[redacted] **STUDY 20110110**

Treatments:

Parent Study: Evolocumab SC Q4W 420 mg

Year 1 treatment: Evolocumab SC Q4W 420 mg + SoC

Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SOC

Report: Myocardial infarction

Subject [redacted] was a 79-year-old white man participating in Study 20110110 who experienced a myocardial infarction. The subject's medical history included angina, appendectomy, coronary artery disease, hypertension, hyperlipidemia, myocardial infarction, nose bleed, and right coronary artery percutaneous coronary intervention. The subject was a former smoker and he had a family history of premature coronary heart disease. Concomitant medications included vitamin E, bisoprolol, ramipril, cyanocobalamin, calcium, and vitamin D. Previous and ongoing treatment for hypercholesterolemia included atorvastatin.

The subject participated in the parent study, Study 20101155, from 22 November one year ago* to 16 February same year* and received the last dose of evolocumab in the parent study on 17 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 16 February [redacted].

Approximately 1 year and 4 months later, on 28 June one year after*, the subject presented with retrosternal chest pressure that was worse on exertion and was hospitalized. The pain started in the morning and was waxing and waning. The subject felt the pain similar to his myocardial infarction pain that he had in the past. His pain settled spontaneously with cessation of activity. The subject had a small rise in troponin level to 0.13 ng/mL. Physical examination showed blood pressure at 119/75 mmHg, heart rate at 70 to 80 beats per minute, low jugular venous pressure, lungs clear, and normal heart sounds. The subject had good peripheral pulses and no peripheral edema. Electrocardiogram (ECG) performed on the same day showed heart rate at 65 beats per minute, PR interval of 171 msec, QRS duration 128 msec, QT interval 437 msec, corrected QT interval (QTc) 455 msec, sinus rhythm showed normal P axis and ventricular rate (V-rate) at 50 to 99 beats per minute, nonspecific intraventricular conduction delay, ST depression, and anterolateral ischemia. The subject had inferior Q-waves consistent with previous infarct. He underwent multiple ECGs. The subject was diagnosed with non-ST elevation myocardial infarction (NSTEMI). Laboratory test results on 29 June one year after* showed sodium level of 138 mEq/L, potassium of 4.2 mEq/L, chloride of 101 mEq/L, carbon dioxide 25 mEq/L, urea 7.5 mmol/L, creatinine 82 µmol/L, fasting glucose 5.7 mmol/L, creatinine kinase (CK) 70 IU/L, troponin I 1.87 ng/mL, triglycerides 2.13 mmol/L, cholesterol 2.51 mmol/L, high-density lipoprotein (HDL) 1.64 mmol/L, and cholesterol/HDL ratio was 1.64. Repeat laboratory test after approximately 12 hours showed CK at 52 IU/L and troponin I at 0.80 ng/mL. On 29 June one year after*, the subject underwent echocardiography with Doppler to assess left ventricular (LV) function. The LV size and function was normal with an estimated ejection fraction of 50% to 55%, severe hypokinesis of the basal septum and the basal inferior wall was noted. The aortic root was mildly dilated at 4.3 cm, trileaflet aortic valve was sclerotic, and moderate aortic insufficiency was noted. Treatment included acetylsalicylic acid, clopidogrel, bisoprolol, ramipril, and heparin. The subject was discharged after 2 days.

The subject's last dose of evolocumab prior to the event of myocardial infarction was on 11 June one year after*. As of the data cutoff date of [redacted], the subject was continuing in Study 20110110 and received the last dose of evolocumab prior to the cutoff date on [redacted].

*新薬承認情報提供時に置き換え

[redacted] **STUYD 20110110**

Treatments:

Parent study: Placebo SC Q4W

Year 1 treatment: Evolocumab SC Q4W 420 mg + SoC

Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SoC

Report: Peripheral ischemia

Subject [redacted] was a 68-year-old white woman participating in Study 20110110 who developed peripheral ischemia (reported term: chronic limb ischemia). The subject's medical history included hypercholesterolemia, osteoarthritis, pneumonia, restless legs syndrome, influenza, vitamin B complex deficiency, hypertension, cystitis, pharyngeal edema, edema, and eczema. The subject was a current smoker, and had a family history of premature coronary heart disease. Concomitant medications included vitamin E, amlodipine, mometasone, colecalciferol, cyanocobalamin, furosemide, potassium chloride, thiamazole, etodolac, nebivolol, ibuprofen, and estradiol. Previous and ongoing treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 10 November one year ago* to 02 February same year* and received the last dose of placebo in the parent study on 05 January same year*.

The subject received her first dose of evolocumab in Study 20110110 on 02 February [redacted]. Approximately 2 months after the first dose of evolocumab, in April same year*, the subject experienced pain in right lower leg. On 24 October one year after*, a computed tomography (CT) lower extremity angiography revealed occlusion of infra-renal abdominal aorta, common iliac artery and internal and external iliac artery bilaterally. Multifocal stenosis of the superficial femoral artery and popliteal artery bilaterally was detected. Normal variant in the form of high take-off of posterior tibial artery was observed. Multifocal stenosis corresponding to deep femoral artery bilaterally, particularly on left side was noted. On 04 November one year after*, the subject developed limb ischemia, and was hospitalized on the same day. Treatment included furosemide, metoprolol, dalteparin, amiodarone, acetazolamide, hydrocortisone sodium succinate, ondansetron, potassium chloride, heparin, combination of fenoterol and ipratropium, loperamide, cefuroxine, and levofloxacin. The subject underwent elective surgery (aortobifemoral bypass). Reportedly, the subject experienced several complications after surgery. Atrial fibrillation was diagnosed and was medically treated. Renal insufficiency was treated with dialysis and medications. Respiratory failure was treated with mechanical respiratory support. Pleural exudate was treated with drainage. Infection was treated with unspecified antibiotics. Tooth extraction of all remaining teeth was done due to bad tooth status. Pacemaker was inserted due to bradycardia. On 04 December one year after*, the subject's husband reported that the subject had died on 03 December one year after*. It was reported that the subject died due to complications after surgery.

The subject's last dose of the evolocumab prior to death was on 31 October one year after*. The investigator reported that there was no reasonable possibility that the event of chronic limb ischemia was related to the investigational product.

[redacted] **STUDY 20110110**

Treatments:

Parent Study: Evolocumab SC Q2W 140 mg

Year 1 treatment: Evolocumab SC Q4W 420 mg + SoC

Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SoC

Report: Transient ischemic attack

*新薬承認情報提供時に置き換え

Subject [redacted] was a 68-year-old white man participating in Study 20110110 who experienced a transient ischemic attack. The subject's medical history included hypercholesterolemia, hypertension, eczema, osteoarthritis, arthralgia, pneumonia, percutaneous coronary intervention with stent placement, and dyspepsia. Concomitant medications included acetylsalicylic acid/magnesium oxide, hydrocortisone, glucosamine, and vitamin E. Previous and current treatment for hypercholesterolemia included simvastatin. Previous treatment for hypercholesterolemia included atorvastatin.

The subject participated in the parent study, Study 20101155, from 15 November one year ago* to 21 February same year* and received the last dose of evolocumab in the parent study on 24 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 21 February [redacted].

Baseline calculated low-density lipoprotein cholesterol was 123 mg/dL on 15 November one year ago* (parent study). Approximately 1 year and 4 months later, on 19 July one year after*, the subject felt numbness of the left leg and was admitted to the hospital on the same day, where he was diagnosed with transient ischemic attack. The investigator reported that the event of transient ischemic attack only lasted for a few hours. Treatment for the event included simvastatin, clopidogrel, and amlodipine. A magnetic resonance imaging was performed which showed no visible fresh infarcts, various white matter lesions which could be a sign of mild chronic ischemia, and mild central and cortical atrophy. The event of transient ischemic attack was reported as resolved without sequelae on 19 July one year after* and the subject was discharged from the hospital on 20 July one year after*. Three days later, on 23 July one year after*, an ultrasound of the carotid arteries was performed which showed mild arteriosclerosis, without significant stenosis.

The subject's last dose of evolocumab prior to the event of transient ischemic attack was on 09 July one year after*. As of the data cutoff date of [redacted], the subject continued in the study and received the last dose of evolocumab prior to the data cut-off date on [redacted]. The investigator reported that there was no reasonable possibility that the event of transient ischemic attack was related to evolocumab, and that there were no co-suspect medications.

[redacted] STUDY 21110110

Treatments:

Parent study: Evolocumab SC Q4W 350 mg

Year 1 treatment: SoC

Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SoC

Report: Congestive cardiac failure

Subject [redacted] was a 72-year-old white man participating in Study 20110110 who developed congestive cardiac failure (reported term: exacerbation of congestive heart failure). The subject's medical history included hypercholesterolemia, hyperlipidemia, ischemic cardiomyopathy, carotid artery stenosis, hypertension, congestive cardiac failure (New York Heart Association Class II, with ejection fraction (35% to 40%), angina, myocardial infarction, coronary artery bypass graft, and percutaneous coronary intervention. The subject had an automatic implantable cardioverter defibrillator placement. The subject had been consuming alcohol (2 to 3 glass of wine weekly), was a former tobacco user, and had an allergy to niacin. The subject had a family history of heart disease, aortic aneurysm, diabetes, and stroke. Concomitant medications included vitamin E, acetyl salicylic acid, clopidogrel, metoprolol, losartan, nitroglycerin, ranolazine, furosemide, and potassium chloride. Previous and ongoing treatment for hypercholesterolemia included rosuvastatin and ezetimibe.

The subject was in the parent study from 11 November two years ago* to 06 February one year ago* and received the last dose of evolocumab in the parent study on 06 January one year ago*.

The subject was randomized to Study 20110110 on 02 May one year ago* and assigned SoC treatment. After completing 1 year in the study, the subject received the first dose of evolocumab on 07 June [redacted]. Approximately 2 months later, on 07 August same year*, computed tomography (CT) angiography of the thoracic aorta, thoracic great vessels, and carotid vertebral arteries revealed soft and hard plaque stenosis at the origin of the right internal carotid artery (maximal stenosis estimated at 75%) and calcified

*新薬承認情報提供時に置き換え

plaque at the origin of the left internal carotid artery at the bifurcation, maximal stenosis estimated no more than 45% to 50%; vertebral arteries appeared benign. On 19 August same year*, the subject underwent elective right carotid stenting with filter protection. The subject tolerated the procedure well without gross evidence of neurologic deficit.

On 12 November same year*, the subject presented to the hospital with complaints of worsening shortness of breath for 2 to 3 days. The subject reported clear orthopnea and exertional dyspnea. Reportedly, the subject was not following his recommended cardiac diet. Upon admission, vital signs examination revealed temperature of 97.7°F, heart rate of 93 beats per minute, blood pressure of 127/76 mmHg, respiratory rate of 20 breaths per minute, and oxygen saturation of 100% on 2 liters nasal O_2. Laboratory test results revealed troponin I of 0.11 ng/mL and brain natriuretic peptide of 1503 pg/mL. Chest radiograph showed bilateral pulmonary vascular congestion. The subject was diagnosed with exacerbation of congestive heart failure. He was ruled-out for acute coronary syndrome with negative cardiac enzymes. Treatment medication included furosemide and heparin. The event was reported as resolved on 14 November same year*, and the subject was discharged from the hospital on the same day. In addition to his ongoing medication, spironolactone was added as a discharge medication for optimization of heart failure management.

The subject's last dose of evolocumab prior to the event was on 18 September same year*. Evolocumab was temporarily withheld but then not restarted. The subject was lost to follow-up and his last dose of evolocumab in the study was on 18 September same year*.

The investigator reported that there was no reasonable possibility that the event exacerbation of congestive cardiac failure was related to the investigational product. No co-suspect medications were reported.

[redacted] STUDY 20110110

Treatment:

Parent study: Evolocumab SC Q2W 70 mg

Year 1 treatment: SoC

Years 2 to 5 treatment: Evolocumab SC Q4W 420 mg + SOC

Report: Cerebrovascular accident

Subject [redacted] was a 56-year-old black woman participating in Study 20110110 who had a cerebrovascular accident (reported term: stroke [CVA]). The subject's medical history included hypercholesterolemia, hypertension, obstructive sleep apnea syndrome, asthma, osteoarthritis, knee and hip replacement, tubal ligation, and hysterectomy. The subject had no prior history of stroke. The subject denied tobacco, alcohol, or drug use. Family history was significant for stroke, hypertension, and diabetes. Concomitant medications included vitamin E, combination of ipratropium bromide and salbutamol, hydrochlorothiazide, and valsartan. Previous and ongoing treatment for hypercholesterolemia included rosuvastatin.

The subject participated in the parent study, Study 20101155, from 26 August two years ago* to 02 December two years ago* and received the last dose of evolocumab in the parent study on 01 November two years ago*. The subject was randomized to Study 20110110 on 02 December two years ago* and assigned SoC treatment. After completing the first year of the study she received the first dose of evolocumab in Study 20110110 on 04 January [redacted].

Approximately 3 days later, on 07 January same year*, the subject noticed weakness and decreased sensation in her right leg and had difficulty walking. Later that same morning she noticed weakness in her right hand and slurred speech. The subject did not have loss of consciousness, seizure, or incontinence. On that same day, she went to the emergency room where her blood pressure was reported as 202/93 mm Hg. The investigator reported this was an unusual rise of blood pressure compared to baseline and other blood pressure measures (baseline blood pressure was 139/100 mm Hg at the 12 February two years ago* screening visit). Neurological examination showed the following: alert and oriented; speech fluent with no aphasia but mild dysarthria; motor 5/5 throughout all muscle groups with normal

*新薬承認情報提供時に置き換え

tone but drift on the right arm and leg; cranial nerves and sensation normal; cerebellar: mild ataxia on right finger nose finger (FNF) and heel to shin (HTS), normal on left, showed rapidly alternating movement on the right. The subject was admitted to the hospital with the impression of possible stroke. Magnetic resonance imaging showed mild old microangiopathic ischemic change, acute left pontine infarction, and mild chronic sinusitis. A transesophageal echocardiogram showed mild concentric left ventricular hypertrophy with ejection fraction 60% to 65% of the neck showing small vessel occlusive changes, mostly the left internal carotid artery. A computerized tomogram of the head was negative. Magnetic resonance imaging of the head and neck showed diffuse intracranial atherosclerosis, possible small left supraclinoid internal carotid artery aneurysm, no flow limiting stenosis. An electrocardiogram showed normal sinus rhythm.

On 09 January same year* a 12-organ system review was negative except for right-sided weakness. Blood pressure was 154/94 mm Hg. On 10 January same year* the subject was transferred to inpatient rehabilitation. At this time the subject was noted to be slightly dysarthric and had right-sided weakness but denied any pain. She received physical and occupational therapy and made some progress. Treatment for the event included enoxaparin, pantoprazole, valsartan, carvedilol, ergocalciferol, amlodipine, atorvastatin, and acetylsalicylic acid. The event of cerebrovascular accident was reported to have resolved on 16 January same year* and the subject was discharged on the same date. At the time of discharge, the subject was independent, able to ambulate without assistive device, and she had a good prognosis. The investigator reported that there were no changes in concomitant medications prior to the event. However, the subject had been non-compliant with all medications.

The subject's last dose of evolocumab prior to the event of cerebrovascular accident was on 04 January same year*. Evolocumab was permanently discontinued at that time, and the subject discontinued the study on 04 February same year* after withdrawing full consent. The investigator reported that there was not a reasonable possibility that the event of cerebrovascular accident was related to evolocumab.

[redacted] STUDY 20110110

Treatments:

Parent Study: Ezetimibe PO QD 10 mg + Evolocumab SC Q4W 420 mg

Year 1 treatment: Evolocumab SC Q4W 420 mg + SoC

Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SoC

Report: Unstable angina

Subject [redacted] was a 62-year-old white woman participating in Study 20110110 who developed unstable angina (reported term: unstable angina requiring hospitalization). The subject's medical history included hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, and nephrectomy. Concomitant medications included vitamin E, glyceryl trinitrate, acetylsalicylic acid, molsidomine, olmesartan, carvedilol, isosorbide dinitrate, and esomeprazole. Previous treatment for hypercholesterolemia included atorvastatin, rosuvastatin, fenofibrate, ezetimibe, and pravastatin.

The subject participated in the parent study, Study 20090159, from 28 November one year ago* to 21 February same year* and received the last dose of ezetimibe and evolocumab in the parent study on 24 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 21 February [redacted].

Approximately 1 year and 6 months later, on 10 September one year after*, the subject developed unstable angina. On 23 September one year after*, the subject had a consultation with cardiology and was hospitalized. Laboratory tests on 23 September one year after* revealed troponin of 13.9 pg/mL, creatine phosphokinase of 57 IU/L, and potassium of 3.9 mmol/L. On 24 September one year after*, a coronarography was performed which revealed a grade 4 lesion in the right circumflex and a stenosis of the right coronary artery. The subject's risk factors for the event included a history of cardiac effort and anger. Treatment included a stent placement, clopidogrel and combination of salmeterol and fluticasone were initiated. The event of unstable angina

*新薬承認情報提供時に置き換え

resolved on 24 September one year after*, and the subject was discharged from the hospital on 25 September one year after*.

The subject's last dose of evolocumab prior to the event of unstable angina was on 09 September one year after*. Evolocumab was continued. .

As of the data cutoff date [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff date on [redacted].

The investigator reported that there was no reasonable possibility that the event of unstable angina was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent Study: Study 20101155, Evolocumab SC Q4W 420 mg Year 1 treatment: Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Nausea, Dizziness

Subject [redacted] was a 77-year-old white woman participating in Study 20110110 who developed nausea and dizziness.

The subject's medical history included rheumatoid arthritis, hammer toes (both feet), osteoarthritis (hands and knees), degenerative disk disease, hypertension, hypercholesterolemia, peptic ulcer, former smoker, fusion of left first metatarsophalangeal joint, and sulfonamide allergy. The investigator reported that the subject did not have any etiological or predisposing risk factors associated with the events. Concomitant medications included alendronate, hydroxychloroquine, methotrexate, prednisone, folic acid, losartan/hydrochlorothiazide, paracetamol, calcium, ergocalciferol, and tocopheryl. Previous and ongoing treatment for hypercholesterolemia was atorvastatin.

The subject received evolocumab in the parent study from 18 August two years ago* to 13 October two years ago* and was randomized to standard of care in Study 20110110 on 17 January one year ago*. The subject completed the 1-year standard of care arm on 11 February same year* and received the first dose of evolocumab in Study 20110110 on 12 February [redacted].

Approximately 1 year and 2 months after the first dose of evolocumab in Study 20110110 (ie, during years 2-5), on 14 April one year after*, the subject underwent elective surgical correction with metatarsal head resection of multiple hammertoes (2nd through 5th) on the right foot that were secondary to rheumatoid arthritis. General anesthesia with local anesthetic infiltrate was used for the surgery. After surgery, the subject developed dizziness and later the same day experienced nausea and vomiting and was hospitalized for observation. Vital signs were normal. The next day, the subject's nausea persisted along with 1 episode of vomiting, but otherwise progressed well. No diagnostic tests were performed and no relevant biochemical values (before, during, or after the event) were provided. The investigator reported that the general anesthetics were considered as suspect for the events.

*新薬承認情報提供時に置き換え

Nausea and dizziness were reported as resolved on 16 April one year after*. The subject was discharged from the hospital on the same day. Additional medications included colecalciferol and tramadol/paracetamol.

The subject's last dose of evolocumab prior to the event was on 08 April one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the events of nausea and dizziness were related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent Study: Study 20110231, Evolocumab SC Q2W 140 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Anal fistula

Subject [redacted] was a 48-year-old Asian man participating in Study 20110110 who developed an anal fistula.

The subject's medical history included dyslipidemia, hypertension, fatty liver, and former smoker. The investigator reported that the subject did not have any risk factors associated with the event. Concomitant medications included tocopheryl. Previous and ongoing treatment for dyslipidemia was pravastatin.

The subject received evolocumab in the parent study from 10 November one year ago* to 19 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 13 April [redacted]. The subject completed the 1-year randomized treatment arm on 09 May one year after*, and received the first dose of evolocumab for years 2-5 on 10 May one year after*.

Approximately 1 year and 1 month after the first dose of evolocumab in Study 20110110, on 10 May one year after*, the subject developed an anal fistula. Treatment medications included loxoprofen and cefdinir. On 14 May one year after*, the subject underwent incision and drainage of anal fistula at a surgical clinic with regional anesthesia. Two weeks later, on 01 June one year after*, the subject was hospitalized for fistula incision surgery under spinal anesthesia that was performed the next day (02 June one year after*). Additional treatment medications included zolpidem, bupivacaine, and a second course of cefdinir. The subject's condition improved and he was discharged from the hospital on 10 June one year after*. The anal fistula was reported as resolving at the time of discharge. The investigator became aware of the event at the week 56 visit on 14 June one year after* and reported that the anal fistula developed from a bacterial infection (unknown pathogen). No laboratory reports were provided.

Anal fistula was reported as resolved on 02 August one year after*.

The subject's last dose of evolocumab prior to the event was on 10 May one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

*新薬承認情報提供時に置き換え

The investigator reported that there was not a reasonable possibility that the event of anal fistula was related to evolocumab.

Subject No: [redacted]
Treatments: Parent Study: Study 20101155, Evolocumab SC Q4W 280 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Mass, Intestinal ischemia

Subject [redacted] was a 78-year-old black woman participating in Study 20110110 who developed a mass (reported term: right retrocrural mass) and intestinal ischemia (reported term: mesenteric ischemia).

The subject's medical history included renal cancer (stage III), renal artery stenosis, peripheral vascular disease, carotid artery disease, hypertension, former smoker, hypercholesterolemia, hyperlipidemia, urinary tract infection, gastroesophageal reflux disease, neuropathy, insomnia, osteoarthritis, iron deficiency anemia, and carotid endarterectomy. Relevant concomitant medications included amlodipine, atenolol, hydralazine, clonidine, acetylsalicylic acid, famotidine, gabapentin, temazepam, darbepoetin alfa, ferrous sulfate, and tocopheryl. The investigator reported that no concomitant medication could be considered as co-suspect for the event mesenteric ischemia. Previous and ongoing treatment for hypercholesterolemia and hyperlipidemia was rosuvastatin.

The subject received evolocumab in the parent study from 21 November one year ago* to 16 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 13 February [redacted]. The subject completed the 1-year randomized treatment arm on 11 March one year after*, and received the first dose of evolocumab for years 2-5 on 12 March one year after*.

Approximately 2 years and 3 months after the first dose of evolocumab in Study 20110110, on 04 May two years after*, the subject referred sudden onset of upper quadrant abdominal pain (exacerbated by movement), aphagia, nausea, diarrhea, and weight loss of 20 pounds in 1 week. On 10 May two years after*, the subject was hospitalized for evaluation. Computed tomography (CT) scan of abdomen and pelvis showed a 3.5 x 3.8 cm heterogeneous low density mass in the right posterior retrocrural region that was identified as a benign tumor with no malignant cells on biopsy (unknown date). Treatment medications included hydromorphone, paracetamol, hydrocodone, and ondansetron. Losartan was added to the antihypertensive regimen. Laboratory tests showed abnormal electrolytes (hypomagnesemia, hypophosphatemia, and hypokalemia) that were attributed to poor nutrition and were corrected with electrolyte supplementation (intravenous magnesium and potassium), and

*新薬承認情報提供時に置き換え

the subject also received intravenous levofloxacin for a urinary tract infection. The subject was discharged from the hospital on 15 May two years after* in stable condition and free of pain. The mass was reported as ongoing at the time of discharge. On 16 May two years after*, positron emission tomography scan of abdominal region showed no abnormal focal areas of hypermetabolism. The mass remained ongoing as of the data cutoff date of [redacted].

On 02 June two years after*, the subject again complained of abdominal pain and difficulty eating. On 26 June two years after*, a CT scan of abdomen and pelvis revealed severe atherosclerosis with probable chronic occlusion of the proximal superior mesenteric artery and inferior mesenteric artery and stenosis of celiac artery. On 27 June two years after*, the pain worsened with nausea and dry heaves, and the subject was hospitalized for further evaluation. Treatment medications included pantoprazole, morphine, and ondansetron. The pain impaired the subject's ability to eat and led to weight loss of approximately 25 pounds in the week following hospitalization. On 28 June two years after*, the subject underwent endoscopy with biopsy that showed minimal chronic gastritis. On 02 July two years after*, the subject underwent mesenteric angiogram with angioplasty and stenting of the stenotic celiac artery. Postoperative diagnosis was chronic mesenteric ischemia. Treatment medications included pantoprazole, morphine, ondansetron, clopidogrel, and metoclopramide. The subject's pain improved after the surgery and she was able to tolerate food.

Intestinal ischemia was reported as resolved on 04 July two years after*. The subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to event was on 08 April two years after*. Evolocumab was permanently discontinued on 29 July two years after*. As of the data cutoff date of [redacted], the subject was continuing in the study.

The investigator reported that there was not a reasonable possibility that the events of mass and intestinal ischemia were related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted] STUDY 20110110
Treatments: Parent study: Study 20101154, Evolocumab SC Q4W 280 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Breast cancer

Subject [redacted] was a 60-year-old white woman participating in Study 20110110 who developed breast cancer (reported term: right breast carcinoma).

The subject's medical history included dyslipidemia, asthma, chronic obstructive pulmonary disease, hypothyroidism, polyarthrosis, right scapulohumeral periarthritis, allergic rhinitis, current smoker, and hysterectomy. Concomitant medications included formoterol, montelukast, budesonide, indapamide, losartan/hydrochlorothiazide, bisoprolol/hydrochlorothiazide, cetirizine, and tocopheryl. Other relevant medications include nicotine for smoking cessation in March and April of one year after* and levothyroxine that was taken during the parent study. No previous or ongoing treatments for dyslipidemia were provided.

The subject received evolocumab in the parent study from 24 October one year ago* to 19 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 18 January [redacted]. The subject completed the 1-year randomized treatment arm on 12 February one year after* and received the first dose of evolocumab for years 2-5 on 13 February one year after*.

Approximately 2 years and 5 months after the first dose of evolocumab in Study 20110110, on 06 June two years after*, a breast biopsy performed due to increased calcification revealed carcinoma. The subject had no symptoms or personal or familial predisposing risk factors. On 14 July two years after*, the subject was hospitalized for tumorectomy and lymphadenectomy of the axillary region. She was discharged from the hospital with no complications on 18 July two years after*. Future treatment for breast cancer was to be determined.

Breast cancer was reported as ongoing.

The subject's last dose of evolocumab prior to the event was on 30 May two years after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

*新薬承認情報提供時に置き換え

The investigator reported that there was not a reasonable possibility that the event of breast cancer was related to evolocumab.

Subject No: [redacted]
Treatments: Parent study: Study 20101155, Evolocumab SC Q2W 105 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Bladder transitional cell carcinoma

Subject [redacted] was a 75-year-old white man participating in Study 20110110 who developed bladder transitional cell carcinoma (reported term: cancer vesica [urotelial carcinoma in situ]).

The subject's medical history included hypertension, hypercholesterolemia, reduced lung capacity due to asbestosis, kidney stone, surgery for thyroid adenoma (twenty-nine years ago*), and former smoker. The investigator reported that the subject did not have etiological or predisposing risk factors associated with the event. Concomitant medications included losartan, paracetamol, phenoxymethylpenicillin, and tocopheryl. Previous and ongoing treatment for hypercholesterolemia was simvastatin (discontinued in March one year after*).

The subject received evolocumab in the parent study from 17 November one year ago* to 26 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 24 February [redacted]. The subject completed the 1-year randomized treatment arm on 21 March one year after* and received the first dose of evolocumab for years 2-5 on 22 March one year after*.

Approximately 2 years and 2 months after the first dose of evolocumab in Study 20110110, on 03 May two years after*, the subject noticed blood in urine. On 13 May two years after*, the subject underwent cystoscopy due to macroscopic hematuria and 5 polyps were observed. Treatment medication included alfuzosin. The subject was hospitalized on 26 May two years after* for transurethral resection of the bladder performed on 27 May two years after*. Eight polyps were observed; the histology report from selected site biopsies showed high grade Ta and carcinoma in situ. Outpatient treatment with Bacillus Calmette-Guerin was scheduled beginning 04 July two years after*.

Bladder transitional cell carcinoma was reported as resolved on 28 May two years after*. The subject was discharged from the hospital on the same day in good condition.

The subject's last dose of evolocumab prior to the event was on 09 May two years after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

*新薬承認情報提供時に置き換え

The investigator reported that there was not a reasonable possibility that the event of bladder transitional cell carcinoma was related to evolocumab.

Subject No: [redacted]
Treatments: Parent study: Study 20090158, Placebo SC Q4W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Prostate cancer

Subject [redacted] was a 61-year-old white man participating in Study 20110110 who developed prostate cancer.

The subject's medical history included hypercholesterolemia. Concomitant medications included acetylsalicylic acid and tocopheryl. Previous and ongoing treatment for hypercholesterolemia was atorvastatin.

The subject received placebo in the parent study from 30 November one year ago* to 26 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 27 February [redacted]. The subject completed the 1-year randomized treatment arm on 19 March one year after* and received the first dose of evolocumab for years 2-5 on 20 March one year after*.

Approximately 2 years and 3 months after the first dose of evolocumab in Study 20110110, on 20 May two years after*, the subject underwent routine prostatic specific antigen (PSA) testing that revealed total PSA 20.26 ng/mL (reference range 0 to 4 ng/mL), free PSA 1.09 ng/mL, and percentage free PSA 5%. On 26 May two years after*, prostate cancer was confirmed based on transrectal needle core biopsies performed on 24 May two years after* that revealed infiltrating adenocarcinoma of the prostate, Gleason score 7 (3+4), and nuclear grade II. Radiation therapy was planned for 2 weeks postsurgery. On 05 June two years after*, the subject received brachytherapy. Treatment medications included tamsulosin, midazolam, granisetron, tramadol/acetaminophen, tramadol, ibuprofen/acetaminophen/codeine, ciprofloxacin, and bicalutamide.

Prostate cancer was reported as ongoing.

The subject's last dose of evolocumab prior to the event was on 20 May two years after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

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

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20101154, Placebo SC Q4W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Fatigue, Back pain

Subject [redacted] was a 54-year-old white woman participating in Study 20110110 who developed fatigue and back pain.

The subject's medical history included depression, mixed dyslipidemia, hyperlipidemia, and hysterectomy radicalis non totalis. Concomitant medication included venlafaxine and estradiol. Previous and ongoing treatment for mixed dyslipidemia and hyperlipidemia was not provided.

The subject received placebo in the parent study from 10 October one year ago* to 05 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 04 January [redacted]. He completed the 1-year randomized treatment arm on 01 February one year after* and received the first dose of evolocumab for years 2-5 on 02 February one year after*.

Approximately 2.4 years after the first dose of evolocumab in Study 20110110, on 26 May two years after*, the subject developed fatigue and back pain and was hospitalized on the same day. The investigator reported that the subject's fatigue was related to the diagnosis of depression with continued venlafaxine treatment. Additional treatment included bed rest. On 27 May two years after*, the event of fatigue was reported as resolved and the subject was discharged from the hospital. The outcome of the event back pain was reported as resolved on 14 June two years after*.

The subject's last dose of evolocumab prior to the event was on 02 May two years after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the events fatigue and back pain were related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20110231, Evolocumab SC Q4W 420 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Chest pain, Positional dizziness

Subject [redacted] was a 65-year-old Asian man participating in Study 20110110 who developed chest pain and positional dizziness.

The subject's medical history included angina pectoris, hypertension, dizziness, hypercholesterolemia, insomnia and hepatitis C. Concomitant medications included acetylsalicylic acid, isosorbide, azelnidipine, gatifloxacin, cyanocobalamin, ketoprofen, and mecobalamin. Additional historical medications included clopidogrel (March two years ago* to August same year*), and glyceryl trinitrate, metoprolol, and iomeprolol for coronary angiography on 21 November same year*. Previous treatment for hypercholesterolemia was not provided; ongoing treatment included atorvastatin.

The subject received evolocumab in the parent study from 03 August one year ago* to 27 September one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 21 March [redacted].

Approximately 12.5 months after the first dose of evolocumab in Study 20110110, on 09 April one year after*, the subject developed chest pain and was hospitalized for testing. Trans-thoracic echocardiography showed no evidence of asynergy, left ventricular hypertrophy or dilation, or evidence of structural valve changes. There was no evidence of pericardial effusion and pleural fluid. The electrocardiogram showed sinus tachycardia of 101/bpm; and, no stenosis was evident in contrast computed tomography (CT).

Treatment medication reported after the onset of the event included fosfomycin. The outcome of the event chest pain was reported as resolved on the same day, 09 April one year after*. The subject was discharged from the hospital on 10 April one year after*.

The subject completed the 1-year randomized treatment arm on 16 April one year after* and received the first dose of evolocumab for years 2-5 on 17 April one year after*.

Approximately 13 months after the first dose of evolocumab in Study 20110110, on 07 May one year after*, the subject developed dizziness which resolved the same day but was

*新薬承認情報提供時に置き換え

admitted for testing. The investigator reported that the subject had previous episodes of dizziness and reported a systolic blood pressure of 170 on an unknown date at home. A head CT scan and magnetic resonance imaging (MRI) did not reveal abnormal finding. The diagnosis was dizziness due to temporal increase of blood pressure. The subject was instructed to rest and no treatment medications were indicated. The outcome of the event was reported as resolved on the same date, and the subject was discharged from the hospital the next day, 08 May one year after*.

The subject's last dose of evolocumab prior to the chest pain event was 20 March one year after*; and the last dose of evolocumab prior to the positional dizziness was 17 April one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event of chest pain was related to evolocumab. The investigator reported that there was a reasonable possibility that the event of positional dizziness was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20101154, Placebo SC Q2W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Diverticulitis

Subject [redacted] was a 53-year-old white woman participating in Study 20110110 who developed diverticulitis.

The subject's medical history included hypertension, former smoker, dyslipidemia, cholecystitis and cholecystectomy. Concomitant medications included enalapril/hydrochlorothiazide and paracetamol. Previous and ongoing treatments for dyslipidemia were not provided.

The subject received placebo in the parent study from 28 October one year ago* to 06 January same year* and was randomized to evolocumab SC Q4W 420 mg and standard of care in Study 20110110 on 03 February [redacted]. The subject completed the 1-year evolocumab and standard of care arm on 28 February one year after* and received the first dose of evolocumab for years 2-5 on 01 March one year after*.

Approximately 2 years and 3.5 months after the first dose of evolocumab, on 23 May two years after*, the subject developed diverticulitis and was hospitalized on the same day. A computerized tomography scan showed diverticula in the colon. Treatment medication included an unspecified antibiotic.

The outcome of the event diverticulitis was reported as resolved on 26 May two years after*. The subject was discharged from the hospital the same day.

The subject's last dose of evolocumab prior to the event was on 23 May two years after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event diverticulitis was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20101155 , Evolocumab SC Q2W 70 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Appendicitis

Subject [redacted] was a 50-year-old white woman participating in Study 20110110 who developed appendicitis.

The subject's medical history included chronic abdominal pain, gastroesophageal reflux disease, diverticulosis, current smoker, hypertension, dyslipidemia, and hyperlipidemia. Concomitant medications included esomeprazole, celecoxib, and hydrochloroclorazide. Previous treatment for dyslipidemia and hypercholesterolemia was atorvastatin and simvastatin. Ongoing treatment included pravastatin.

The subject received evolocumab in the parent study from 09 September same year* to 17 November same year*. The subject received the first dose of evolocumab in Study 20110110 on 15 December [redacted]. The subject completed the 1-year randomized treatment arm on 09 January two years after* and received the first dose of evolocumab for years 2-5 on 10 January two years after*.

Approximately 2 years and 4 months after the first dose of evolocumab in Study 20110110 on 27 April three years after*, the subject developed abdominal pain and was hospitalized the same day. Abdominal and pelvic computed tomography (CT) scan showed a slightly edematous appendix with scant inflammatory changes.

The subject underwent laparoscopic appendectomy. On 28 April three years after*, the post-operative pathological report confirmed the diagnosis of acute appendicitis. Treatment medication included ketorolac. The investigator confirmed that the subject did not have identified etiological or pre-disposing risk factors associated with the event. The appendicitis event was reported as resolved on 28 April three years after*.

The subject's last dose of evolocumab prior to the event was on 02 April three years after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event appendicitis was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20101155, Placebo SC Q2W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Rocky Mountain spotted fever

Subject [redacted] was a 69-year-old white woman participating in Study 20110110 who developed Rocky Mountain spotted fever.

The subject's medical history included simple partial seizures, headache, osteoarthritis, hypothyroidism, depression, former smoker, and hypercholesterolemia. Concomitant medications included lamotrigine, oxcarbazepine, levothyroxine, cetirizine, and tocopheryl. Previous and ongoing treatment for hypercholesterolemia included atorvastatin.

The subject received placebo in the parent study from 17 October one year ago* to 12 December same year*. The subject received the first dose of evolocumab in Study 20110110 on 09 January [redacted]. The subject completed the 1-year randomized treatment arm on 03 February one year after* and received the first dose of evolocumab for years 2-5 on 04 February one year after*.

Approximately 2 years and 4 months after the first dose of evolocumab, on 06 May two years after*, the subject developed Rocky Mountain spotted fever. The subject reported progressive fatigue associated with rash and fever and was evaluated in the emergency department on 10 May two years after*where treatment included prednisone Approximately one week later on 16 May two years after*, the subject was evaluated by a dermatologist and on the same day, the subject's Rocky Mountain spotted fever immunoglobulin G (IgG) and immunoglobulin M (IgM) were more than 1:1024. Additional treatment included doxycycline. The subject was hospitalized on 19 May two years after* for further evaluation. Treatment included increasing the dose of prednisone and the subject was discharged from the hospital on 20 May two years after*. On 23 May two years after*, Rocky Mountain spotted fever testing showed positive results and treatment with prednisone was continued.

Rocky Mountain spotted fever was reported as resolved on 02 June two years after*.

The subject's last dose of evolocumab prior to the event was on 25 April two years after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

*新薬承認情報提供時に置き換え

The investigator reported that there was not a reasonable possibility that the event Rocky Mountain spotted fever was related to evolocumab.

Subject No: [redacted]
Treatments: Parent study: Study 20110231, Evolocumab SC Q4W 420 mg + Standard of Care Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Urinary tract infection

Subject [redacted] was a 60-year-old Asian woman participating in Study 20110110 who developed a urinary tract infection.

The subject's medical history included type 2 diabtes mellitus, hypertension, gastritis and hypercholesterolemia. The investigator reported that the subject had no predisposing risk factors associated with the reported event. Concomitant medication included rebamipide, loxoprofen, and liraglutide. Previous and ongoing treatment for hypercholesterolemia was rosuvastatin.

The subject received evolocumab in the parent study from 15 November one year after* to 10 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 30 May [redacted]. The subject completed the 1-year randomized treatment arm on 25 June one year after* and received the first dose of evolocumab for years 2-5 on 26 June same year*.

Approximately 1 year and 1month after the first dose of evolocumab in Study 20110110, on 01 July one year after*, the subject presented with fever, hematuria, and pain upon urination and was diagnosed with a urinary tract infection. The subject also developed vomiting along with poor oral intake, fever and fatigue and was hospitalized on 04 July one year after*.

Laboratory results on 04 July one year after* showed creatinine 0.81 mg/dl, BUN 11.2 mg/dl, GFR 56, white blood cell (WBC) count 133, (reference range 40 to 90, units not provided). Urinalysis showed, WBC count 2+with positive ketones and nitrites. On 05 July one year after*, computed tomography scan showed absence of renal calculi. Treatment included sitafloxacin, ceftriaxone, and paracetamol.

The event urinary tract infection was reported as resolved on 10 July one year after*. The subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event was on 26 June one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

*新薬承認情報提供時に置き換え

The investigator reported that there was not a reasonable possibility that the event urinary tract infection was related to evolocumab.

Subject No: [redacted]
Treatments: Parent Study 20101154, Ezetimibe PO QD 10 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Bursitis infective, Skin infection

Subject [redacted] was a 65-year-old white woman participating in Study 20110110 who developed infective bursitis (reported term: infection in left burse trochanterica) and skin infection (reported term: abscess in cicatrice).

The subject's medical history included hypercholesterolemia, rheumatoid arthritis, excoriation, drug hypersensitivity (unspecified arthrosis medications), lymphoma, cholelithiasis, hip arthroplasty in five years ago*, and meningioma surgery. No current concomitant medications were reported. Previous treatment for hypercholesterolemia included ezetimibe. Ongoing treatment for hypercholesterolemia was not provided.

The subject was in the parent study from 26 October one year ago* to 18 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 18 January [redacted]. The subject completed the 1-year randomized treatment arm on 12 February one year after* and received the first dose of evolocumab for years 2-5 on 13 February one year after*.

Approximately 2 years and 2 months after the first dose of evolocumab in Study 20110110, on 13 March two years after*, the subject developed pain in the region of the previously replaced hip. She was diagnosed with an infection in the left trochanteric bursa. The subject was hospitalized the same day, and underwent soft tissue surgical revision, and received phenoxymethylpenicillin, flucloxacillin, morphine and paracetamol. Blood cultures were negative. The infection was reported resolved on 31 March two years after*. Additionally, it was reported that there were no etiology or predisposing risk factors associated with the event. Also, it was confirmed that the subject did not undergo any recent surgeries or modification of left hip replacement.

On 14 April two years after*, the subject was again hospitalized due to skin infection (reported term: abscess in cicatrice). He underwent ultrasound guided drainage of old blood from the infected area. Blood culture was negative and treatment included flucloxacillin and paracetamol. The investigator noted that the subject was predisposed to the abscess in cicatrice event due to the surgery and infection in the left trochanteric bursa. The skin

*新薬承認情報提供時に置き換え

infection was reported as resolved on 21 April two years after*. The subject was discharged from the hospital on the same day with plans for a 3-month course of unspecified antibiotics.

The subject's last dose of evolocumab prior to the event was on 12 February two years after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the events of infection in left bursa trochanteric and skin infection were related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20101155, Evolocumab SC Q2W 140 mg Year 1 treatment: Evolocumab SC Q4W 420 mg +Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Tendon injury

Subject [redacted] was a 55-year-old white man participating in Study 20110110 who developed a tendon injury (reported term: fourth proximal flexor tendon injury).

The subject's medical history included hypercholesterolemia, hypertension, type 2 diabetes mellitus, hypogonadism, and erectile dysfunction. Concomitant medications included methocarbamol, meloxicam, lisinopril, amlodipine, hydrochlorothiazide, carvedilol, tadalafil, testosterone, metformin, glimepiride, dapagliflozin, paroxetine, omeprazole, and tocopheryl. Previous and ongoing treatment for hypercholesterolemia was pravastatin.

The subject received evolocumab in the parent study from 28 September one year ago* to 09 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 04 January [redacted]. The subject completed the 1-year randomized treatment arm on 31 January one year after* and received the first dose of evolocumab for years 2-5 on 01 February one year after*.

Approximately 2 years and 3.5 months after the first dose of evolocumab in Study 20110110, on 23 April two years after*, the subject was hospitalized for repair of a traumatic amputation of the second middle phalanx and injury to the fourth proximal flexor tendon on right hand due to an accident. Distal amputation was confirmed by x-ray. The subject was discharged on 24 April two years after*; the tendon injury was reported as resolving.

The subject's last dose of evolocumab prior to the event was on 22 April two years after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event of tendon injury was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20090158, Placebo SC Q4W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Post procedural hematoma, Procedural pain

Subject [redacted] was a 45-year-old white man participating in Study 20110110 who developed post procedural hematoma (reported term: hematoma after inguinal hernia surgery in abdominal and dorsal muscles) and procedural pain (reported term: serious complaints of abdominal pain after surgery).

The subject's medical history included hypercholesterolemia and elevated creatine kinase. No relevant concomitant medications were reported. Previous and ongoing treatments for hypercholesterolemia were fluvastatin and ezetimibe.

The subject received placebo in the parent study from 21 December one year ago* to 14 February same year*. The subject received the first dose of evolocumab in Study 20110110 on 14 March [redacted]. The subject completed the 1-year randomized treatment arm on 9 April one year after* and received the first dose of evolocumab for years 2-5 on 10 April one year after*.

Approximately 2 years and 3 months after the first dose of evolocumab in Study 20110110, on 04 June two years after*, the subject developed bilateral inguinal hernias and underwent surgical repair on 27 June two years after*. The next day (28 June two years after*), the subject had serious abdominal pain and was hospitalized on 29 June two years after*. Based on computed tomography results (date unknown), the investigator reported that the pain was due to a large hematoma that had developed in the abdominal and dorsal muscles after the inguinal hernia surgery. No treatment medications were provided. On 02 July two years after*, the subject was discharged from the hospital with the events ongoing. On 04 August two years after*, the events of post procedural hematoma and procedural pain were reported as resolved.

The subject's last dose of evolocumab prior to the event was on 04 June two years after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the events of post procedural hematoma and procedural pain were related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20101155, Evolocumab SC Q4W 420 mg Year 1 treatment: Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Heart rate increased, Dizziness, Dyspnea

Subject [redacted] was a 57-year-old black woman participating in Study 20110110 who developed increased heart rate (reported term: rapid heartbeat), dizziness (reported term: light headedness), and dyspnea (reported term: shortness of breath).

The subject's medical history included obesity, hypertension, hypothyroidism, hypercholesterolemia, ankle edema, and postmenopausal. Concomitant medications included lisinopril, hydrochlorothiazide, levothyroxine, and acetylsalicylic acid. Previous and ongoing treatment for hypercholesterolemia was simvastatin.

The subject received evolocumab in the parent study from 13 October two years ago* to 08 December two years ago*, and was randomized to standard of care in Study 20110110 on 04 January one year ago*. The subject completed the 1-year standard of care arm on 29 January same year* and received the first dose of evolocumab in Study 20110110 on 30 January [redacted].

Approximately 1 year and 5 months after the first dose of evolocumab in Study 20110110, years 2-5, on 24 June one year after*, the subject was hospitalized for observation after developing an increased heart rate, dizziness, and dyspnea. Laboratory results, computed tomography scan, and electrocardiography revealed normal results. No definitive diagnosis was determined and the events were attributed to stress.

Increased heart rate, dizziness, and dyspnea were reported as resolved on 26 June one year after*.

The subject's last dose of evolocumab prior to the events was on 18 June one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the events of increased heart rate, dizziness, and dyspnea were related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20101154, Placebo SC Q2W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Osteoarthritis

Subject [redacted] was a 75-year-old white woman participating in Study 20110110 who developed osteoarthritis (reported term: worsening of right knee osteoarthritis).

The subject's medical history included spine and bilateral knee osteoarthritis, herniated lumbar and cervical disc, spondylolistehesis, scoliosis, hypercholesterolemia, hypothyroidism and water retention. Concomitant medications included hydrochlorothiazide, levothyroxine. Concomitant supplements included hyaluronic acid, bromelain, calcium, and osteo bi-flex. No previous or ongoing treatments for hypercholesterolemia were provided.

The subject received placebo in the parent study from 9 September same year* to 15 November same year*. The subject received the first dose of evolocumab in Study 20110110 on 13 December [redacted]. The subject completed the 1-year randomized treatment arm on 08 January two years after* and received the first dose of evolocumab for years 2-5 on 09 January two years after*.

Approximately 2 years and 5 months after the first dose of evolocumab, on 08 May three years after*, the subject was hospitalized for total right knee replacement due to osteoarthritis of the right knee. Treatment medication after the onset of the event included oxycodone. The subject was discharged from the hospital on 11 May three years after*.

Osteoarthritis was reported as resolved on 11 May three years after*.

The subject's last dose of evolocumab prior to the event was on 23 April three years after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event osteoarthritis was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20101155, Evolocumab SC Q4W 280 MG Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Renal failure acute

Subject [redacted] was a 65-year-old white man participating in Study 20110110 who developed a renal failure acute (reported term: acute renal failure).

The subject's medical history included benign prostatic hypertrophy (BPH), bladder outlet obstruction, positive hepatitis C, hypercholesterolemia, type 2 diabetes mellitus, hypertension, stroke, and dyslipidemia. Concomitant medications included metformin, allopurinol, trandolapril, amlodipine, meloxican, perindopril, and pioglitazone. Previous or ongoing treatment for hypercholesterolemia was rosuvastatin.

The subject received evolocumab in the parent study from 25 August same year* to 22 Sep same year*. The subject received the first dose of evolocumab in Study 20110110 on 09 December [redacted]. The subject completed the 1-year randomized treatment arm on 10 January two years after* and received the first dose of evolocumab for years 2-5 on 15 Jan two years after*.

Approximately 1 year and 9 months after the first dose of evolocumab in Study 20110110, on 03 September two years after*, the subject had nonserious adverse events of nephrolithiasis and left renal cortical cyst, which did not resolve. Nine months after these events, on 27 May three years after*, cystoscopy and multichannel urodynamics showed residual urine, apparently secondary to BPH. The subject was hospitalized on 29 May three years after* with a diagnosis of acute renal failure. Symptoms included dysuria, fever, and abnormal creatinine level (118 µmol/L [reference range 58 to 110 µmol/L]). Urinary tract infection (UTI)/sepsis were also suspected due to symptoms and evidence of residual urine (over 1 liter) shown by a bladder scan (date unknown). Abnormal laboratory results on 29 May three years after* included white blood cell (WBC) 21.4 x 10^9/L (reference range 1 to 4 x 10^9/L) and neutrophils 16.5 x 10^9/L (reference range 2.5 to 7.4 x 10^9/L). The investigator's impression was that the subject had a UTI secondary to post-void residual, and the subject likely had post-void residual secondary to BPH with some atonic bladder component. Cultures were negative for methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, and extended spectrum beta lactamase.

*新薬承認情報提供時に置き換え

The subject's metformin, meloxicam, and ACE inhibitors were withheld due to acute renal failure. The subject underwent catheterization and treatment included ceftriaxone, pioglitazone, amlodipine, perindopril, pantoprazole, pinaverium and intravenous fluids.

The subject's creatinine level normalized (100 µmol/L) on 30 May three years after* and remained in the reference range through 06 June four years after*. The subject's WBC and neutrophil counts improved on the same day, but remained elevated (16.1 x 10^9/L and 10.7 x 10^9/L, respectively). Additional laboratory results for WBCs and neutrophils were not provided.

Renal failure acute was reported as resolved on 07 June three years after*, and the subject was discharged from the hospital the same day.

The subject's last dose of evolocumab prior to the event was on 28 May three years after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event of renal failure acute was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20090159, Evolocumab SC QW 420 mg Year 1 treatment: Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Nephrolithiasis

Subject [redacted] was a 58-year-old white man participating in Study 20110110 who developed nephrolithiasis (reported term: nephrolithiasis).

The subject's medical history included kidney stones, hypercholesterolemia, and former smoker. No concomitant medications were reported. Previous treatment for hypercholesterolemia was ezetimibe. No ongoing treatment was provided for hypercholesterolemia.

The subject received evolocumab in the parent study from 26 October two years ago* to 28 December two years ago* and was randomized to standard of care in Study 20110110 on 18 January one year ago* The subject completed the 1-year treatment arm on 19 February same year*, and received the first dose of evolocumab for years 2-5 on 12 March [redacted].

Approximately one year and one month after the first dose of evolocumab in Study 20110110, on 22 April one year after*, the subject was hospitalized with nephrolithiasis. The subject underwent an unspecified surgical intervention to remove two kidney stones. Treatment included levofloxacin, paracetamol, hydromorphine, codeine, ondansetron, tamsulosin, and phenazopyridine.

Nephrolithiasis was reported as resolved on 24 April one year after*, and the subject was discharged from the hospital the same day.

The subject's last dose of evolocumab prior to the event was on 08 April one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event nephrolithiasis was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20101155, Placebo SC Q4W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg+ Standard of Care
Report: Pulmonary embolism

Subject [redacted] was a 68-year-old white woman participating in Study 20110110 who developed pulmonary embolism (reported term: lung embolus).

The subject's medical history included hypercholesterolemia, right knee meniscus injury, and former smoker. No concomitant medications were reported. Previous treatment for hypercholesterolemia was simvastatin. Ongoing treatment was not provided for hypercholesterolemia.

The subject received placebo in the parent study from 02 November two years ago* to 28 December two years ago*. The subject received the first dose of evolocumab in Study 20110110 on 25 January [redacted]. The subject completed the 1-year randomized treatment arm on 25 February same year* and received the first dose of evolocumab for years 2-5 on 26 February same year*.

Approximately two years and four and a half months after the first dose of evolocumab in Study 20110110, on 12 June one year after*, the subject developed pulmonary embolism. Symptoms included increased dyspnea and shortness of breath upon physical activity. Previous to the pulmonary embolism, the subject underwent out-patient arthroscopic surgery for the meniscus injury (right knee) on 24 April one year after* with possible immobilization. The investigator could not rule out this association between the surgery and the pulmonary embolism; however, it seemed unlikely. On 30 June one year after*, echocardiography showed moderate pulmonary hypertension, and the investigator confirmed the diagnosis of pulmonary embolism. The subject was also diagnosed with stable angina pectoris, treatment included glyceryl trinitrate. The subject's condition worsened and was hospitalized on 07 July one year after* due to pulmonary embolism. Treatment included rivaroxaban.

On 11 July one year after*, the pulmonary embolism resolved, and the subject was discharged from the hospital the same day.

*新薬承認情報提供時に置き換え

The subject's last dose of evolocumab prior to the event was on 11 June one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event pulmonary embolism was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20090159, Evolocumab SC Q4W 280 mg Year 1 treatment: Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Bladder cancer

Subject [redacted] was a 66-year-old white man participating in Study 20110110 who developed bladder cancer.

The subject's medical history included overactive bladder, basal cell carcinoma on forehead, seborrheic keratosis on back and head, decreased libido, hypercholesterolemia, lumbar stenosis, osteoarthritis, muscle fatigue, migraine headaches, pollinosis, asymptomatic arrhythmia, and appendectomy. Social history included alcohol use (1 drink daily). Concomitant medications included acetylsalicylic acid, acetylsalicylic acid/caffeine/paracetamol, naproxen, and sulfamethoxazole/trimethoprim. Previous treatment for hypercholesterolemia was ezetimibe; ongoing treatments were ezetimibe (discontinued in June one year ago*).

The subject received evolocumab in the parent study from 28 November two years ago* to 23 January one year ago*, and was randomized to standard of care in Study 20110110 on 21 February one year ago*. The subject completed the 1-year standard of care arm on 19 March same year* and received the first dose of evolocumab during years 2-5 in Study 20110110 on 20 March [redacted].

Approximately 1 year and 2 months after the first dose of evolocumab in Study 20110110 (ie, during years 2-5), on 26 April one year after*, the subject developed grade 3 hematuria (reported term: blood in urine) and was treated as an outpatient with sulfamethoxazole/trimethoprim. On 01 June one year after*, the subject was diagnosed with stage 2 metastatic bladder cancer. On 09 June one year after*, the subject was hospitalized for cystoscopy and transurethral resection of bladder tumor that took place on 10 June one year after*. Pathology report of resected bladder tumor showed high-grade urothelial carcinoma focally invasive into muscularis propria. Biopsies of bladder dome and posterior, right, and left walls showed benign urothelial mucosa negative for atypia or neoplasm. Treatment medications included ciprofloxacin, hydrocodone/paracetamol, ketorolac, fentanyl, pethidine, hydromorphone, promethazine, oxycodone/paracetamol, ibuprofen, and ondansetron. On an unknown date, the subject

*新薬承認情報提供時に置き換え

was discharged from the hospital. On 15 June one year after*, at a follow-up visit, the Foley catheter was removed.

Bladder cancer was reported as resolving.

The subject's last dose of evolocumab prior to the event was on 15 May one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event of bladder cancer was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20101155, Evolocumab SC Q4W 280 mg Year 1 treatment: Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Cerebral hemorrhage

Subject [redacted] was a 67-year-old white woman participating in Study 20110110 who developed a cerebral hemorrhage.

The subject's medical history included apoplexy, cerebrovascular accident (nine years ago*), slight left arm and leg hemiparesis (five years ago*), dyslipidemia, hypertension, cough, right hip fracture, thyroidectomy, and current smoker. Concomitant medications included clopidogrel, ramipril, atenolol, bendroflumethiazide, phenoxymethylpenicillin, dicloxacillin, codeine, and ibuprofen. Additional relevant medications included acetylsalicylic acid/dipyridamole that was taken from nine years ago* to November same year*. Previous treatments for dyslipidemia included rosuvastatin and simvastatin; ongoing treatment was simvastatin.

The subject received evolocumab in the parent study from 04 November two years ago* to 02 January one year ago*, and was randomized to standard of care in Study 20110110 on 27 January one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 22 February [redacted].

Approximately 7 months after the first dose of evolocumab in Study 20110110, on 26 September same year*, the subject experienced an epileptic attack (grade 2) that resolved on the same day without treatment, and was advised to follow up with a neurologist. Approximately 1 year and 2 months after the first dose of evolocumab in Study 20110110 (ie, during years 2-5), on 20 April one year after*, the subject was hospitalized for a cerebral hemorrhage. A magnetic resonance imaging (MRI) scan showed hemorrhage with hemiparesis on left side and hemorrhage in right corpus callosum. Treatment medications included amlodipine, metoclopramide, and labetalol. On an unknown date, the subject was discharged from the hospital with slight expressive aphasia and ataxia. The investigator reported that the hemiparesis in five years ago* was considered an etiological or predisposing risk factor for the cerebral hemorrhage event, and indicated that the subject had reached a potential endpoint of the study.

Cerebral hemorrhage was reported as ongoing.

*新薬承認情報提供時に置き換え

The subject's last dose of evolocumab prior to the event was on 11 April one year after*. Evolocumab was permanently discontinued. As of the data cutoff date of [redacted], the subject was continuing in the study.

The investigator reported that there was not a reasonable possibility that the event of cerebral hemorrhage was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted] STUDY 20110110
Treatments: Parent study: Study 20101154, Placebo SC Q2W Year 1 treatment: Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Diverticulitis

Subject [redacted] was a 45-year-old white woman participating in Study 20110110 who developed diverticulitis.

The subject's medical history included hypercholesterolemia, chronic sinusitis, chronic bronchitis, hypokalemia, anemia, sleep apnea, migraine headache, right calcaneal spur, right fibular fracture, endometrial ablation, tubal ligation, tonsillectomy, and environmental allergies. Concomitant medications included tocopheryl, ramipril, hydrochlorothiazide, and naproxen.

Previous and ongoing treatments for hypercholesterolemia were not provided.

The subject received placebo in the parent study from 17 October two years ago* to 28 December two years ago* and was randomized to standard of care in Study 20110110 on 23 January one year ago*. The subject completed the 1-year standard of care arm on 10 February same year* and received the first dose of evolocumab for years 2-5 on 11 February [redacted].

Approximately 1 year and 3 months after the first dose of evolocumab in Study 20110110 (years 2-5), on 03 May one year after*, the subject developed irritable bowel syndrome and was treated with hyoscine, ketorolac, and dimenhydrinate. On 14 May one year after*, the subject developed abdominal discomfort and was referred to the emergency room by her physician. Computerized tomography scan of the abdomen showed diverticulitis, and she was admitted to the hospital. Laboratory tests revealed hemoglobin 108 g/L (reference range 120 to 160 g/L), white blood cell (WBC) count 12.6 x 10^9/L (reference range 4.8 to 10.8 x 10^9/L), and blood cultures were negative. Treatment medications included ketorolac, dimenhydrinate, metronidazole, enoxaparin, and fentanyl. On 19 May one year after*, laboratory tests showed hemoglobin 119 g/L and WBC count 10.9 x 10^9/L. On 20 May one year after*, the subject received additional treatment with ciprofloxacin and was discharged from the hospital with ongoing treatment.

The outcome of the event diverticulitis was reported as resolved on 27 May one year after*.

*新薬承認情報提供時に置き換え

The subject's last dose of evolocumab prior to the event was on 08 May one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event diverticulitis was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20090159, Evolocumab SC QM 420 MG Year 1 treatment: Evolocumab QM 420 MG + Standard of Care Years 2-5 treatment: Evolocumab QM 420 MG + Standard of Care
Report: Peripheral Vascular Disorder

Subject [redacted] was a 70-year-old white man participating in Study 20110110 who developed peripheral vascular disorder (peripheral vascular disease [stable]).

The subject's medical history included peripheral vascular disease, coronary artery disease, stable angina pectoris, hypertension, hypercholesterolemia, claudication, nocturnal leg cramps, osteoarthritis, chronic back pain, bilateral leg pain, sleep apnea, right carotid endarterectomy, coronary artery bypass graft (3 times), allergies to penicillin, and morphine, and statin intolerance (not specified). Concomitant medications included acetylsalicylic acid, glyceryl trinitrate, isosorbide mononitrate, quinine bisulfate, meloxicam, paracetamol, and tocopheryl.

Previous and ongoing treatments for hypercholesterolemia included rosuvastatin and ezetimibe.

The subject received evolocumab in the parent study from 05 December one year ago* to 31 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 23 April [redacted] and completed the 1-year standard of care arm on 26 May one year after*.

Approximately 2 years and 1 month after the first dose of evolocumab in Study 20110110, on 05 June two years after*, the subject was hospitalized and underwent elective bifemoral digital subtraction angiography (DSA) to assess status for possible lower back spinal surgery for chronic back or lumbar pain. The subject had a history of radiating bilateral calf pain described as worse upon incline and relieved with rest. The DSA showed the infrarenal aorta was calcified and diseased with no flow limiting lesions.

The outcome of the event peripheral vascular disorder was reported as resolved on 06 June two years after*.

The subject's last dose of evolocumab prior to the event was on 25 March one year after*. Evolocumab was continued and the subject received the first dose of evolocumab for years

*新薬承認情報提供時に置き換え

2-5 on 19 June two years after*. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event peripheral vascular disorder was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20101155, Evolocumab SC Q2W 105 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Cardiac arrest

Subject [redacted] was a 67-year-old Pacific Islander man participating in Study 20110110 who developed a fatal cardiac arrest.

The subject's medical history included hypertension, obesity, dyslipidemia, erectile dysfunction, psoriasis, and androgenetic alopecia. Social history included smoking. Concomitant medications included losartan, hydrochlorothiazide, finasteride, triamcinolone, and tocopheryl acetate. Other relevant medications included sildenafil (March same year* to August same year*) and tadalafil (August same year* to September same year*).

Previous and ongoing treatment for dyslipidemia was simvastatin.

The subject received evolocumab in the parent study from 16 November two years ago* to 25 January one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 22 February one year ago*. The subject completed the 1-year randomized treatment arm on 19 March same year* and received the first dose of evolocumab for years 2-5 on 20 March [redacted].

Approximately 2 years and 2 months after the first dose of evolocumab in Study 20110110, on 20 April one year after*, the subject developed chest pain but did not seek medical attention. On 22 April one year after*, the subject was found unresponsive in the car by his neighbor. Emergency medical services reported that the subject was found in asystole. Cardiopulmonary resuscitation with aggressive defibrillation was unsuccessful. The subject was pronounced dead at the hospital on the same day at approximately 03:00 hours.

Laboratory values during the open-label extension (hemoglobin, hematocrit, platelets, bilirubin, and creatinine) were within normal limits. The investigator reported that the subject did not experience any episodes of angina prior to the episode in April and that risk factors that might have predisposed the subject to the event of cardiac arrest included hyperlipidemia, hypertension, male sex, advanced age, cigarette smoking, mild obesity, and sedentary lifestyle.

The subject's last dose of evolocumab prior to the event was on 16 April one year after*.

*新薬承認情報提供時に置き換え

The investigator reported that there was not a reasonable possibility that the event of fatal cardiac arrest was related to evolocumab.

Subject No: [redacted]
Treatments: Parent study: Study 20101155, Placebo SC Q2W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of Care
Report: Osteoarthritis

Subject [redacted] was a 77-year-old white woman participating in Study 20110110 who developed osteoarthritis (reported term: right knee degenerative osteoarthritis).

The subject's medical history included osteoarthritis, osteopenia, vitamin D deficiency, obesity, dyslipidemia, hyperlipidemia, hypertension, former smoker, depression, anxiety, and insomnia. Concomitant medications included colecalciferol, acetylsalicylic acid, sertraline, alprazolam, and cyanocobalamin. Other relevant medications included alendronate that the subject received from five years ago* to 04 December same year*. Previous and ongoing treatment for dyslipidemia and hyperlipidemia was pravastatin.

The subject received evolocumab in the parent study from 02 November one year ago* to 11 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 10 February [redacted]. The subject completed the 1-year randomized treatment arm on 06 March one year after* and received the first dose of evolocumab for years 2-5 on 07 March one year after*.

Approximately 1 year and 8 months after the first dose of evolocumab in Study 20110110, on 13 October one year after*, the subject developed worsening right knee pain. On 18 December one year after*, magnetic resonance imaging of right knee revealed advanced tricompartmental osteoarthritis. On 13 May two years after*, the subject was hospitalized overnight for elective total right knee arthroplasty. Post-procedural x-ray showed prosthesis in good position. Treatment medications included cefazolin, vancomycin, nicotinamide, ketorolac, paracetamol, hydrocodone, and docusate. The subject was ambulatory before discharge.

Osteoarthritis (right knee) was reported as resolved on 14 May two years after*. The subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event was on 19 September 2013. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

*新薬承認情報提供時に置き換え

The investigator reported that there was not a reasonable possibility that the event of osteoarthritis (right knee) was related to evolocumab.

Subject No: [redacted]
Treatments: Parent study Evolocumab SC Q4W 350 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Year 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Lung neoplasm malignant

Subject [redacted] was a 42-year-old white woman participating in Study 20110110 who was diagnosed with a malignant lung neoplasm (reported term: fatal event of pulmonic cancer). Her medical history included hypercholesterolemia, hypertension, smoking from thirty years ago* to two years after*,and knee pain. Concomitant medications while on study included medroxyprogesterone, nebivolol, lercanidipine, doxazosin, varenicline, ibuprofen, hydrochlorothiazide, and tocopheryl. Previous and current treatment for hypercholesterolemia included ezetimibe and rosuvastatin; and rosuvastatin was changed to fluvastatin.

The subject was in the parent study from 17 October one year ago* to 10 January same year* and received the last dose of evolocumab in the parent study on 15 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 23 January [redacted].

Approximately 2.5 years after the first dose of evolocumab, on 04 March two years after*, a computed tomography (CT) of neck and thorax prescribed because of hoarseness arising in January two years after* showed a mass (possibility of lymphadenopathy). On 19 March two years after*, positron emission tomography computed tomography (PET CT) of left lung showed suspected primary bronchocarcinoma. On 26 March two years after*, magnetic resonance imaging (MRI) was performed that showed cervical, thoracic and skeletal metastasis. The stage of lung cancer at the time of diagnosis was T1bN2M1b, adenocarcinoma left lung lower segment, stage IV. On 10 April two years after*, the subject was started on palliative chemotherapy (carboplatin and pemetrexed) as treatment for the event. Investigational product was withheld. The event was not considered related to evolocumab.

The last dose of evolocumab prior to event onset was on 17 March two years after*. As of the data cutoff date of [redacted], the subject was continuing in the study, and the last dose of evolocumab prior to the cutoff date was on [redacted].

*新薬承認情報提供時に置き換え

On 20 July two years after*, the subject died due to malignant lung neoplasm.

The investigator stated that there was not a reasonable possibility that the event malignant lung neoplasm was related to investigational product.

[redacted]

SAE of Mass leading to discontinuation of IP in Study 20110110. See Subject [redacted] in SAE narratives.

*新薬承認情報提供時に置き換え