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

Ako, Junya ; Hibi, Kiyoshi ; Kozuma, Ken ; Miyauchi, Katsumi ; Morino, Yoshihiro ; Shinke, Toshiro ; Tsujita, Kenichi ; Uno, Kiyoko ;…

(Citation)
Journal of Cardiology,71(6):583-589

(Issue Date)
2018-06

(Resource Type)
journal article

(Version)
Version of Record

(URL)
https://hdl.handle.net/20.500.14094/90005010

Journal of Cardiology 71 (2018) 583–589

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

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)[a,*], Kiyoshi Hibi (MD, PhD, FJCC)[b], Ken Kozuma (MD, PhD)[c], Katsumi Miyauchi (MD, PhD, FJCC)[d], Yoshihiro Morino (MD, PhD, FJCC)[e], Toshiro Shinke (MD, PhD, FJCC)[f], Kenichi Tsujita (MD, PhD)[g], Kiyoko Uno (MD, PhD)[h], Yumiko Kawabata (MS)[i], Takafumi Hiro (MD, PhD, FJCC)[j]

[a] Department of Cardiovascular Medicine, Kitasato University Hospital, Sagamihara-City, Kanagawa, Japan
[b] Division of Cardiology, Yokohama City University Medical Center, Yokohama-City, Kanagawa, Japan
[c] Division of Cardiology, Teikyo University Hospital, Itabashi-ku, Tokyo, Japan
[d] Division of Cardiovascular Medicine, Department of Internal Medicine, Juntendo University Hospital, Bunkyo-ku, Tokyo, Japan
[e] Division of Cardiology, Department of Internal Medicine, Iwate Medical University, Morioka-city, Iwate, Japan
[f] Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe-city, Hyogo, Japan
[g] Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto-City, Kumamoto, Japan
[h] Cardiovascular Medical, Sanofi, Shinjuku-ku, Tokyo, Japan
[i] Clinical Sciences and Operations, R&D, Sanofi, Shinjuku-ku, Tokyo, Japan
[j] Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Itabashi-ku, Tokyo, Japan

ARTICLE INFO

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

ABSTRACT

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.

* Corresponding author at: 1-15-1 Kitasato, Mianami-ku, Sagamihara-City, Kanagawa 252-0374, Japan.
E-mail address: jako@kitasato-u.ac.jp (J. Ako).

https://doi.org/10.1016/j.jjcc.2017.11.013
0914-5087/

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 $\geq$70 mg/dL [11]. In the Heart Institute of Japan PRoper level of lipid lOwering with Pitavastatin and Ezetimibe in acute coRonary syndrome (HIJ-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 [21,24–27]. 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 [28–36]. 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 $\geq$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 $\geq$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 $\geq$100 mg/dL (2.6 mmol/L) at diagnosis will switch to atorvastatin $\geq$10 mg/day or rosuvastatin $\geq$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 $\geq$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 $\geq$100 mg/dL (2.6 mmol/L) (or $\geq$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 $\geq$1 mm of ST elevation in $\geq$2 consecutive chest leads or $\geq$2 consecutive limb leads on an electrocardiogram, or a newly occurring left bundle branch block, and elevated cardiac markers (troponin T $\geq$0.1 ng/mL or troponin I $\geq$0.04 ng/mL, or creatine phosphokinase $\geq$2 times the upper limit of normal). NSTEMI is defined as symptoms suggesting ischemia,

Table 1
Study exclusion criteria.

	Exclusion criteria related to study methodology
1.	Patients who have been treated previously with at least one dose of any anti-PCSK9 monoclonal antibody.
2.	Uncontrolled hypertension (multiple reading with systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg) between the acute coronary syndrome diagnosis and randomization visit.
3.	Known history of hemorrhagic stroke.
4.	Currently under treatment for cancer.
5.	Patients on lipoprotein apheresis.
6.	Conditions/situations such as: • 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. • Considered by the investigator or any sub-investigator as inappropriate for this study for any reason, for example: ◦ Those deemed unable to meet specific protocol requirements, such as scheduled visits; ◦ Investigator or any sub-investigator, pharmacist, study coordinator, other study staff, or relative thereof directly involved in the conduct of the protocol, etc.; ◦ 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.
7.	Laboratory findings measured within 2 weeks after the acute coronary syndrome diagnosis (positive serum or urine pregnancy test in women of childbearing potential).
	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).

PCSK9, proprotein convertase subtilisin/kexin type 9.

with ST depression >0.5 mm (0.05 mV), negative T-wave (≥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 (≥3 mm: dynamic T-wave inversion); elevated troponin T (≥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 ultrasonography; 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 ≥10 mg/day or rosuvastatin ≥5 mg/day). At week 14, patients whose LDL-C value at week 12 remains ≥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 ≥10 mg/day or rosuvastatin ≥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 ± 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 ≥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 ≥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 ≥24 weeks of treatment after randomization. The normalized TAV will be calculated as the

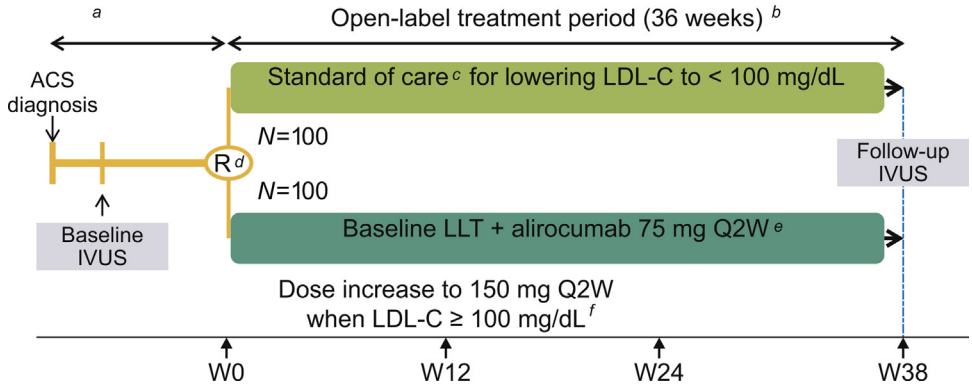

Fig. 1. Study design.
[a] Patients who are not on statin therapy at the time of the ACS should start either atorvastatin 10 mg/day or rosuvastatin 5 mg/day immediately after the diagnosis.
[b] Patients who self-administer the study drug (alirocumab) at home are required to visit the study site at least every 4 weeks, and at weeks 0, 4, 12, 14, 24, and 36.
[c] At the time of randomization, patients should have been on stable statin therapy (with either atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day) for ≥2 weeks.
[d] Stable-dose atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day monotherapy (within the range of approved statin doses) will be administered and adjusted by physicians to achieve the LDL-C target of <100 mg/dL. Use of concomitant non-statin LLTs will be considered by physicians if the LDL-C target cannot be achieved with statin monotherapy.
[e] Alirocumab 75 mg Q2W on a background of a stable dose of atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day therapy ± other LLTs. Concomitant non-statin LLTs will be considered by physicians, if patients are already taking them, in addition to statin monotherapy, at the time of ACS diagnosis. Background statin and/or non-statin LLT regimens should remain unchanged throughout the study period.
[f] In the alirocumab arm, if the LDL-C value at week 12 visit (measured by the central laboratory) is ≥100 mg/dL, the alirocumab dose will increase to 150 mg Q2W at week 14.
ACS, acute coronary syndrome; IVUS, intravascular ultrasound; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; R, randomization; Q2W, every 2 weeks.

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:

$$\mathrm{TAV}(\mathrm{mm}^3) = \sum(\mathrm{EEM_{CSA}} - \mathrm{Lumen_{CSA}})\delta$$

$$\mathrm{NormalizedTAV}(\mathrm{mm}^3) = \mathrm{TAV} \times \frac{C}{n}$$

where n is the number of analyzed frames, C is the median of the number of analyzed frames in the cohort, external elastic membrane ($\mathrm{EEM_{CSA}}$) is the cross-sectional area of the EEM border, and $\mathrm{Lumen_{CSA}}$ 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:

$$\mathrm{PAV} = \left(\frac{\sum(\mathrm{EEM_{CSA}} - \mathrm{Lumen_{CSA}})}{\sum \mathrm{CSA}}\right) \times 100$$

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.

Total cholesterol, calculated LDL-C, HDL-C, triglycerides, and non-HDL-C will be measured by the central laboratory at weeks 0, 4, 12, 24, and 36. Blood sampling will be performed in the morning under fasting conditions (defined as an overnight fast of ≥8 h). Apolipoprotein B, apolipoprotein A-1, apolipoprotein B/apolipoprotein A-1 ratio, and lipoprotein(a) will be measured at weeks 0 and 36. LDL-C will be calculated using the Friedewald formula [37]. If triglyceride values exceed 400 mg/dL (4.5 mmol/L), the central laboratory will automatically measure LDL-C directly, using the beta-quantification method.

Safety endpoints, including cardiovascular events (coronary heart disease death, non-fatal myocardial infarction, fatal and non-fatal ischemic and/or hemorrhagic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, and ischemia-driven coronary revascularization procedure), laboratory data, and vital signs will be assessed throughout the study. The treatment-emergent adverse event period is defined as the time from the day of randomization to the last administration +21 days, or end of study, whichever comes first.

Statistical design and analyses

The study is expected to enroll approximately 200 patients. The sample size calculations are based on the primary efficacy variable of percent change in normalized TAV from baseline to week 36. According to the eZEtimibe Ultrasound Study (ZEUS) [24] and the Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound (PRECISE-IVUS) study [27], it is assumed that the difference in percent change in normalized TAV from baseline between the alirocumab and standard-of-care arms is 8%, and the common standard deviation (SD) of percent change in normalized TAV is 15%. Under this assumption, a sample size of 150 patients (75 in the alirocumab arm and 75 in the standard-of-care arm) will have 90% power to detect the treatment difference with a 2-sided significance level of 5%. Assuming that the proportion of non-evaluable primary endpoints is 25%, 200 patients (100 in alirocumab arm, 100 in standard-of-care arm) will be needed.

Efficacy analyses

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, run 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 of ≥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 Jimro 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 Biosensors Japan Co., Ltd, grants from Goodman Co., Ltd, grants from Medtronic Japan Co., Ltd, grants from MSD Co., Ltd, grants from Solve Co., Ltd, grants from St. Jude Medical Japan Co., Ltd, grants from Teijin Pharma Co., Ltd, grants from Terumo Co., Ltd, personal fees from Amgen Astellas BioPharma K.K., personal fees from Terumo Co., Ltd, personal fees from St. Jude Medical Japan Co., Ltd, personal fees from Sanofi K.K., outside the submitted work.

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

K.M. reports personal fees from Sanofi K.K., during the conduct of the study; personal fees from Amgen Astellas, 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, 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, grants and personal fees from AstraZeneca, personal fees from Boston Scientific, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Bayer, personal fees from Pfizer, grants and personal fees from Novartis, grants 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 Amgen Astellas 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., 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 Amgen 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 Ozaki, Makiko Usami, Shogo Yamada, Yoshiharu 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

[1] Pilgrim T, Vranckx P, Valgimigli M, Stefanini GG, Piccolo R, Rat J, et al. Risk and timing of recurrent ischemic events among patients with stable ischemic heart disease, non-ST-segment elevation acute coronary syndrome, and ST-segment elevation myocardial infarction. Am Heart J 2016;175:56–65.

[2] Krumholz HM, Anderson JL, Bachelder BL, Fesmire FM, Fihn SD, Foody JM, et al. ACC/AHA 2008 performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Performance Measures for ST-Elevation and Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American Academy of Family Physicians and American College of Emergency Physicians endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, Society for Cardiovascular Angiography and Interventions, and Society of Hospital Medicine. J Am Coll Cardiol 2008;52:2046–99.

[3] Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey Jr DE, et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e179–347.

[4] Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2008;51:210–47.

[5] Newman C, Tsai J, Szarek M, Luo D, Gibson E. Comparative safety of atorvastatin 80 mg versus 10 mg derived from analysis of 49 completed trials in 14,236 patients. Am J Cardiol 2006;97:61–7.

[6] Cholesterol Treatment Trialists (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, 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.

[7] Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623–30.

[8] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto Jr AM, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.

[9] Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004;291:1071–80.

[10] Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387–97.

[11] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–22.

[12] Hagiwara N, Kawada-Watanabe E, Koyanagi R, Arashi H, Yamaguchi J, Nakao K, et al. Low-density lipoprotein cholesterol targeting with pitavastatin + ezetimibe for patients with acute coronary syndrome and dyslipidaemia: the HIJ-PROPER study, a prospective, open-label, randomized trial. Eur Heart J 2017;38:2264–76.

[13] Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, et al. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan – 2012 version. J Atheroscler Thromb 2013;20:517–23.

[14] Daida H, Miyauchi K, Ogawa H, Yokoi H, Matsumoto M, Kitakaze M, et al. Management and two-year long-term clinical outcome of acute coronary syndrome in Japan: prevention of atherothrombotic incidents following ischemic coronary attack (PACIFIC) registry. Circ J 2013;77:934–43.

[15] Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, et al. Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. Stroke 2000;31:2616–22.

[16] Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA 2010;304:1350–7.

[17] Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, et al. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2001;37:1478–92.

[18] Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med 2005;352:29–38.

[19] Ballantyne CM, Raichlen JS, Nicholls SJ, Erbel R, Tardif JC, Brener SJ, et al. Effect of rosuvastatin therapy on coronary artery stenoses assessed by quantitative coronary angiography: a study to evaluate the effect of rosuvastatin on intravascular ultrasound-derived coronary atheroma burden. Circulation 2008;117:2458–66.
[20] Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med 2011;365:2078–87.
[21] Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H, et al. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. Circulation 2004;110:1061–8.
[22] Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. JAMA 2016;316:2373–84.
[23] Nicholls SJ, Hsu A, Wolski K, Hu B, Bayturan O, Lavoie A, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. J Am Coll Cardiol 2010;55:2399–407.
[24] Nakajima N, Miyauchi K, Yokoyama T, Ogita M, Miyazaki T, Tamura H, et al. Effect of combination of ezetimibe and a statin on coronary plaque regression in patients with acute coronary syndrome ZEUS trial (eZEtimibe Ultrasound Study). IJC Metab Endocr 2014;3:8–13.
[25] Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, et al. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: a multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol 2009;54:293–302.
[26] Takayama T, Hiro T, Yamagishi M, Daida H, Hirayama A, Saito S, et al. Effect of rosuvastatin on coronary atheroma in stable coronary artery disease: multicenter coronary atherosclerosis study measuring effects of rosuvastatin using intravascular ultrasound in Japanese subjects (COSMOS). Circ J 2009;73:2110–7.
[27] Tsujita K, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K, et al. Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: the multicenter randomized controlled PRECISE-IVUS trial. J Am Coll Cardiol 2015;66:495–507.
[28] 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.
[29] Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med 2012;367:1891–900.
[30] Stein EA, Gipe D, Bergeron J, Gaudet D, Weiss R, Dufour R, 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.
[31] Roth EM, Taskinen MR, Ginsberg HN, Kastelein JJ, Colhoun HM, Robinson JG, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized phase 3 trial. Int J Cardiol 2014;176:55–61.
[32] Bays H, Gaudet D, Weiss R, Ruiz JL, Watts GF, Gouni-Berthold I, et al. Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial. J Clin Endocrinol Metab 2015;100:3140–8.
[33] Cannon CP, Cariou B, Blom D, McKenney JM, Lorenzato C, Pordy R, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. Eur Heart J 2015;36:1186–94.
[34] Kastelein JJ, Ginsberg HN, Langslet G, Hovingh GK, Ceska R, Dufour R, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Eur Heart J 2015;36:2996–3003.
[35] Kereiakes DJ, Robinson JG, Cannon CP, Lorenzato C, Pordy R, Chaudhari U, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study. Am Heart J 2015;169:906–15. e13.
[36] Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372:1489–99.
[37] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.
[38] Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med 1990;323:1289–98.
[39] Amarenco P, Labreuche J, Lavallee P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. Stroke 2004;35:2902–9.
[40] Kume T, Okura H, Yamada R, Koyama T, Fukuhara K, Goryo Y, et al. In vivo assessment of vasa vasorum neovascularization using intravascular ultrasound: a comparison between acute coronary syndrome and stable angina pectoris. J Cardiol 2017;69:601–5.
[41] Puri R, Nissen SE, Shao M, Ballantyne CM, Barter PJ, Chapman MJ, et al. Antiatherosclerotic effects of long-term maximally intensive statin therapy after acute coronary syndrome: insights from Study of Coronary Atheroma by Intravascular Ultrasound: effect of Rosuvastatin Versus Atorvastatin. Arterioscler Thromb Vasc Biol 2014;34:2465–72.
[42] Takagi T, Yoshida K, Akasaka T, Hozumi T, Morioka S, Yoshikawa J. Intravascular ultrasound analysis of reduction in progression of coronary narrowing by treatment with pravastatin. Am J Cardiol 1997;79:1673–6.
[43] Schartl M, Bocksch W, Koschyk DH, Voelker W, Karsch KR, Kreuzer J, et al. Use of intravascular ultrasound to compare effects of different strategies of lipid-lowering therapy on plaque volume and composition in patients with coronary artery disease. Circulation 2001;104:387–92.