaque regression with combination therapy comprising ezetimibe and atorvastatin versus atorvastatin monotherapy in 202 Japanese patients with coronary artery disease (ACS or stable angina) [27]. Both the SATURN [41] and the PRECISE-IVUS [27] studies showed greater plaque regression in ACS patients versus non-ACS patients; despite having a higher initial clinical risk profile, ACS patients appear to harbor a more modifiable disease substrate and seem to benefit the most from potent lipid-lowering therapy [27,41].

The multinational GLAGOV trial [22] examined the effect of PCSK9 inhibition with evolocumab on progression of coronary atherosclerosis in statin-treated patients with angiographic coronary artery disease and LDL-C ≥80 mg/dL (or 60–80 mg/dL in the presence of one major or three minor cardiovascular risk factors). The authors reported a statistically significant difference between placebo-treated and evolocumab-treated patients for both PAV (\( p < 0.001 \)) and normalized TAV (\( p < 0.001 \)) after 76 weeks of treatment, and greater LDL-C lowering and atheroma regression with evolocumab. The study was, however, limited by the rate of patient retention (87%), necessitating the use of imputation modeling.

The ODYSSEY-J-IVUS study will provide insights into the ability of alirocumab to slow or reduce progression of coronary atheroma volume over time in Japanese patients who recently experienced an ACS and who, despite statin therapy, fail to achieve the goals as defined in the JAS guidelines [13] (or <70 mg/dL, if the physician determines appropriate). In PRECISE-IVUS [27], PAV was selected as the primary endpoint and normalized TAV as a secondary endpoint, whereas TAV has been used as the primary endpoint in other key Japanese IVUS studies [21,24–26]. Consequently, to facilitate comparison of our trial results with these Japanese studies, we chose normalized TAV as the primary endpoint and absolute change in PAV as a secondary endpoint. Furthermore, we selected an ACS population based on evidence that these patients are expected to benefit to a greater degree from early aggressive lipid-lowering therapy [21] than patients with stable coronary artery disease (CAD) [26,27,42,43]. The treatment duration in ODYSSEY J-IVUS is similar to that used in previous Japanese IVUS studies involving ACS patients [21,25,27], which ranged from 6 to 12 months, and will therefore allow for direct comparison. Based on data from other Japanese studies [21,24–27], the treatment duration is also sufficient to provide information on the efficacy of alirocumab in terms of atherosclerosis disease progression or regression. The study duration is consistent with the standard practice in Japan of follow-up coronary angiography 8–10 months after the ACS event, which should ensure a high rate of patient retention. The study should also provide a sufficient length of exposure to offer insights into the tolerability and safety of alirocumab in the ACS setting.

Funding

This research was supported by Sanofi and Regeneron Pharmaceuticals, Inc. The sponsor was involved in the study design; the collection, analysis and interpretation of data; the writing of the report; and the decision to submit the article for publication.

Disclosures

J.A. reports personal fees from Sanofi K.K., during the conduct of the study; grants from Medtronic Japan Co. Ltd, grants and personal fees from Abbott Vascular, grants from Teijin Pharma Co., Ltd., grants and personal fees from Mitsubishi Tanabe Pharma Co. Ltd., grants from Sumitomo Dainippon Pharma Co. Ltd., grants from Otsuka Pharmaceutical Co. Ltd., grants and personal fees from Takeda Pharmaceutical Company Ltd., grants and personal fees from Mochida Pharmaceutical Co. Ltd., grants and personal fees from Shionogi & Co. Ltd., grants and personal fees from AstraZeneca K.K., grants from Boston Scientific Corporation, grants and personal fees from Astellas Pharma Inc, grants and personal fees from Eisai Co. Ltd., grants from Kyowa Hakko Kirin Co. Ltd., grants and personal fees from Pfizer Japan Inc., grants and personal fees from Ono Pharmaceutical Co. Ltd., grants from Toa Eiyo Ltd., grants and personal fees from Novartis Pharma K.K., grants and
personal fees from Boehringer Ingelheim, grants and personal fees from Daiichi Sankyo Co. Ltd., grants and personal fees from Kowa Company, Ltd., grants and personal fees from MSD K.K., personal fees from Bayer Yakuhin, Ltd., personal fees from Bristol-Myers Squibb K.K., personal fees from Edwards Lifesciences Corporation, personal fees from Jímro Co. Ltd., personal fees from Kaneka Corporation, personal fees from Kyowa Hakko Kirin Co. Ltd., personal fees from Sanofi K.K., personal fees from St. Jude Medical Japan Co. Ltd., personal fees from Terumo Corporation, personal fees from Toa Eiyo Ltd., personal fees from Volcano Corporation, outside the submitted work.

K.H reports personal fees from Sanofi K.K., during the conduct of the study; grants from AstraZeneca Co., Ltd, grants from Boehringer Ingelheim, and Bristol-Myers Squibb, outside the submitted work.

K.M reports personal fees from Sanofi K.K., during the conduct of the study; personal fees from Sanofi, personal fees from Astellas from personal fees from Sanofi, outside the submitted work.

K.K reports personal fees from Sanofi, during the conduct of the study; personal fees from AstraZeneca, Astellas, MSD, Bayer Health Care, Sanofi, Takeda, Dai-Ichi Sankyo, Boehringer-Ingelheim, and Bristol-Myers Squibb, outside the submitted work.

Y.M. reports personal fees from Sanofi K.K., during the conduct of the study; grants and personal fees from Daiichi-Sankyo, grants and personal fees from Astellas Pharma K.K., grants and personal fees from Takeda Pharmaceutical, grants and personal fees from Otsuka Pharmaceutical, personal fees from Mochida, grants and personal fees from Abbott Vascular, grants and personal fees from Terumo, and personal fees from AstraZeneca, personal fees from Boston Scientific, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Pfizer, personal fees from Novartis, and personal fees from Sanofi, outside the submitted work.

T.S. has no conflict of interest.

K.T. reports personal fees from Sanofi K.K., during the conduct of the study; personal fees from AstraZeneca BIOPharma K.K., grants from AstraZeneca K.K. (trust research/joint research funds), grants and personal fees from Bayer Yakuhin, Ltd, personal fees from Daiichi Sankyo Co., Ltd., personal fees from MSD K.K., grants and personal fees from Sanofi K.K., grants from Astellas Pharma Inc, grants from Boston Scientific Japan K.K., grants from Chugai Pharmaceutical Co, Ltd, grants from MSD K.K., and grants from Pfizer Japan Inc, outside the submitted work.

K.U. is an employee of Sanofi.

Y.K. is an employee of Sanofi.

T.H. reports personal fees from Sanofi, during the conduct of the study; and personal fees from Kyowa Hakko Kirin, Dainihon Sumitomo, Novartis Pharma, Takeda, Nihon Boehringer Ingelheim, Eisai, Toa Eiyo, Kissei, MSD, Kowa, Astellas, Astellas Agen Biopharma, Bayer, Pfizer, Daiichi Sankyo, Astra Zeneca, Medtronic, Terumo, Shionogi. Dr Hiro also works for the Department of Advanced Cardiovascular Imaging, Nihon University School of Medicine, endowed by Boston Scientific Japan. Co. Ltd.

Acknowledgments

We thank the following persons from Sanofi for their contributions to research and development, data collection and analysis, statistical analysis, or critical review of the manuscript: Asuka Otsaki, Makiko Usami, Shogo Yamada, Yosiharu Takagi, and Takahiro Nakama. We also thank Dr Hiromasa Otake, Kobe University Hospital, Kobe, Japan (imaging advisor at the core laboratory); the EPS Corporation, Tokyo, Japan (contract research organization); and Micron, Kobe, Japan (imaging laboratory). Writing support was provided by Sophie K. Rushton-Smith, PhD, funded by Sanofi and Regeneron Pharmaceuticals, Inc.

References


