Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110116, Evolocumab SC Q2W 140 mg + Placebo PO QD Year 1: Standard of Care
Report: Acute coronary syndrome, Unstable angina

Subject [redacted] was a 70-year-old white man participating in Study 20120138 who had acute coronary syndrome (reported term: chest pain - troponin negative acute coronary syndrome) and unstable angina. The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, stable angina, coronary artery bypass graft, ischemic heart disease, gastroesophageal reflux disorder, myalgia due to statin intolerance, acute myocardial infarction, heart wall aneurysm, appendectomy, and transient ischemic attack. Concomitant medications included acetylsalicylic acid, bisoprolol, ramipril, temazepam, glyceryl trinitrate, furosemide, and clopidogrel. Previous and ongoing treatment for hyperlipidemia included ezetimibe.

The subject participated in the parent study from 21 May same year* to 28 August same year* and received the last dose of evolocumab in the parent study on 14 August same year*. The subject was enrolled into Study 20120138 on 28 August [redacted] and assigned standard of care treatment.

On 19 September same year*, the subject experienced chest pain unrelieved by vasodilatory spray. Troponin T levels were negative for acute coronary syndrome (values were 0.009 to 0.01 ng/mL). Electrocardiogram tests showed no ischemic changes. Additional laboratory tests did not disclose any significant abnormality in electrolytes, renal function, coagulation, or hemogram.

No further interventions were performed. The subject was diagnosed with troponin-negative acute coronary syndrome and received increased doses of isosorbide and rabeprazole.

The event of troponin-negative acute coronary syndrome was reported as resolved on 20 September same year* and the subject was discharged from the hospital on the same day. Discharge medications included clopidrogel, glyceryl trinitrate patch, and polyethyline glycol. Ezetimibe was discontinued on 15 October same year*.

On an unknown date, the subject experienced chest pain while walking, which was relieved by rest and glyceryl trinitrate. On 12 February one year after*, the subject experienced a second episode of

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chest pain associated with diaphoresis, which worsened gradually in 2 to 3 hours. The subject went to the emergency room. Relevant laboratory tests revealed troponin 0.009 to 0.012 ng/mL (negative), and hematocrit of 0.38. On the same day, ECG showed sinus bradycardia, left ventricular hypertrophy and ST-T change and probable recent acute myocardial infarction. The subject was treated with heparin infusion and glyceryl trinitrate for suspected non ST elevated myocardial infarction (NSTEMI). The subject experienced ongoing chest pain overnight. Treatment included morphine.

On 13 February one year after*, cardiac catheterization revealed single vessel stenosis in mid left anterior descending. Grafts and stents (in diagonal and left circumflex) were reportedly patent, allowing perfusion of the dominant right coronary artery and distal LAD.

The subject remained hemodynamically stable throughout hospitalization and serial ECGs were unchanged. The event unstable angina was reported as resolved on 13 February one year after* and the subject was discharged pain free. The subject was advised to continue regular medications including dual antiplatelet therapy and proton pump inhibitor.

The subject's last dose of evolocumab as of the data cutoff date of [redacted] was on 14 August same year* (his last dose in the parent study). As of the data cutoff date of [redacted], the subject continued in the study.

The investigator reported that there was not a reasonable possibility that the events of troponin negative acute coronary syndrome and unstable angina were related to study conduct.

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Subject No: [redacted]
Treatment: Parent study and regimen: Study 20110116, Evolocumab SC QM 420 mg +Placebo PO QD. Year 1: Evolocumab SC QM 420 mg + Standard of care
Report: Gait disturbance

Subject [redacted] was a 56-year-old white man participating in Study 20110138 who developed a gait disturbance (reported term: exacerbation of difficulty walking). The subject's medical history included hypertension, hypercholesterolemia, type IIA hyperlipidemia, mixed dyslipidemia, abnormal computerized tomogram coronary artery, electrocardiogram T wave inversion, gout, xanthoma, smoking, severe back pain, trauma 43 years ago (fall from height), with limp, and dragging of the right foot, arthritis, thalassemia, umbilical hernia, and arcus lipoides of the cornea. Concomitant medications included clopidrogrel, zinc, fish oil, vitamin D, allopurinol, diclofenac, combination of candesartan and hydrochlorothiazide, and combination of perindopril combination of docusate sodium, sennoside a+b, combination of macrogol, potassium chloride, sodium bicarbonate and indapamide. Previous and ongoing treatment for primary hyperlipidemia included rosuvastatin.

The subject received evolocumab and placebo in the parent study (Study 20110116) from 07 March same year* to 20 June same year*, and received the first dose of evolocumab in Study 20120138 on 09 September [redacted].

On 10 October same year*, the subject's gait disturbance became exacerbated. The subject also reported an electrical sensation passing up his back during back flexion/extension, right lower paresthesia and multiple falls. Magnetic resonance imaging showed thoracic myelopathy, and a T8/9 decompression surgery was scheduled. The subject was admitted to the hospital on 09 December same year* for a planned T8/9 laminectomy and discectomy. After surgery, the subject's mobility progressed with improvement in lower limb motor function but no change in lower limb paresthesia.

The subject was discharged from the hospital on 13 December same year* with pain medication.

The investigator reported that investigational product was withheld because the week-12 visit was conducted on the same day as surgery. The subject's last dose of evolocumab prior to the event was on 09 September same year*.

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The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose was documented on 09 December same year*.

The investigator considered thoracic myelopathy as contributing factor for the reported event but not a unifying diagnosis. The event of gait disturbance was reported as resolving. The investigator reported that there was not a reasonable possibility that the event exacerbation of difficulty walking was related to evolocumab.

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Subject No: [redacted]
Treatment: Parent study and regimen: Study 20110116; Evolocumab SC Q2W 140 mg + Placebo PO QD Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Coronary artery disease

Subject [redacted] was a 71-year-old white man participating in Study 20120138 who developed coronary artery disease (reported term: worsening of coronary artery disease). The subject's medical history included primary hyperlipidemia/mixed dyslipidemia, coronary artery disease, and transient ischemic attack. Concomitant medications included ranitidine, mometasone, fexofenadine, acetylsalicylic acid, and psyllium hydrophilic mucilloid. Previous and ongoing treatment for primary hyperlipidemia/mixed dyslipidemia included fish oil since two years ago*. Standard of care treatment in Study 20120138 included ezetimibe.

The subject received evolocumab and placebo in the parent study (Study 20110116) from 04 April same year* to 27 June same year* and received the first dose of evolocumab in Study 20120138 on 11 July [redacted]. Approximately 9 days later, on 20 July same year*, the subject reported increasing exertional angina and was diagnosed with coronary artery disease. The baseline electrocardiogram (ECG) showed sinus bradycardia, heart rate 57 beats per minute, and his blood pressure was reported as 140/75 mmHg. A stress echo was performed on 08 October same year* and revealed exercise induced severe hypokinesia of the apical and mid septum, apical inferior wall, apical anterior wall and extending into the mid inferior wall and apical lateral walls. There was exercise induced myocardial ischemia detected in the left anterior descending (LAD) coronary artery territory. On 12 October same year*, the subject was referred to a cardiologist and was started on diltiazem and nicorandil with improvement in angina. A non-urgent coronary angiogram was planned.

On 27 October same year*, computerized tomography (CT) coronary angiogram revealed coronary calcium score of 542 (75th percentile for age), moderate mid LAD stenosis of 50% to 70%, distal left main/ostial LAD stenosis of 25%, mildly dilated ascending aorta of 4.0 cm. A CT angiogram on 01 November two years ago* had previously showed a moderate LAD lesion.

On 06 November same year*, the subject was hospitalized and coronary angiography showed a 95% eccentric lesion in the mid LAD with minor disease of the arteries. The left ventricle contracted normally. On 08 November same year*, ventriculogram revealed severe angina vessel disease. Electrocardiogram showed sinus bradycardia with first-degree atrioventricular block, abnormal

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left axis deviation, and RSR (QR) in V1/V2 consistent with right ventricular conduction delay. On the same day, coronary revascularization was done and percutaneous coronary intervention was performed to the LAD with a drug-eluting stent. Medication included prasugrel, diltiazem, nicorandil, acetylsalicylic acid, glyceryl trinitrate, warfarin, heparin, lidocaine, ezetimibe, iohexol, and midazolam. The event of coronary artery disease was reported to have resolved on 08 November same year*. On 09 November same year*, laboratory tests disclosed creatine kinase of 33 U/L and troponin T of 0.031 ng/mL. The subject was discharged from the hospital on 09 November same year*.

The following medical conditions were reported as predisposing risk factors associated with the reported event: known coronary artery disease, moderate stenosis mid LAD (50% to 70%) per CT angiogram performed on 21 November two years ago*, bilateral thickening of internal carotid arteries (1% to 15% right carotid artery), amaurosis fugax of left eye in 2009, history of tobacco use (fifty-five years ago* to forty-nine years ago*), and age (more than 45 years old).

The date of the subject's last dose of evolocumab prior to the event was not known. Evolocumab was continued. The subject was continuing home dosing as of the data cutoff date of [redacted] and the last in-clinic dose was documented on 19 December same year*.

The investigator reported that there was not a reasonable possibility that the event of coronary artery disease was related to evolocumab or to the device.

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Subject No: [redacted]
Treatment: Parent study and regimen: Study 20110116, Evolocumab SC QM 420 mg+ Placebo PO QD Year 1: Standard of care
Report: Post procedural infection

Subject [redacted] was a 56-year-old white woman participating in Study 20110138 who developed a post procedural infection (reported term: postoperative knee infection). The subject's medical history included hyperlipidemia, mixed dyslipidemia, diabetes mellitus, knee arthroplasty, osteoporosis, and reflux gastritis. Concomitant medication included ergocolecalciferol, a combination of calcium and magnesium, ubidecarenone, and esomeprazole. Previous and ongoing treatment for primary hyperlipidemia or mixed dyslipidemia included ezetimibe.

The subject received evolocumab and placebo in the parent study (Study 20110116) from 28 February same year* to 09 May same year*. She was randomized to standard of care in Study 20120138 on 01 October [redacted].

On 02 October same year*, the subject underwent a procedure reported as a planned tendonotomy. On 04 October same year*, the subject was admitted to the hospital for planned release of iliotibial band as a day surgery procedure and received unspecified prophylaxis antibiotics. After the procedure, on the same day, the subject experienced severe pain, and swelling that did not resolve. The subject was started on cefalexin for knee infection on 09 October same year* and continued with acetaminophen. Approximately 13 days after randomization in Study 20120138, on 14 October same year*, the subject was re-hospitalized due to extensive bruising, pain, and inflammation and was diagnosed with post procedural infection. The subject was treated with intravenous cefazolin from 14 October same year* to 16 October same year* and a combination of caffeine, codeine, doxylamine, and acetaminophen for pain, plus metoclopramide and bisacodyl.

On 15 October same year*, a right knee ultrasound was performed that revealed a small knee joint effusion with fluid in the suprapatellar pouch, up to 5 mm in depth, over the anterolateral aspect of the knee, and subjacent to the recent skin wound; poorly defined increased echogenicity of the subcutaneous tissues with swelling consistent with contusion, with small organizing hematomata was noted. A right knee aspiration was performed under local anesthesia and

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ultrasound guidance. The collection was drained completely with the small volume of blood stained fluid and was sent for microscopy, and culture. On 16 October same year*, the subject was discharged from the hospital; the event of post procedural infection was reported as resolved on 01 November same year*.

As of the data cutoff date of [redacted], the subject was continuing in Study 20120138 on the standard of care arm.

The investigator reported that there was no reasonable possibility that the event of post procedural infection was related to the study conduct.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110116, Placebo SC Q2W + Ezetimibe PO QD 10 mg Year 1: Evolocumab SC 140 mg Q2W + Standard of care
Report: Acute myocardial infarction, Coronary artery stenosis

Subject [redacted] was a 77-year-old white woman participating in Study 20120138 who had acute myocardial infarction (reported term: ST segment elevation myocardial infarction [STEMI]), and coronary artery stenosis (reported term: stenosis of right coronary artery 2). The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, pituitary adenoma, colonic diverticula, atypical chest pain (more frequent since October same year*), gastroesophageal reflux disease, carotid stenosis (50% right, 60% left), hypertension, and atheromatosis of the aorta. Concomitant medications included plantago afra, amlodipine, valsartan, and acetylsalicylate lysine. No prior treatment for hyperlipidemia/dyslipidemia was reported; ongoing treatment included ezetimibe.

The subject participated in the parent study (Study 20110116) from 06 May same year* to 12 August same year* and received the last dose of placebo in the parent study on 26 July same year*. The subject received the first dose of evolocumab in Study 20120138 on 09 October [redacted].

On 12 November same year*, the subject experienced angina-like chest pain and was hospitalized for myocardial infarction. Electrocardiogram showed ST elevation in V1, V2, V3, and V4 and mirror image in V5A, and V9. Peak troponin level was 7.162 ng/ml and creatine phosphokinase was 4089 U/L. On the same day the subject underwent coronary angiography which revealed thrombosis of the left anterior interventricular artery, successfully treated with two stents. Stenosis of the right coronary was also observed. Electrocardiogram showed regular sinus rhythm at 68/min and regression of anterior ST elevation. Echocardiography showed normal sized left ventricle; wall thickness within limits; slight reduction in global systolic function; moderate inferoseptal hypokinesis and normal transmitral flow. It also reported ejection fraction at 50%; subaortic velocity time integral at 17 cm. The subject`s pulmonary artery pressure was 29 mmHg with normal pericardium with no signs of pleural effusion.

The subject's last dose of evolocumab prior to the event of acute myocardial infarction was on 06 November same year*.

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On 05 December same year*, elective angioplasty of right coronary artery was performed with successful placement of 2 stents. The subject was discharged from the hospital on 06 December same year*. On 05 December same year*, the event stenosis of right coronary artery was reported as resolved.

Treatment medications included furosemide, combination of acetylsalicylic acid, and clopidogrel, ramipril, bisoprolol, and esomeprazole. The event STEMI remained as not resolved; however, the subject was discharged from the hospital on 18 November same year*.

The investigator reported that there was not a reasonable possibility that the event STEMI was related to investigational product or to the device.

The subject's last dose of evolocumab prior to the event of coronary artery stenosis was on 03 December same year*. The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose was documented on 08 January one year after*.

The investigator reported that there was not a reasonable possibility that the event stenosis of right coronary artery was related to investigational study drug or to the device.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110116, Evolocumab SC Q2W 140 mg + Placebo PO QD Year 1: Standard of Care
Report: Joint dislocation

Subject [redacted] was a 53-year-old white woman participating in Study 20120138 who experienced a joint dislocation (reported term: dislocation of the right foot metatarsal). The subject's medical history included dyslipidemia, Morton's neuralgia, right foot arthralgia, and right hallux valgus. Previous treatment for hyperlipidemia included cholestyramine. Concomitant medication included ezetimibe.

The subject received evolocumab in the parent study (Study 20110116) from 23 May same year* to 09 October same year*. She was randomized to standard of care in Study 20120138 on 09 October [redacted].

On an unknown date in August same year*, the subject had pain in the right foot. Magnetic resonance imaging showed potential worsening of Morton's disease with dislocation of the right foot metatarsal.

On 29 November same year*, the subject was hospitalized and was treated with tramadol and paracetamol. The subject had moderate hallux valgus deformity of 15 degrees with complete dislocation of the lateral sesamoid bone. The subject was treated for Morton's second and third metatarsal space with infiltration and resection. On the same date, the subject underwent surgical correction of hallux valgus deformity and dislocation of the right foot metatarsal including a Chevron osteotomy. The subject was treated postoperatively with unspecified anticoagulants and analgesic medications, and was recommended to walk on postoperative shoes for joint mobilization. The subject was discharged from the hospital on 02 December same year*, and the event of dislocation of right foot metatarsal was reported as resolved on the same day.

The subject's last dose of evolocumab prior to the event was unknown. As of the data cutoff date of [redacted], the subject was continuing in the study.

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The investigator reported that there was not a reasonable possibility that the event of dislocation of right foot metatarsal was related to study participation.

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110116, Placebo SC QM + Ezetimibe PO QD 10 mg Year 1: Standard of Care
Report: Unstable angina

Subject [redacted] was a 69-year-old white woman participating in Study 20120138 who experienced unstable angina (reported term: unstable angina pectoris). The subject`s medical history included dyslipidemia, hypercholesterolemia, hypertension, type 2 diabetes mellitus, chronic gastritis, diabetic polyneuropathy, right bundle branch block, prolactinoma, and goiter. Previous treatment for hyperlipidemia was not provided. Concomitant medications included combination of candesartan and hydrochlorothiazide, metoprolol, and diclofenac.

The subject received placebo and ezetimibe in the parent study (Study 20110116) from 30 April same year* to 23 July same year*. The subject was randomized to standard of care in Study 20120138 on 18 September [redacted].

On 20 February one year after*, the subject experienced angina pectoris. The subject did not have any previous episodes of angina. On 26 February one year after*, myocardial scintigraphy showed ischemia. On 28 February one year after*, the subject was hospitalized. Myocardial scintigraphy was repeated and confirmed ischemia. Additionally on the same date, the subject underwent cardiac catheterization and stent implantation. The subject was also treated with atorvastatin, acetylsalicylic acid and clopidogrel. The outcome of the event unstable angina was reported as resolved on 01 March one year after* and the subject was discharged from the hospital on the same date. The patient started atorvastatin 20 mg once daily on 03 March one year after*.

The subject did not receive evolocumab. As of the data cutoff date of [redacted], the subject continued in the study on the standard of care arm.

The investigator reported that there was not a reasonable possibility that the event of unstable angina was related to study participation.

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Subject No: [redacted]
Treatment: Parent study and regimen: Study 20110116; Placebo SC Q2W + Ezetimibe PO QD 10 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of care
Report: Peripheral artery aneurysm

Subject [redacted] was a 56-year-old white man participating in Study 20120138 who was diagnosed with peripheral artery aneurysm (reported term: progressive peripheral artery disease, aneurysm left groin). The subject's medical history included dyslipidemia. The subject had complaints of claudication since three years ago*. Previous treatment for the condition under study was not provided. Ongoing concomitant medications included carbasalate calcium, clopidogrel, and pantoprazole.

The subject received placebo and ezetimibe in the parent study from 22 May same year* to 22 August same year*, and received the first dose of evolocumab in Study 20120138 on 22 August [redacted].

On an unknown date in October same year*, the subjected reported an event of progressive peripheral artery disease. On 17 October same year*, the subject's ultrasound showed left common femoral artery stenosis (> 50%), an aneurysm, and left superficial femoral artery stenosis (> 50%). The subject underwent endarterectomy and intraoperative percutaneous transluminal angioplasty on 08 January one year after*. On 10 January one year after*, the subject was discharged from the hospital. The outcome of the event progressive peripheral artery disease was resolved on 10 January one year after*. Evolocumab was continued and the subject continued in the study.

The subject's last dose of evolocumab prior to the event was not known. As of the data cutoff date of [redacted], the subject was continuing home dose administration and the last in-clinic dose was documented on 14 November same year*.

The investigator reported that there was not a reasonable possibility that the event of progressive peripheral artery disease was related to evolocumab or to the device.

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Subject No: [redacted]
Treatment: Parent study and regimen: 20110116; Placebo SC QM + Ezetimibe PO QD 10 mg Year 1: Standard of care
Report: Osteoarthritis

Subject [redacted] was a 62-year-old white woman participating in Study 20120138 who had osteoarthritis (reported term: joint locking right knee). The subject's medical history included dyslipidemia, cholecystectomy, osteoarthritis diagnosed after arthroscopy in 1996, and hysterectomy. Previous treatment for the condition under study was not reported. Concomitant medications included ergocalciferol.

The subject received placebo and ezetimibe in the parent study (Study 20110116) from 24 May same year* to 19 July same year*, and was randomized to standard of care in Study 20120138 on 21 August [redacted].

On an unknown date in December same year*, the subject was noted to have gradual worsening of right knee pain and developed joint locking. On 08 January one year after*, the subject visited the orthopedic surgery department and was diagnosed with worsening of osteoarthritis. On 29 January one year after*, the subject was admitted to the hospital and underwent implantation of prosthetic knee. Treatment medications reported after the onset of event included paracetamol, diclofenac, fondaparinux, and oxycodone. The outcome of the event of joint locking right knee was reported as resolved on 29 January one year after* and the subject was discharged on 01 February one year after*.

At the time of the data cutoff date of [redacted], the subject was continuing standard of care treatment.

The investigator reported that there was not a reasonable possibility that the event of joint locking of right knee was related to the study conduct.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110116, Placebo SC QM + Ezetimibe PO QD 10 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Prostate cancer

Subject [redacted] was a 60-year-old white man participating in Study 20120138 who was diagnosed with prostate cancer (reported term: prostate carcinoma). The subject's medical history included primary hyperlipidemia and mixed dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea syndrome with continuous positive airway pressure (CPAP), hypertension; prostate biopsy in four years ago* (nontumor pathology), in December two years ago* (normal rectal examination), and in February one year ago* (nontumor pathology); and worsening of prostate related urinary symptoms. Concomitant medications included metformin and sitagliptin. Ongoing treatment for primary hyperlipidemia and mixed dyslipidemia included ezetimibe.

The subject received placebo and ezetimibe in the parent study from 27 May same year* to 16 August same year*. The subject received the first dose of evolocumab in Study 20120138 on 03 October [redacted]. The subject had benign prostatic hypertrophy with elevated prostate-specific antigen (PSA) since four years ago*. The subject had several biopsies performed and the results were negative. The subject had continued clinical symptoms, so prostatectomy surgery was scheduled. On 21 October same year*, the subject's PSA was 6.28 ng/mL.

On 20 January one year after*, the subject was admitted to the hospital for transurethral resection of the prostate (TURP). On 21 January one year after*, TURP was performed under general anesthesia. On the same day, prostate pathologyindicated prostate carcinoma and noted benign hyperplasia and adenocarcinoma of conventional pattern with "Gleason score 6 (3+3)" affecting 2% of the tissues provided. The outcome of the event prostate carcinoma was reported as resolving. On 24 January one year after*, the subject was discharged

The subject's last dose of evolocumab prior to event was on 19 December same year*. The subject was continuing home dosing as of the data cutoff date of [redacted] and the last in-clinic dose was documented on 26 December same year*.

The investigator reported that there was not a reasonable possibility that the event of prostate carcinoma was related to evolocumab or to the device.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110116, Evolocumab SC QM 420 mg + Placebo PO QD Year 1: Standard of Care
Report: Atrioventricular block

Subject [redacted] was a 56-year-old white man participating in Study 20120138 who had atrioventricular (AV) block (reported term: syncope by AV block). The subject's medical history included dyslipidemia, hypercholesterolemia, hypertension and prior hospital admission in sixteen years ago* for chest pain and left bundle branch block with benign coronarography. Concomitant medication included bisoprolol. Ongoing treatment for hypercholesterolemia included ezetimibe.

The subject received evolocumab in the parent study from 29 July same year* to 07 October same year*. The subject was randomized to standard of care in Study 20120138 on 21 October [redacted].

On 13 December same year*, the subject had syncope. The subject recovered, then had a pre-syncope episode on 18 December same year* and was hospitalized. On the same day, the subject underwent electrocardiographic monitoring during stress test, which revealed AV block. Subsequently, a pacemaker was implanted. Treatment medication after the onset of the event included ramipril. The outcome of the event syncope by AV block was reported as resolved on 03 January one year after* and the subject was discharged from the hospital on the same day.

As of the data cutoff date of [redacted], the subject continued in the study and was receiving standard of care.

The investigator reported that there was not a reasonable possibility that the event of syncope by atrioventricular block was related to study conduct.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110116, Evolocumab SC QM 420 mg + Placebo PO QD Year 1: Evolocumab SC 420 mg QM + Standard of care
Report: Accelerated hypertension

Subject [redacted] was a 61-year-old white man participating in Study 20120138 who had accelerated hypertension. The subject's medical history included angina due to atherosclerotic disease, myocardial infarction, coronary artery bypass graft, congestive heart failure, anxiety, depression, atrial fibrillation, carotid or vertebral artery disease, arthritis, asthma, hypertension, obesity, cerebrovascular or peripheral arterial disease, stroke/cerebral infarction, transient ischemic attack, and type 2 diabetes mellitus. Concomitant medications included fluoxetine, acetylsalicylic acid, prednisone, celecoxib, omega-3 fatty acids, and ubidecarenone.

The subject participated in the parent study (Study 20110116) from 12 April same year* to 08 July same year* and received the last dose of evolocumab in the parent study on 08 July same year*. The subject received the first dose of evolocumab in Study 20120138 on 10 July [redacted].

Approximately 8 months later, on 24 March one year after*, the subject presented to emergency room with symptoms of left arm pain. His blood pressure was found to be out of control. All cardiac diagnostics were within normal limits. On 25 March one year after*, the subject was hospitalized for further treatment and observation, as his blood pressure was not lowered or stabilized. Left arm pain was determined to be musculoskeletal. No treatment information was reported. The outcome of the event accelerated hypertension was reported as resolved on 26 March one year after*. The subject was discharged from the hospital on an unknown date.

The subject's last dose of investigational product prior to the event was on 19 March one year after*. Investigational product was continued.

The subject's last dose of evolocumab prior to the event was on 23 December same year*. The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose was documented on 23 December same year*.

The investigator reported that there was not a reasonable possibility that the event accelerated hypertension was related to investigational study drug or device.

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Subject No: [redacted]
Treatment: Parent study and regimen: Study 20110116, Evolocumab SC Q2W 140 mg + Placebo PO QD Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Osteoarthritis

Subject [redacted] was a 63-year-old black woman participating in Study 20120138 who had osteoarthritis (reported term: worsening left knee osteoarthritis). The subject's medical history included hyperlipidemia, hypertension, type 2 diabetes mellitus, gastroesophageal reflux disease, anxiety, depression, menopausal symptoms, seasonal allergy, sleep apnea syndrome, cholelithiasis, dyspepsia, neuralgia, obesity, back pain, spinal osteoarthritis, rubber sensitivity, and drug hypersensitivity. Concomitant medications included metoprolol, warfarin, paracetamol, hydrocodone, insulin glargine, insulin lispro, folic acid, meloxicam, multivitamins, fexofenadine, citalopram, furosemide, gabapentin, lisinopril, magnesium, potassium chloride, omeprazole, iron, and cyanocobalamin. Previous and ongoing treatment for hypercholesterolemia included pravastatin.

The subject received evolocumab and placebo in the parent study (Study 20110116) from 04 April same year* to 20 June same year*. She received the first dose of evolocumab in Study 20120138 on 18 July [redacted]. Approximately 2 months later, on 14 September same year*, a serious adverse event of osteoarthritis was reported. The subject was hospitalized and action taken was reported as surgical intervention (left knee replacement). The event of osteoarthritis was reported as resolved on 21 September same year* and the subject was discharged on the same day.

The date of the subject's last dose of evolocumab prior to the event was not known. Evolocumab was continued. The subject was continuing home dosing as of the data cutoff date of [redacted] and the last in-clinic dose was documented on 09 January one year after*. The subject continued in the study.

The investigator reported that there was no reasonable possibility that the event of osteoarthritis was related to evolocumab or to the device.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110116, Placebo SC QM + Ezetimibe PO QD 10 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Urosepsis

Subject [redacted] was a 63-year-old white man participating in Study 20120138 who experienced urosepsis (reported term: urinary tract infection with sepsis). The subject's medical history included hypercholesterolemia, gastroesophageal reflux disease, gout, previous intracranial hemorrhage with consequent seizure disorder, hyperkeratosis, palpitations, hypertension, cerebrovascular disease, and transient ischemic attack. Previous treatment for hyperlipidemia was not provided. Concomitant medications included allopurinol, clonidine, metoprolol, acetylsalicylic acid, and paracetamol with codeine.

The subject received placebo and ezetimibe in the parent study from 19 March same year* to 10 June same year*. The subject received the first dose of evolocumab in Study 20120138 on 21 June [redacted].

On 23 December same year*, the subject was diagnosed with urosepsis. Other events reported included acute renal failure and abnormal liver function test. The subject was treated with ciprofloxacin, sodium chloride infusion, paracetamol, heparin, docusate, and senna. The event of urosepsis was resolved by 07 January one year after*.

The subject's last dose of evolocumab prior to event was on 16 December same year*. As of the data cutoff date of [redacted], home dosing was continuing, with 16 December same year* the last documented in-clinic dose.

The investigator reported that there was not a reasonable possibility that the event of urosepsis was related to evolocumab or to the device.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110116, Placebo SC Q2W + Ezetimibe PO QD 10 mg Year 1: Standard of Care
Report: Acute myocardial infarction

Subject [redacted] was a 70-year-old white man participating in Study 20120138 who experienced acute myocardial infarction (reported term: non ST elevation myocardial infarction). The subject's medical history included dyslipidemia; coronary artery bypass surgery with internal mammary artery and saphenous vein graft (SVG); coronarography (in nine years ago*) showing left main trunk < 50%, left anterior descending (LAD) > 50%, left internal mammary artery (LIMA) to LAD patent, right coronary artery > 50%, right internal mammary artery (RIMA) to obtuse marginal patent, SVG to PDA 80% and ejection fraction (EF) 60%; percutaneous transluminal coronary angioplasty to mid right coronary artery, and stenting (drug eluting); of the SVG to posterior descending artery (PDA), both in nine years ago*. Concomitant medications included clopidogrel, hydrochlorothiazide, lisinopril, and amlopidine.

The subject received placebo and ezetimibe in the parent study from 09 May same year* to 30 July same year*. The subject was randomized to standard of care in Study 20120138 on 05 December [redacted].

On 03 January one year after*, the subject presented to the emergency department with chest pain. Laboratory tests diagnosed non ST elevation myocardial infarction and the subject was hospitalized on the same day. Laboratory tests showed troponin t 0.553 to 0.819 ng/mL, blood creatine phosphokinase (CK) 376 to 391 μL, blood creatine phosphokinase MB (CK MB) 9.0% to 8.5% of total CPK, potassium 3.8 mg/dL, magnesium 1.8 mg/dL, creatinine 1.17 mg/dL, myoglobin 33.2 to 33.7 ng/mL; chest radiograph showed no acute changes, electrocardiogram was normal with right bundle branch block (RBBB), echocardiogram with EF 40%.

On the same day, cardiac catheterization revealed that LIMA and RIMA were open, SVG to PDA were occluded with thrombus. On 04 January one year after*, laboratory tests revealed troponin t 0.918 ng/mL, CK 299 μL, CK MB 8.1% (of total CPK), potassium 4.4 mg/dL, magnesium 2.6 mg/dL, creatinine 1.24 mg/dL, myoglobin 24.1 mg/mL and normal electrocardiogram with partial RBBB. On 05 January one year after*, laboratory tests revealed potassium 4.1 mg/dL, magnesium 2.2 mg/dL, creatinine 1.45 mg/dL and normal echocardiogram with EF 62%. Treatment medications reported after the onset of event included ticagrelor, heparin, acetylsalicylic acid, magnesium sulphate, and potassium

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chloride. On 05 January one year after*, the event was reported as resolved and the subject was discharged from the hospital on the same day.

As of the data cutoff date of [redacted], the subject was continuing in the study and was receiving standard of care.

The investigator reported that there was not a reasonable possibility that the event of non ST elevation myocardial infarction was related to study conduct.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110116; Evolocumab SC QM 420 mg + Placebo PO QD Year 1: Standard of care
Report: Transient ischemic attack

Subject [redacted] was a 72-year-old white woman participating in Study 20120138 who had a transient ischemic attack (TIA) (reported term: right hemisphere TIA of the brain). The subject's medical history included hyperlipidemia, mixed dyslipidemia, codeine allergy and a family history (mother, at the age of 90) of stroke. The subject's medical history also included statin intolerance, metabolic syndrome, but no previous history of hypertension. The subject did not receive any previous treatment for the condition under study due to statin intolerance. The subject did not have similar illness in the past or any similar symptoms. Ongoing concomitant medications include pitavastatin, clopidogrel, lisinopril, acetylsalicylic acid, and cetirizine.

The subject received evolocumab and placebo in the parent study from 26 February same year* to 21 May same year*. The subject started receiving standard of care in Study 20120138 on 20 June [redacted].

On 06 November same year*, the subject developed numbness of the left arm and weakness of the left leg and was hospitalized on that day. The subject reported that the numbness of the left side lasted only for a few minutes. On arrival to the hospital, a stroke alert was called, however, the subject was not a candidate for thrombolysis. On the same day, an electrocardiogram was normal, sinus rhythm at a rate of 66, a computerized tomogram (CT) scan of the brain showed no acute intracranial hemorrhage or any mass effect. Radiograph of the chest showed no acute findings, carotid ultrasound showed scattered calcified atheromatous plaques and no evidence of hemodynamically significant stenosis. A magnetic resonance imaging of the brain showed no evidence of stroke or hemorrhage, innumerable foci of T2 hyperintensity surrounding the lateral ventricles; suspicious for demyelinating disease or hypertensive small vessel changes. Treatment for the event included clopidogrel and acetylsalicylic acid. The event right hemisphere TIA of the brain was reported as resolved on 06 November same year*. On 07 November same year*, the subject was discharged from the hospital.

As of the data cutoff date of [redacted], the subject was continuing in the study and receiving standard of care treatment.

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The investigator reported that there was no reasonable possibility that the events of right hemisphere TIA of brain and chronic microvascular disease were related to any study activity.

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110116; Placebo SC QM + Ezetimibe PO QD 10 mg Year 1: Standard of care
Report: Hyponatremia

Subject [redacted] was a 75-year-old white woman participating in Study 20120138 who developed hyponatremia. The subject's medical history included hyperlipidemia, mixed dyslipidemia, hypertension and diabetes mellitus. Previous and ongoing treatment for the condition under study included an omega-3-acid ethyl ester and ezetimibe. Concomitant medications included nitrofurantoin, acetylsalicyclic acid, omeprazole, diphenhydramine, hydroxyzine, lisinopril, metformin, sitagliptin, cefalexin and a combination of sulfamethoxazole and trimethoprim.

The subject received ezetimibe and placebo in the parent study from 30 April same year* to 25 July same year*. The subject started receiving standard of care in Study 20120138 on 31 July [redacted].

Laboratory tests performed on 31 July same year*, revealed sodium of 137 mEq/L, potassium of 4.6 mEq/L, chloride of 95 mEq/L and bicarbonate of 24 mEq/L. At the week-12 follow up visit on 23 October same year*, the subject reported an infection in her lower leg requiring antibiotic treatment. Subsequently, the subject complained of nausea attributed to antibiotics she received. Laboratory tests revealed hyponatremia with a sodium level of 127 mEq/L. Additional laboratory tests revealed potassium of 5.7 mEq/L, chloride of 89 mEq/L, bicarbonate of 18 mEq/L. On 25 October same year*, the subject was hospitalized for the evaluation of hyponatremia and hyperkalemia. Upon admission, the subject gave a history of excessive water intake while on antibiotics for leg infection. Admission laboratory investigations showed sodium 125 mEq/L, potassium 5.3 mEq/L, chloride 88 mEq/L, and bicarbonate 25 (mEq/L) and urinalysis revealed 13-30 white blood cells. Treatment for the event included water restriction, antibiotics (clindamycin, cephalexin, combination of sulfamethoxazole and trimethoprim) and nitrofurantoin for urinary tract infection.

On 27 October same year*, the subject was feeling much better with improving sodium levels and was discharged from the hospital. The outcome of the event hyponatremia was reported as resolved on 27 October same year*. At the time of discharge laboratory investigations showed potassium 4.8 mEq/L (within normal limit) and sodium 131 mEq/L. As of the data cutoff date of [redacted], the subject was continuing in the study and was receiving standard of care treatment.

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The investigator reported that there was not a reasonable possibility that the events of hyponatremia and urinary tract infection were related to any study activity.

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110117, Evolocumab SC QM 420 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Acute myocardial infarction; Hematoma; Acute pulmonary edema; Chest discomfort

Subject [redacted] was a 74-year-old white man participating in Study 20120138 who experienced acute myocardial infarction (reported term: non-ST elevation myocardial infarction); hematoma; acute pulmonary edema (reported term: acute pulmonary edema), and chest discomfort (reported term: chest tightness and dull chest ache). The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, hypercholesterolemia, abdominal aortic aneurysm (AAA) diagnosed on 23 October five years ago*, renal artery aneurysm, coronary artery bypass grafting in twelve years ago* and two years ago*, ventricular tachycardia (VT), hypertension, aortic valve replacement, acute pancreatitis, hypotension, emphysema, benign prostatic hyperplasia, left bundle branch block, and gastroesophageal reflux disease. Previous and ongoing treatment for hyperlipidemia included rosuvastatin. Concomitant medication included acetylsalicylic acid, clopidogrel, esomeprazole, folic acid, olmesartan, lercanidipine, tamsulosin, fentanyl, midazolam, and paracetamol.

The subject received evolocumab in the parent study from 13 March same year* to 09 May same year*, and received the first dose of evolocumab in Study 20120138 on 25 September [redacted].

On 18 December same year*, the subject was hospitalized for planned open repair of the AAA. Postoperatively, the subject developed respiratory distress and required respiratory support with continuous positive airway pressure (CPAP) until the fourth postoperative day. The subject's electrocardiogram showed T wave inversion and the creatine kinase (CK) level increased from 105 to 275 IU/L. On 23 December same year*, the subject's temperature was 38.1°C and laboratory tests revealed troponin I 0.97 ng/mL and CK 274 IU/L. The cause of respiratory difficulty was thought to be related to a non-ST elevation myocardial infarction (NSTEMI). Additional treatment medications reported after onset of the event included furosemide, acetylsalicylic acid, clopidogrel, potassium chloride, magnesium, normal saline, heparin, ceftriaxone, metronidazole, piperacillin sodium and tazobactam sodium, lercanidipine, tamsulosin, fresh frozen plasma, platelets, albumin, compound sodium lactate, oxygen, etofibrate, metoclopramide, ondansetron, oxycodone, temazepam, lidocaine, and a combination of dried aluminum hydroxide gel, magnesium hydroxide, and simethicone.

The subject's last dose of evolocumab prior to event was on 16 December same year*. On 31 December same year*, the outcome of the event NSTEMI was reported as resolved and the

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subject was discharged. The investigator indicated that the event of NSTEMI was a potential endpoint of the study. Evolocumab was continued.

The investigator reported that there was not a reasonable possibility that the event acute myocardial infarction was related to evolocumab or to the device.

Following the open repair of AAA, the subject developed a left groin wound. On 14 January one year after*, the subject was hospitalized and underwent debridement of the left groin wound, which was revealed to be a hematoma. Treatment reported after the onset of the event included lidocaine, temazepam, paracetamol, and a combination of dried aluminum hydroxide gel, magnesium hydroxide, and simeticone. The outcome of the hematoma was reported as resolved on 15 January one year after* and the subject was discharged from the hospital on the same day. Evolocumab was continued.

The subject's last dose of the evolocumab prior to the event was on 16 December same year*.

The investigator reported that there was not a reasonable possibility that the event of hematoma was related to evolocumab or to the device.

On 02 February one year after*, the subject began having shortness of breath, palpitation, and chest discomfort and developed acute pulmonary edema. The investigator reported that recently the subject's furosemide and antihypertensive medications were discontinued because of miscommunication with the vascular surgeon.

On 04 February one year after*, the subject was admitted to the emergency department and placed on biphasic intermittent positive airway pressure (BIPAP); CPAP 7, and fraction of inspired oxygen (FiO2) 60% with respiratory rate of 30. On the same day, the subject was admitted to the intensive care unit (ICU) with high blood pressure of 190/110 mmHg. The subject's electrocardiogram (ECG) showed VT with 120 bpm with troponin rise, and he was treated according to acute coronary syndrome protocol. Echocardiogram showed ejection fraction (EF) > 30% and dyskinetic left ventricle (LV). On the same day, computed tomography (CT) pulmonary angiogram showed no evidence of pulmonary embolism. The subject's laboratory test showed brain natriuretic peptide 25300 ng/L. The subject was given glyceryl trinitrate and responded well and was re-introduced to another antihypertensive. The subject was also treated with furosemide.

On 05 February one year after*, the subject's ECG showed ventricular tachycardia (VT); T wave inversion in leads II and III, and V1 to V6. The subject was asymptomatic during the VT with

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an associated BP of 78/41 mmHg. Echocardiogram showed a mild LV dilation with moderately severe regional impairment of systolic function (EF 29%), mild bi-atrial dilatation, moderate mitral regurgitation, mild to moderate aortic biologic prosthesis paravalvular regurgitation, and elevated estimated pulmonary artery systolic pressure of 46 mmHg.

On 06 February one year after*, electrocardiogram (ECG), echocardiogram and chest radiogram did not differ from the previous days. The subject also had episodes of sleep apnea with apnea events of 40 seconds.

On 07 February one year after*, troponin was 0.3 to 1 ng/mL and the subject was stable. Treatment medications after the onset of event included acetylsalicylic acid, pantoprazole, and magnesium aspartate. The outcome of the event of acute pulmonary edema was reported as resolved on 07 February one year after* and the subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event was on 17 January one year after*. Evolocumab was continued.

The investigator reported that there was not a reasonable possibility that the event acute pulmonary edema was related to evolocumab or to the device.

On 18 March one year after*, the subject presented to the hospital with chest tightness and dull chest ache relieved by glyceril trinitrate and was hospitalized on the same day. ECG showed left bundle branch block (LBBB) and no acute changes. Additionally, laboratory test showed troponin of less than 0.04 ng/ml. On 25 March one year after*, the post-dipyridamole tomographic images (study) demonstrated a small, predominantly fixed defect involving the apex and apical inferior wall with peri-infarct reversibility. There was no evidence of moderate or large size reversible ischemia. There was evidence of dilated cardiomyopathy, and impairment of the left ventricular systolic function. The subject's principal diagnosis was suspected angina with mild troponin leak. Treatment reported after the onset of event included furosemide, enoxaparin sodium, bisoprolol, clopidogrel, glyceryl trinitrate, olmesartan, pantoprazole, and rosuvastatin. The outcome of the events of chest tightness and dull chest ache was reported as resolved on 19 March one year after* and the subject was discharged from the hospital on the same day in a stable condition.

The subject's last dose of evolocumab prior to the event was on 12 March one year after*, also the last known dose before the data cutoff. Evolocumab was continued. As of the data cutoff date of [redacted], the subject continued in the study.

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The investigator reported that there was not a reasonable possibility that the event “chest pain and discomfort” was related to evolocumab or to the device.

Subject No: [redacted]
Treatment: Parent study and regimen: Study 20110117, Evolocumab SC QM 420 mg Year 1: Evolocumab SC QM 420 mg + Standard of care
Report: Uterine leiomyoma

Subject [redacted] was a 48-year-old white woman participating in Study 20120138 who developed a uterine leiomyoma. The subject's medical history included familial hypercholesterolemia, dyslipidemia, myocardial infarction with coronary artery bypass graft, epilepsy, hyperhomocysteinemia, phenytoin hypersensitivity, arthritis, past smoking, allergy to arthropod bite, menorrhagia, and uterine leiomyoma diagnosed by ultrasound in one year ago*. Concomitant medications included gabapentin, acetylsalicylic acid, fish oil, and folic acid. Previous and ongoing treatment for primary hyperlipidemia or mixed dyslipidemia included rosuvastatin and ezetimibe.

The subject received evolocumab in the parent study from 09 July same year* to 03 September same year*, and received the first dose of evolocumab in Study 20120138 on 02 October [redacted].

Approximately 2 weeks later, on 15 October same year*, the subject was hospitalized for total abdominal hysterectomy and salpingo-oophorectomy due to the history of menorrhagia and uterine fibroids. Histopathology report of the same date revealed adenomyosis of the uterus with no diagnostic abnormalities in the cervix, right tube and ovary. The event of hysterectomy was reported as resolved on 18 October same year* and the subject was discharged on that day.

The subject's last dose of evolocumab prior to the event was on 02 October same year*. Evolocumab was continued. The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose was documented on 19 December same year*.

The investigator reported that there was not a reasonable possibility that the event of uterine leiomyoma was related to evolocumab or device.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110117, Placebo SC Q2W Year 1: Standard of Care
Report: Chest pain, Musculoskeletal chest pain

Subject [redacted] was a 51-year-old white woman participating in Study 20120138 who developed chest pain and musculoskeletal pain. The subject's medical history included hyperlipidemia, familial hypercholesterolemia since one year ago*, familial dyslipidemia, coronary artery disease, atypical retrosternal pain, atherosclerotic coronary and vascular disease, hysterectomy, surgery for cerebrovascular accident in five years ago*, tabagism until approximately 1 year ago, and unilateral ovariectomy. Concomitant medications reported included clopidogrel, glyceryl trinitrate, acetylsalicylic acid, amlodipine, candesartan, cholestyramine, pantoprazole, phenoxymethylpenicillin, azithromycin, mometasone, cyclobenzaprine and codeine. Previous and ongoing treatment for hyperlipidemia included ezetimibe, rosuvastatin and colestyramine.

The subject received evolocumab in the parent study (Study 20110117) from 09 July same year* to 17 September same year* and was randomized to the standard of care arm in Study 20120138 on 24 October [redacted].

On 15 January one year after*, the subject referred atypical retrosternal pain during external cardio visit. The subject was hospitalized on 06 February one year after* for stent placement in left iliac.

On 01 March one year after*, the subject experienced chest pain at work and was hospitalized. The subject was treated with nitroglycerine (glyceryl trinitrate) and heparin. According to the subject, cardiac enzymes were normal and there were no changes in the electrocardiogram (ECG). On 02 March one year after*, coronaro/ventriculo, bronchial angiography, and transthoracic echocardiogram was performed. On 03 March one year after*, the subject was discharged from hospital. The event chest pain was reported as resolved as of that date.

On 05 March one year after*, the subject complained of retrosternal pain. ECG was found abnormal with ventricular frequency 110 b/min, PR interval 128 ms, QRS duration 92 ms, QT/QTc 328/443 ms, P-R-T axes 54-29-149, sinus tachycardia, and left ventricular hypertrophy with abnormal repolarization. Laboratory tests did not show significant abnormalities.

On 06 March one year after*, heart echocardiography with doppler showed diffuse thickening (sclerosis) of the aortic valve without significant functional change; there was a presence of small septum aneurysm without left-right shunt. All other examinations were within normal limits.

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On 07 March one year after*, coronarography showed no changes. However, coronary anatomy was found abnormal with 30% stenosis at the distal location of common trunk segment, and at the proximal location of circumflex segment, and 40% stenosis at the mid location of IVA, and right segment, atherosclerosis was found < 50%. Fraction flow reserve (FFR) was noted in range of 0.85 to 0.90, and fractional flow reserve [FFR (10 cc adenosine)] was 0.78 to 0.87

Treatment medications reported after the onset of the event included pantoprazole, dexlansoprazole, fentanyl, paracetamol, oxazepam, and oral unspecified hypoglycemic agents except glucophage.

The event was reported as resolved on 11 March one year after* and the subject was discharged from the hospital on the same day. The subject was started on bisoprolol and the dose was later increased.

As of the data cutoff date of [redacted], the subject was continuing in Study 20120138 and was receiving standard of care treatment.

The investigator reported that there was not a reasonable possibility that the event of chest pain was related to investigational drug or device.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110117,Evolocumab SC Q2W 140 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Lower respiratory tract infection

Subject [redacted] was a 58-year-old Asian woman participating in Study 20120138 who experienced a lower respiratory tract infection (reported term: chest infection). The subject's medical history included hyperlipidemia and familial hypercholesterolemia since 1996 and impaired fasting glucose.

Concomitant medications included acetylsalicylic acid, and famotidine. Previous and ongoing treatment for hyperlipidemia included simvastatin and ezitimibe.

The subject received evolocumab in the parent study from 04 July same year* to 09 September same year*. The subject received the first dose of evolocumab in Study 20120138 on 11 October [redacted].

On 25 February one year after*, the subject complained of cough and fever along with diarrhea and vomiting. The subject had visited a general practitioner and was prescribed unspecified medications. On 28 February one year after*, the subject was hospitalized as she had respiratory tract infection symptoms and her fever with a temperature of 38 to 39 degrees Celsius had not subsided. A chest radiograph showed left lower zone haziness and right lower zone consolidation. A nasopharyngeal aspirate (NPA) test for influenza was positive for influenza A. Laboratory tests revealed white blood cell count of 3.8 x 10^9/L and lymphocyte count of 0.9 x 10^9/L. The subject was diagnosed with chest infection. The subject was treated with oseltamivir and a combination of pseudoephedrine and triprolidine.

On 28 February one year after*, a sputum culture was performed which showed heavy growth of oral commensals isolated. Peripheral blood culture showed no growth after five days of incubation. The subject's mid stream urine showed mixed bacterial growth which was considered to be probably due to contamination. Nucleic acid detection using RT-PCR (reverse transcriptase polymerase chain reaction) for influenza virus A RNA and influenza A subtype H1 RNA were found to be positive. Nucleic acid detection using RT-PCR for influenza A subtype H3 RNA was found to be negative.

The outcome of the event was reported as resolving and the subject was discharged from hospital on the same day.

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The subject's last dose of evolocumab before the event was on 28 February one year after*. As of the data cutoff date of [redacted], the subject continued in the study and received last dose of evolocumab on 28 February one year after*.

The investigator reported that there was not a reasonable possibility that the event of influenza A was related to evolocumab or to the device.

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Subject No: [redacted]
Treatment: Parent study and regimen: Study 20110117; Evolocumab SC QM 420 mg Year 1: Standard of care
Report: Asthenia, Syncope, Esophagitis, Arterial stenosis

Subject [redacted] was a 53-year-old white woman participating in Study 20120138 who developed asthenia (reported term: weakness), syncope (reported term: collapse [syncope]), esophagitis, and arterial stenosis (reported term: stenosis arteria carotis left). The subject's medical history included primary hyperlipidemia/mixed dyslipidemia, angina due to atherosclerotic coronary disease, arteriosclerosis, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, transient ischemic attack, stroke/cerebral infarction, , New York Heart Association (NYHA) class II congestive heart failure with left ventricular ejection fraction between 40% and 49%, type 2 diabetes mellitus, gastric bypass, past smoking, obesity, and a family history of premature coronary heart disease. Concomitant medications included acetylsalicylic acid, metformin, dipyridamole, isosorbide dinitrate, paroxetine, pantoprazole, and isosorbide mononitrate. Previous and current treatment for primary hyperlipidemia or mixed dyslipidemia included atorvastatin, ezetimibe, and colesevelam.

The subject received evolocumab in the parent study (Study 20110117) from 19 April same year* to 13 June same year*. She was randomized to standard of care in Study 20120138 on 03 September [redacted].

Approximately 1 month later, on 14 October same year*, the subject went to the emergency room after collapsing. The subject complained of melena for 6 days and was admitted to the hospital. On admission, her hemoglobin was 8.1 g/dL. On 15 October same year*, hemoglobin was 7.7 g/dL and an esophago-gastro-duodenoscopy was performed. Endoscopy showed chronic esophagitis, and no further abnormalities. The subject's final diagnosis was esophagitis. Treatment included pantoprazole. The events of asthenia and collapse were reported to have resolved on 15 October same year*, and the subject was discharged from the hospital on that date. The event of esophagitis was reported to have resolved on 29 October same year*.

On 25 October same year*, the subject was diagnosed with left carotid stenosis, and was admitted to the hospital on the same day. Treatment included stent placement in the left carotid artery on 25 November same year*, diazepam and clopidogrel. The subject was discharged from the hospital on 26 October same year*. The event of arterial stenosis was reported as resolved on 25 November same year*.

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As of the data cutoff date of [redacted], the subject was continuing in the study on the standard of care arm.

The investigator reported that there was not a reasonable possibility that the events of asthenia, syncope, esophagitis and arterial stenosis were related to any study activity.

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110117, Placebo SC QM Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Interstitial lung disease, Pulmonary fibrosis

Subject [redacted] was a 58-year-old white man participating in Study 20120138 who experienced interstitial lung disease (reported term: interstitial pneumonitis), and pulmonary fibrosis (reported term: lung fibrosis). The subject's medical history included metabolic syndrome, angina due to atherosclerotic coronary disease, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, atrial fibrillation/flutter with implantation of pacemaker, congestive heart failure, carotid or vertebral artery disease, stroke/cerebral infarction, transient ischemic attack, eczema, osteoporosis, peripheral arterial disease, treated hypertension, previous smoking and type 2 diabetes mellitus. Previous and ongoing treatment for the condition under study included pravastatin and ezetimibe. Concomitant medications included lercanidipine, nebivolol, risedronate, and lisinopril.

The subject participated in the parent study (Study 20110117) from 14 June same year* to 10 September same year* and received the last dose of placebo in the parent study on 08 August same year*. The subject received the first dose of evolocumab in Study 20120138 on 03 December [redacted].

On 21 January one year after*, the subject developed exertional dyspnea and was diagnosed with interstitial lung disease. On 14 February one year after*, the subject's computed tomography (CT) of thorax showed interstitial fibrosis, which in retrospect was present in two years ago* (chest radiograph and CT of thorax in two years ago* revealed interstitial fibrosis). On 28 March one year after*, video-assisted thoracoscopic surgery (VATS) lung biopsy showed interstitial fibrosis (usual interstitial pneumonia). Evolocumab was temporarily held. The event of interstitial lung disease was ongoing at the time of last report.

On 31 January one year after*, the subject was diagnosed with pulmonary fibrosis. Evolocumab was temporarily held. The event of pulmonary fibrosis was ongoing as of the date of last report received.

The subject's last dose of evolocumab prior to the events was on 03 December same year*. The subject was continuing home dosing as of the data cutoff date of [redacted] and the last in-clinic dose was documented on 25 February one year after*.

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The investigator considered the event of interstitial lung disease to be possibly related to evolocumab. The investigator reported that there was not a reasonable possibility that the event pulmonary fibrosis was related to the investigational product or to the device.

Subject No: [redacted]
Treatment: Parent study and regimen: 20110117; Evolocumab SC Q2W 140 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of care
Report: Acute myocardial infarction

Subject [redacted] was a 47-year-old Asian man participating in Study 20120138 who experienced an acute myocardial infarction (reported term: non-ST-elevated myocardial infarction). The subject's medical history included dyslipidemia since twenty-seven years ago* (heterozygous familiar hypercholesterolemia), hypertension, ischemic heart disease since twenty-two years ago*, penicillin allergy, coronary artery bypass graft in six years ago*, myocardial infarction in sixteen years ago*, twelve years ago*, two years ago* and 21 August same year* , NYHA class II congestive cardiac failure, gastroesophageal reflux disease, type II diabetes mellitus, obesity, smoking, cerebrovascular accident in fourteen years ago*, anxiety, carpal tunnel repair, intermittent headaches, and chronic bronchitis. Concomitant medications included atorvastatin, furosemide, enalapril, acetylsalicylic acid, clopidogrel, omeprazole, isosorbide dinitrate, salbutamol, atenolol, and fluoxetine.

The subject received evolocumab in the parent study (Study 20110117) from 31 July same year* to 11 October same year*, and received the first dose of evolocumab in Study 20120138 on 21 November [redacted].

On 08 January one year after*, the subject developed angina and worsening of dyspnea, and presented to the cardiac emergency department. Electrocardiogram showed new atrial flutter. Laboratory investigations revealed a troponin I 5.525 ng/mL, confirming non-ST-elevated myocardial infarction.

On the same day, the subject was admitted for the treatment. Additional medications during the hospitalization included enoxaparin, furosemide, amiodarone, spironolactone, warfarin, metformin, tramadol, paracetamol, and ciprofloxacin. The outcome of the non-ST-elevated myocardial infarction was considered resolved on 08 January one year after*. On 09 January one year after*, an angiogram showed no new occlusions.

The subject's last dose of evolocumab prior to the event was on 01 January one year after*. The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose was documented on 21 February one year after*.

The investigator reported that there was not a reasonable possibility that the event non-ST-elevated myocardial infarction was related to investigational drug or to device.

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Subject No: [redacted]
Treatment: Parent study and regimen: 20110117; Evolocumab SC Q2W 140 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of care
Report: Inguinal hernia, Incision site hematoma, Incision site hematoma (worsening), and Myocardial infarction

Subject [redacted] was a 55-year-old white man participating in Study 20120138 who experienced an inguinal hernia (reported term: right inguinal hernia), incision site hematoma (reported term: surgical site hematoma), incision site hematoma (worsening) (reported term: worsening surgical site hematoma), and myocardial infarction (reported term: myocardial infarction). The subject's medical history included primary hyperlipidemia and mixed dyslipidemia. Additional medical history included hypertension and increased thickness of the carotid intima-media. Previous and current treatment for hyperlipidemia included ezetimibe and atorvastatin. Concomitant medications included ramipril, metamizole, paracetamol, acetylsalicylic acid, bisoprolol, caffeine, clopidogrel, glyceryl trinitrate, and omeprazole.

The subject received evolocumab in the parent study (Study 20110117) from 29 May same year* to 05 August same year*, and was randomized to evolocumab and standard of care in Study 20120138 on 16 October [redacted].

On 20 November same year*, the subject was admitted to the hospital to undergo surgery for the right inguinal hernia. No laboratory values or other diagnostic procedures were performed. Treatment during hospitalization included diazepam, pantoprazole, tramadol, metoclopramide, paracetamol, and metamizole. No further information was provided. The event of surgery of right inguinal hernia was reported to have resolved on 21 November same year* and the subject was discharged from hospital on that same day.

On 26 November same year*, the subject was reported to have developed a surgical site hematoma and presented to the emergency with worsening of the surgical site hematoma. Upon admission, white blood cell (WBC) count was 19.7 x 10^9/L. The subject's surgical wound was infected and antibiotics (amoxicillin/clavulanate and levofloxacin) were administered. Treatment for the event also included dexketoprofen.

During readmission on 26 November same year* the subject developed a ST segment elevation myocardial infarction and was transferred to another hospital on the same day. Upon admission to the hospital, the subject received nitrates preparation, double antiagregation

*新薬承認情報提供時に置き換え

with ticagrelor, and unspecified statin. Laboratory tests disclosed troponin I > 50 ng/mL and 0.9 ng/ml.

On an unspecified date in November same year*, culture of wound exudate was positive for *Staphylococcus aureus* sensitive to methicillin; therefore, amoxicillin/clavulanate was changed to cloxacillin and after that, the subject continued on levofloxacin for 10 days. During hospitalization in November same year*, a computerized tomography of the abdomen was carried out disclosing no intra-abdominal liquid or collection.

On an unspecified date in December same year*, a coronary scan disclosed severe coronary atheromatosis. On 03 December same year*, coronary angiogram showed a 3 vessel disease. Subsequently, on 16 December same year*, a percutaneous coronary intervention was carried out, with stenting of the proximal descendent artery.

As of 17 December same year*, the events of worsening surgical site hematoma and myocardial infarction were reported as resolved. The subject was discharged from hospital on that same day without complications.

The subject's last dose of evolocumab prior to the event was on 13 November same year*. The subject was continuing home dosing as of the data cutoff date of [redacted] and the last in-clinic dose was documented on 31 January one year after*.

The investigator reported that there was not a reasonable possibility that the event of myocardial infarction was related to the investigational product or to the device.

*新薬承認情報提供時に置き換え