Subject No: [redacted]
Treatment: Parent Study: Study 20101155, Evolocumab SC Q4W 350 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: Pneumonia

Subject [redacted] was a 70-year-old white woman participating in Study 20110110 who developed pneumonia. The subject's medical history included hypercholesterolemia, chronic obstructive pulmonary disease, hypertension, asthma, allergic bronchopulmonary aspergillosis, bronchiectasis, pneumonia, mycobacterium avium complex infection, aspergillus infection, and pseudomonas infection. Concomitant medications included diphenhydramine, colecalciferol, salbutamol, ascorbic acid, esomeprazole, fluticasone, hydroxychloroquine, diclofenac, hydrocodone/paracetamol, fluticasone/salmeterol, pramipexole, pravastatin, hydrochlorothiazide/triamterene, zoledronic acid, glucosamine, chondroitin, and vitamin/mineral combination. Previous and ongoing treatment for hypercholesterolemia included rosuvastatin, ezetimibe, and fish oil.

The subject was in the parent study from 07 December one year ago* to 28 February same year* and received the last dose of evolocumab in the parent study on 01 February same year*. The subject received the first dose of evolocumab in Study 20110110 on 28 February [redacted].

Approximately 8 months later, on 23 October same year*, the subject experienced intermittent burning pain in her left arm and shoulder that spread to her chest. The pain was not exacerbated by factors such as movement, or exertion or deep breaths, and was partially alleviated by paracetamol and hydrocodone. The pain was associated with low grade fevers and cough with streaks of blood in sputum for 2 weeks. On 06 November same year*, the subject was hospitalized due to pneumonia. On admission, the subject had intermittent burning pain in left shoulder and left arm, chest pain, and hemoptysis. The subject denied chest pressure and dyspnea on exertion. Physical examination revealed bilaterally clear lungs and normal breathing. Vital signs revealed body temperature 36.1°C, blood pressure 120/61 mmHg, pulse rate of 65 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation 98%. A computerized tomogram of chest revealed bronchial wall thickening in the left upper, middle and lower lobes, suggestive of multilobar pneumonia, mucus plugging, associated exacerbation of bronchiectasis. There was an increase in inflammatory peripheral opacities compared to the prior examination.

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The appearance was representative of progression versus acute exacerbation of overlying inflammatory process. There was an occlusion of the lingular inferior bronchus. Given a medical history of pseudomonas pneumonia and recent visits to nursing facility, the subject was started on cefepime and vancomycin. She also began using an Acapella device (Positive Expiratory Pressure with flow oscillations). On 07 November same year*, laboratory test results revealed white blood cell count (WBC) of 9.5 x 10^9/L, hemoglobin of 12.2 g/dL, hematocrit of 36.6%, platelet count of 235 x 10^9/L, sodium of 141 mmol/L, potassium of 3.4 mmol/L, chloride of 103 mmol/L, creatinine of 0.88 mg/dL, blood urea nitrogen of 11 mmol/L, glucose of 94 mg/dL, and calcium of 8.8 mg/dL. On 08 November same year*, laboratory test results revealed WBC count of 7.1 x 10^9/L, hemoglobin of 12.9 g/dL, hematocrit of 38.4%, and platelet count of 240 x 10^9/L. As eosinophil count was slightly elevated, the suspicion for allergic bronchopulmonary aspergillosis as the cause of current symptoms was low. Work up for cardiac etiology was negative with negative troponins and normal electrocardiogram (normal sinus rhythm). Two days later after admission, the subject had pain in her thoracic, spine and scapula that was most consistent with musculoskeletal etiology. Gabapentin was increased and salbutamol was discontinued. Additional treatment medication included levofloxacin, ceftriaxone, azithromycin, and tramadol. The subject was discharged from hospital on 09 November same year* in stable condition. The event of pneumonia was considered as resolved on 16 November same year*. On 17 November same year*, laboratory testing revealed IgE of 8960.0 KU/L (reference ranges: < 25 KU/L negative, 25-100 KU/L equivocal, >100 KU/L positive).

The subject's last dose of evolocumab prior to the event of pneumonia was on 06 November same year*. Evolocumab was continued. As of the data cutoff date of [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 pneumonia was related to evolocumab. No medications were considered co-suspect.

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Subject No: [redacted]
Treatment: Parent Study: Study 20101155, Evolocumab SC Q4W 420 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: Chest pain, Accelerated hypertension, Presyncope, Hypertension

Subject [redacted] was a 66-year-old black woman participating in Study 20110110 who developed chest pain (reported term: non-ischemic chest pain), accelerated hypertension, presyncope (reported term: near syncope), and hypertension (reported term: accelerated hypertension). The subject's medical history included hypercholesterolemia, coronary artery disease, myocardial infarction, transient ischemic attack, cerebrovascular accident, chronic cardiac failure, congestive cardiac failure, hypertension, glaucoma, constipation, gastroesophageal reflux disease, gout, osteoporosis, anxiety, anemia, and chronic renal failure. Concomitant medications included captopril, travoprost, docusate, combination of acetylsalicylic acid and dipyridamole, carvedilol, allopurinol, folic acid, furosemide, digoxin, alendronate, ondansetron, famotidine, alprazolam, ferrous sulfate, Vitamin D, and latanoprost. Previous and ongoing treatment for hypercholesterolemia included ezetimibe and simvastatin.

The subject was in the parent study from 29 August same year* to 22 November same year* and received the last dose of evolocumab in the parent study on 27 October same year*. The subject received the first dose of evolocumab in Study 20110110 on 22 November [redacted].

Approximately 17 days after the first dose of evolocumab in Study 20110110, on 09 December same year*, the subject was hospitalized with complaints of atypical left sided, non-radiating chest pain not related to exertion or activity. The subject had no other symptoms or complaints. Laboratory tests performed on the same date, 09 December same year*, included troponin T between <0.01 ng/mL and <0.05 ng/mL, creatine kinase muscle and bone (MB) between < 1.0 ng/mL and 2.0 ng/mL, and myoblobin between 132 ng/mL and 139 ng/mL. An electrocardiogram (ECG) did not show any evidence of ischemia. A computerized tomography of the chest was unremarkable with no evidence of pulmonary embolism (PE). The following day, on 10 December same year*, repeated laboratory tests showed troponin T <0.01 ng/mL, creatine kinase MB of 1.62 ng/mL, and creatine kinase of 80 IU/L. Cardiac enzymes were negative. Repeat ECG on 11 December same year* confirmed no evidence of cardiac ischemia. The event of chest pain was considered non-cardiac and resolved without any treatment on

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11 December same year* after the subject had a bowel movement. The subject was discharged from hospital on that same date, with no complaints. The subject's last dose of evolocumab prior to the event of chest pain was on 22 November same year*. Evolocumab was continued. The investigator reported that there was no reasonable possibility that the event of non-ischemic chest pain was related to evolocumab.

The subject's baseline blood pressure reading was 116/74 mmHg. Approximately 3 weeks after the first dose of evolocumab in Study 20110110, on 13 December same year*, the subject had a sudden increase in blood pressure at home and experienced presyncope. The subject's systolic blood pressure reading was 180 mmHg and the diastolic blood pressure reading was not known. The subject had been compliant with antihypertensive therapy. A computed tomography of head revealed old infarct and no acute findings. The following day, on 14 December same year*, the subject was hospitalized, and her blood pressure was 105/65 mmHg. The subject's blood pressure was normal upon arrival; hence no additional medications were given. Blood pressure improved, and symptoms resolved. Additional workup was unremarkable. The investigator stated that the event of presyncope was most likely related to the accelerated hypertension. The events of accelerated hypertension and presyncope were considered as resolved on 13 December same year*, and the subject was discharged from the hospital on 15 December same year*, with no complaints. The subject's last dose of evolocumab prior to events of accelerated hypertension and presyncope was on 22 November same year*. Evolocumab was continued. The investigator reported that there was no reasonable possibility that the events of accelerated hypertension and near presyncope were related to evolocumab.

Approximately 4 months after the first dose of evolocumab in Study 20110110, on 03 March one year after*, the subject had headache, dizziness and her blood pressure was 194/77 mmHg at home. On the same date, 03 March one year after*, the subject was hospitalized due to hypertension for further evaluation. Laboratory tests revealed creatinine 1.4 mg/dL, glucose 111 mg/dL, potassium 3.8 mEq/L, sodium 142 mEq/L, chloride 103 mEq/L, urea 21 mg/dL, carbon dioxide 30.8 mEq/L, digoxin 0.9 ng/mL, troponin I < 0.05 ng/mL, and white blood cell count 6.4 x 10^9/L. A computed tomography of head revealed old infarct and no new findings. A chest radiography was unremarkable. The subject was started on amlodipine. Blood pressure was controlled, and the headache and dizziness resolved. The event of hypertension was considered as resolved on 05 March one year after*, and the subject was discharged from the hospital on 06 March one year after*, with no complaints.

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The subject's last dose of evolocumab prior to the event of hypertension was on 14 February one year after*. Evolocumab was continued. As of the data cutoff date of [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 accelerated hypertension was related to evolocumab.

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Subject No: [redacted]
Treatment: Parent study: Placebo SC Q4W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care (SOC) Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care (SOC)
Report: Coronary artery disease

Subject [redacted] was a 75-year-old white man participating in Study 20110110 who developed ischemic stroke (cerebrovascular accident). The subject's medical history included dyslipidemia, coronary artery disease, arteriosclerotic heart disease, dizziness, hypertension, shortness of breath, dyspepsia, hyperlipidemia, dysphagia, and cataract; family history included hypertension. He was a former smoker and alcohol user and had no history of atrial fibrillation, cardiac arrhythmia, stroke or transient ischemic attack (TIA). Concomitant medications included fosinopril and multivitamins. Previous and current treatment for hypercholesterolemia included atorvastatin.

The subject was in the parent study from 12 September same year* to 05 December same year* and received the last dose of placebo in the parent study on 07 November same year*. The subject received the first dose of evolocumab in Study 20110110 on 05 December [redacted].

Approximately 2 years later on 19 November two years after*, the subject underwent a nuclear imaging stress test, which revealed inferolateral wall perfusion defect. A medium-sized perfusion defect in the inferolateral wall of moderate severity was noted, which was completely reversible. A stress electrocardiogram (ECG) was found positive for ischemia and negative for arrhythmia. Baseline ECG revealed normal sinus rhythm.

On 09 December two years after*, the subject was diagnosed with worsening of coronary artery disease and was hospitalized on the same day. Coronary arteriogram and left heart catheterization revealed severe triple vessel disease and good contractility. The subject's vital signs were temperature 36.5°C, blood pressure 162/74 mmHg, pulse 73 beats per minute, respiratory rate 20 breaths per minute, and oxygen saturation (SPO_2) 98%. On the same day, bilateral carotid Doppler ultrasonography revealed 50% to 69% stenosis in the right cervical internal carotid artery (ICA). Additionally, less than 50% stenosis was observed in the left cervical ICA. The ECG showed normal sinus rhythm and inferior infarct.

The next day on 10 December two years after*, the subject underwent coronary artery bypass surgery (CABG) and had a cerebrovascular accident post surgery. On the same day, a complete

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echocardiogram revealed mild to moderate concentric left ventricular hypertrophy. The estimated left ventricular ejection fraction was noted as 50% to 55%. Mild mitral regurgitation and mild pulmonic regurgitation were also observed

Post CABG and extending to the next day, 11 December two years after* the subject experienced mild right sided weakness and was unable to communicate. On the same day, speech-language pathologist's evaluation was done at bedside and a swallow test was performed; new expressive aphasia was noted. The subject's neurological examination revealed right hemispheric cerebrovascular accident with right hemiparesis, right homonymous field defect, right-sided neglect, and expressive aphasia, and possibly some receptive component. On 12 December two years after*, the subject's computerized tomography (CT) of head/brain with contrast revealed a small subacute infarct was seen in the left anterior parietal lobe in the left middle cerebral artery (MCA) distribution. A small old infarct in the right cerebellum was also observed. Nonspecific periventricular low density compatible with small vessel disease was noted. There was no evidence of intracranial hemorrhage or significant mass effect.

The investigator indicated post-exposure prophylaxis (PEP) for coronary revascularization and cerebrovascular event.

On 18 December two years after*, the subject's physical examination revealed difficulty in speech, and vital signs were body temperature 36.7°C to 37.1°C, blood pressure 137/63 to 143/77 mmHg, pulse 76 to 106 beats per minute, SPO_2 95% to 99%, and respiratory rate 16 to 21 breaths per minute. On the same day, laboratory tests showed RBCs 2.68 Mil/µL, hemoglobin 8.6 g/dL, and hematocrit 25.5%. On the same day, his chest radiograph revealed mild congestion. No significant consolidation was observed. The subject was treated with heparin, acetylsalicylic acid, metoprolol, docusate, famotidine, glucagon, morphine, ipratropium/salbutamol, acetaminophen, hydrocodone/paracetamol, bisacodyl, magnesium, insulin/isophane, cefalexin, insulin, and pneumococcal vaccine. The event of worsening of coronary artery disease was reported as resolved on 10 December two years after* and the subject was discharged on 18 December two years after*.

The subject's last dose of evolocumab prior to the events was on 04 December two years after*. Evolocumab was temporarily withheld and had not been restarted as of the data cutoff date of [redacted]. As of the data cutoff date, the event of cerebrovascular accident was not resolved and the subject was continuing in the study.

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The investigator reported that there was no reasonable possibility that the events of worsening of coronary artery disease and cerebrovascular accident were related to evolocumab.

Subject No: [redacted]
Treatments: Parent study: 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 63-year-old white man participating in Study 20110110 who had appendicitis. The subject's medical history included depression, hypercholesterolemia, squamous cell skin carcinoma, hypertension, paroxysmal supraventricular tachycardia, prostate cancer with suprapubic prostatectomy, and erectile dysfunction. The subject was a nonsmoker and an alcohol drinker. Concomitant medications included valsartan, atenolol, bupropion, multivitamins (ascorbic acid, ergocalciferol, folic acid, nicotinamide, panthenol, retinol, riboflavin, thiamine hydrochloride), acetylsalicylic acid, sildenafil, paracetamol (acetaminophen), lidocaine, triamcinolone, naproxen, varicella zoster vaccine, cetirizine, DTC vaccine (diphtheria, tetanus, pertussis) and continuous positive airway pressure. Previous and current treatment for hypercholesterolemia included atorvastatin.

The subject was in the parent study from 17 October one year ago* to 20 January same year* and received the last dose of evolocumab in the parent study on 27 December one year ago*. The subject received his first dose of evolocumab in the Study 20110110 on 20 January [redacted].

Approximately 8.5 months after receiving the first dose evolocumab on Study 20110110, on 09 October same year*, he was presented to the emergency room with right lower quadrant abdominal pain early in the morning. A computerized tomogram of the abdomen and pelvis with contrast revealed appendicitis without evidence for rupture, and a small anterior abdominal wall hernia at the level of the umbilicus containing a piece of non-obstructed small bowel. On 10 October same year*, the subject was hospitalized and underwent a laparoscopic appendectomy and umbilical herniorrhaphy. The pathology report showed acute appendicitis. The event of appendicitis was resolved on 10 October same year* and the subject was discharged from the hospital on the same day.

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The subject's last dose of evolocumab before the event was on 24 September same year*. As of the data cutoff date of [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 appendicitis was related to evolocumab.

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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: Chest pain, Chest discomfort, Abdominal discomfort, Constipation, Chronic obstructive pulmonary disease, Hypertension

Subject [redacted] was a 69-year-old black man participating in Study 20110110 who experienced chest pain (3 episodes), chest discomfort (reported term: restroternal tightness), abdominal discomfort, constipation (reported term: worsening constipation), chronic obstructive pulmonary disease (COPD) (reported term: COPD exacerbation), and hypertension (reported term: worsening hypertension). The subject's medical history included hypercholesterolemia, coronary artery disease, coronary artery bypass, dyslipidemia, hypertension, vascular graft, angioplasty, COPD, drug hypersensitivity (to vancomycin), dementia, hypersensitivity, allergic rhinitis, chest pain, dehydration, vomiting, abdominal pain, bronchitis, glaucoma, cataract, asthma, upper respiratory tract infection, gastroesophageal reflux disease, constipation, cerebrovascular accident, anxiety, osteoarthritis, knee operation, surgery (back surgery), and benign prostatic hyperplasia. The subject was currently a smoker (tobacco user). Concomitant medications included Vitamin E, acetylsalicylic acid, hydrochlorothiazide, lisinopril, combination of hydrochlorothiazide and lisinopril, clopidogrel, omeprazole, dutasteride, tamsulosin, potassium chloride, combination of fluticasone and salmeterol, alprazolam, donepezil, docusate, finasteride, levofloxacin, famotidine, esomeprazole, diazepam, carisoprodol, diphenhydramine, fluticasone, hydrocodone, ibuprofen, fexofenadine, combination of polyethylene glycol and electrolytes, pirenzepine, intravenous solutions, morphine, bisacodyl, combination of hydrocodone and paracetamol, cyclobenzaprine, and combination of ipratropium and salbutamol. Previous and ongoing treatment for hypercholesterolemia was simvastatin.

The subject was in the parent study from 30 September one year ago* to 06 January same year* and received the last dose of evolocumab in the parent study on 09 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 06 January [redacted].

Approximately 1 month later, on 10 February same year*, the subject developed chest pain, and was hospitalized on 13 February same year*. The subject had slightly elevated blood pressure.

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Laboratory tests revealed normal cardiac enzymes, and possibility of myocardial infarction was ruled out. The event chest pain was reported as resolved on 14 February same year*, and the subject was discharged from the hospital on the same day.

On 10 May same year*, the subject was hospitalized due to constipation, chest discomfort, and abdominal discomfort with nausea and vomiting. An abdominal and pelvic computerized tomography (CT) scan revealed mild nonspecific distention of the small bowel, with a moderate to large amount of stool retained within the colon; these findings were suggestive of a mild generalized ileus and/or constipation. A CT scan also revealed atherosclerosis and fatty liver. A chest radiograph revealed no consolidation or effusion; the cardiomediastinal silhouette and bones were within normal limits; no active intrathoracic disease was noted. An electrocardiogram (ECG) revealed left anterior fascicular block, possible left ventricular hypertrophy, and possible anterior/septal and lateral T wave changes due to hypertrophy and/or ischemia. Treatment included unspecified gastrointestinal "cocktail", lactulose, ondansetron, meglumine amidotrizoate/sodium amidotrizoate, macrogol/potassium chloride/sodium bicarbonate/ sodium chloride/sodium sulfate, and pantoprazole. The events of chest discomfort and abdominal discomfort were reported as resolved on 14 May same year*, and the subject was discharged from the hospital on the same day. The event of constipation was ongoing at the time of this report.

On 12 September same year*, the subject developed chest pain. Two days later, on 14 September same year*, the subject was hospitalized due to severe shooting pain in the left side of the chest with left arm radiation. The chest pain was reported as reproducible and non-cardiac in nature. A cardiologist was consulted, and it was reported that in the past, the subject had several emergency room visits due to chest pain or severe chest pain with weakness and shortness of breath; however, cardiac enzymes were negative in all instances. The subject was afebrile with blood pressure of 110/50 mmHg, pulse rate of 70 beats per minute, and regular respirations of 20 breaths per minute. Tenderness was present on the chest wall, with the left third and fourth ribs having more tenderness, due to which subject was experiencing pain. The subject's B-type natriuretic peptide was 23 pg/mL, and his 3 sets of cardiac enzymes were normal. Ejection fraction was approximately 35%. The investigator reported that the event of severe headache did not meet seriousness criteria. The event of chest pain was reported as resolved on 15 September same year*, and the subject was discharged from the hospital on the same day.

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On 21 May one year after*, the subject was hospitalized due to chronic obstructive pulmonary disease. Laboratory tests revealed albumin of 3.9 g/dL, calcium of 9.3 mg/dL, creatine phosphokinase of 140 U/L, creatine phosphokinase-muscle and brain (MB) of 2.2 ng/mL, troponin T of < 0.010 ng/mL, glucose of 98 mg/dL, potassium of 3.9 mmol/L, sodium of 142 mmol/L, hemoglobin of 13.4 g/dL, neutrophil count 1.9 X 10^9/L, red blood cell count of 3.97 X 10^{12}/L, and white blood cell count of 5.3 X 10^9/L. A chest radiograph revealed well inflated lungs. There was no evidence of pneumonia, pulmonary edema, pleura effusions, or pneumothorax. No acute thoracic abnormality was noted. A CT scan of thorax showed moderate centrilobular emphysema bilaterally, predominantly in the upper lungs. The lungs were hyperinflated. There were no pleura effusions or pneumothorax and no evidence of pneumonia. The esophagus was mildly patulous. An ECG revealed sinus bradycardia, possible left anterior fascicular block, possible anterior infarct. Inferior/lateral T abnormality due to myocardial ischemia was seen. Treatment included methylprednisolone, and combination of ipratropium and salbutamol. The event of COPD was reported as resolved on 23 May 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 first instance of the event of chest pain was on 03 February same year*, and prior to the events of constipation, chest discomfort, and abdominal discomfort was on 27 April same year*. The subject's last dose of evolocumab prior to the second instance of chest pain was on 20 August same year*, prior to COPD was on 26 April one year after*, and prior to the third instance of the event of chest pain was on 09 November one year after*. Evolocumab was continued.

Approximately 2 years after the first dose of evolocumab, on 13 January two years after*, the subject developed worsening of hypertension and was hospitalized on the same day. On 15 January two years after*, the subject was discharged from the hospital. Treatment for the event was not known. The worsening hypertension was reported as resolved on 15 January two years after*. The last dose prior to the event of hypertension was not known. Evolocumab was continued.

As of the data cutoff date of [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 events of chest pain, retrosternal tightness of chest, abdominal discomfort, constipation, worsening of HTN, and COPD exacerbation were related to evolocumab.

Subject No: [redacted]
Treatments: Parent Study: 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: Intraductal proliferative breast lesion, Thyroid adenoma, Cellulitis, Acute renal failure, Sepsis

Subject [redacted] was a 44-year-old white postmenopausal woman participating in Study 20110110 who developed an intraductal proliferative breast lesion (reported term: bilateral ductal carcinoma in situ), thyroid adenoma (reported term: adenomatous nodules of thyroid), cellulitis (reported term: chest wall cellulitis), acute renal failure, and sepsis. The subject's medical history included hypercholesterolemia, dyslipidemia, hemangioma, lipoma, deafness, hypothyroidism, sterilization, type 2 diabetes mellitus, migraine, nervous system disorder (Bannayan-Riley-Ruvalcaba syndrome), Cowden's disease, Vitamin D deficiency, osteoarthritis, back pain, anxiety, benign breast neoplasm, thyroid neoplasm, morbid obesity, menopausal symptoms, intraductal papilloma of breast, breast inflammation, breast cyst, and gene mutation (phosphate and tension mutation). Concomitant medications included Vitamin E, citalopram, fluticasone, salbutamol, mometasone, paracetamol, valaciclovir, and linezolid. Previous and ongoing treatment for hypercholesterolemia was pravastatin.

The subject was in the parent study from 15 November one year ago* to 08 February same year* and received the last dose of evolocumab in the parent study on 06 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 08 February [redacted]. Approximately 1 month later, on 20 March same year*, the subject developed a thyroid adenoma, and she was hospitalized for total thyroidectomy. Thyroidectomy revealed adenomatous nodules (multinodular goiter). Microscopic examination of right and left lobes of thyroid showed multiple nodules with variable-sized follicles, no malignancy was identified. On the same day, the subject underwent an ultrasound-guide preoperative hookwire needle localization of biopsy-proven papilloma within the subareolar right breast. Microscopic examination of "right breast mass at 6 o'clock" showed 2 foci of ductal carcinoma in situ (A4, A6) size of 0.3 and 0.3 cm from superior margin (A4) and 0.4 cm from anterior margin (A6), and no invasive malignancy was identified. The subject was diagnosed with intraductal proliferative breast lesion. The event of thyroid adenoma was reported as resolved on 20 March same year*, and the subject was discharged from the hospital on

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22 March same year* with low salt and low cholesterol diet recommendation. On 17 October same year*, the subject underwent a double mastectomy. Additional treatment included dexlansoprazole, levothyroxine, azithromycin, sumatriptan, promethazine, indomethacin, furosemide, metoclopramide, levofloxacin, hydroxyzine, atorvastatin, famciclovir, amitriptyline, liothyronine, amoxicillin, clonazepam, hydrocodone, trazodone and acetaminophen.

On 26 October same year*, the subject presented to the emergency room due to redness to her breast after mastectomy. Blood tests showed alkaline phosphatase (ALP) of 116 U/L, calcium of 7.1 mg/dL, creatinine of 2.9 mg/dL, blood urea nitrogen (BUN) of 48 mg/dL, protein of 7.6 g/dL, and albumin of 4.6 g/dL. The subject was diagnosed with cellulitis, acute renal failure, and sepsis. The next day, 27 October same year*, the subject was hospitalized for further management with intravenous antibiotics, and underwent an ultrasound which revealed a large fluid collection in the lateral aspect of the right breast. During hospitalization, blood tests showed alanine aminotransferase ranging from 7 to 14 U/L, chloride from 98 to 101 mEq/L, glucose from 89 to 106 mg/dL, potassium from 3.8 to 3.7 mEq/L, and sodium from 143 to 139 mEq/L. On 28 October same year*, blood tests showed ALP of 111 U/L, albumin of 3.9 g/dL, calcium of 9.2 mg/dL, creatinine of 0.9 mg/dL, BUN of 10 mg/dL, white blood cell count of 9.4 x 10^9/L, red blood cell count of 2.85 x 10^{12}/L, hemoglobin of 9.9 g/dL, hematocrit of 30.1%, eosinophils of 5.4%, platelet count of 556 x 10^9/L, mean cell volume of 105.7 fL, and mean cell hemoglobin of 34.6 pg. Two days later, on 30 October same year*, the subject underwent ultrasound guided fluid aspiration of the lateral aspect of the right breast which showed a 7.3 x 3.3 x 7.1 cm fluid collection with echogenic debris at its dependent aspect. Approximately 162 cc of yellow serous fluid was aspirated. Post-aspiration ultrasound images demonstrated a marked decrease in the size of the fluid collection to 4.8 x 3.4 x 4.5 cm. Treatment included linezolid and valaciclovir. On 31 October same year*, gram stain of the aspirated fluid showed no organisms, and on 04 November same year*, culture revealed no isolated anaerobic organisms. Treatment for the event of sepsis included trimethoprim, sulfamethoxazole, and intravenous fluids. The subject was discharged from the hospital on 30 October same year*. The event of cellulitis was reported as resolved on 26 November same year* and the event of sepsis was reported as resolved on 02 April one year after*. The event of intraductal proliferative breast lesion was ongoing at the time of this report. The event of acute renal failure was considered resolved on 02 April one year after*. .

The subject's last dose of evolocumab prior to the events of intraductal proliferative breast lesion and thyroid adenoma was on 07 March same year*, and prior to the events of cellulitis, acute renal failure, and sepsis was on 30 May same year*. Evolocumab was withheld due to the event of

thyroid adenoma and re-initiated on 04 May same year*. Subsequently, evolocumab was permanently discontinued due to the event of intraductal proliferative breast lesion, and the subject received the last dose of evolocumab in the study on 30 May same year*. The investigator reported that there was no reasonable possibility that the events of intraductal proliferative breast lesion, thyroid adenoma, cellulitis, acute renal failure, and sepsis were related to evolocumab.

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Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q4W 280 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care (SOC) Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SOC
Report: Meningitis

Subject [redacted] was a 49-year-old native Hawaiian woman participating in Study 20110110 who developed meningitis. The subject's medical history included hypertension, dyslipidemia, anemia and chronic migraine. Concomitant medications included ferrous sulfate, lisinopril, potassium, nebivolol, and olmesartan. Previous treatment for hypercholesterolemia included simvastatin.

The subject received evolocumab in the parent study (Study 20101155) from 22 November one year ago* to 18 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 20 February [redacted].

Approximately 2 years later, on 11 February two years after*, the subject was hospitalized due to viral meningitis, as confirmed by cerebrospinal fluid analysis and culture. Brain computerized tomography (CT) and magnetic resonance imaging (MRI) incidentally disclosed a left middle cranial fossa meningioma, without significant mass effect. The subject was discharged from the hospital on 12 February two years after*. The meningitis was resolved on 13 February two years after* and the outcome of the event meningioma was reported as ongoing. The subject continued in the study without interruptions in dosing.

The last dose before the event was on 24 December one year after*. As of the data cutoff date [redacted], the subject was continuing in the study, with the last dose before the cutoff date given on [redacted]. The investigator reported that the meningitis was not considered related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Parent Study: 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: Musculoskeletal pain

Subject [redacted] was a 64-year-old white man participating in Study 20110110, who experienced musculoskeletal pain (reported term: worsening of pre-existing left rotator cuff pain). The subject's medical history included hypercholesterolemia. Concomitant medications included ibuprofen, testosterone, naproxen, hydrochlorothiazide, lisinopril, hydrocodone, paracetamol, combination of hydrocortisone and pramoxine, dextromethorpha, combination of dextromethorphan, doxylamine, pseudoephedrine, and paracetamol, combination of guaifenesin and codeine, flunisolide, and Vitamin E. Previous and ongoing treatment for hypercholesterolemia included simvastatin and atorvastatin.

The subject was in the parent study from 29 September one year ago* to 04 January same year* and received the last dose of evolocumab in the parent study on 05 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 04 January [redacted]. Approximately 1 year and a month later, on 06 February one year after*, the subject was hospitalized and underwent an elective repair of left rotator cuff injury. Treatment medication included combination of oxycodone hydrochloride, oxycodone terephthalate, and paracetamol. The event of musculoskeletal pain was reported to have resolved on 08 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 of musculoskeletal pain was on 04 February one year after*. Evolocumab was continued. 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]. The investigator reported that there was no reasonable possibility that the event of musculoskeletal pain was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Parent Study: 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: Chronic sinusitis, Staphylococcal cellulitis, Non-cardiac chest pain, Upper respiratory tract infection

Subject [redacted] was a 39-year-old white woman participating in Study 20110110, who developed chronic sinusitis, non-cardiac chest pain, upper respiratory tract infection and staphylococcal cellulitis (reported term : L groin cellulitis + MRSA [methicillin resistant S. aureus]). The subject's medical history included hypercholesterolemia, hypothyroidism, gastrooesophageal reflux disease, hypertension, anxiety, chronic back pain, asthma, psoriatic arthropathy, respiratory failure, nephrolithiasis, sleep apnea syndrome, sterilization, obesity, stress urinary incontinence, hiatus hernia, H1N1 influenza, menorrhagia, depression, attention deficit/hyperactivity disorder and rubber sensitivity. Concomitant medications included levothyroxine, omeprazole, clonazepam, methocarbamol, clobetasol, calcipotriol, betamethasone, tramadol, bupropion, cetirizine, hydrocodone, ibuprofen, fluticasone, paracetamol, combination of codeine and paracetamol, combination of fluticasone and salmeterol, and combination of alginic acid, aluminium hydroxide gel, dried magnesium trisilicate, sodium alginate, influenza vaccine and sodium bicarbonate. Previous and ongoing treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 29 November one year ago* to 23 February same year* and received the last dose of evolocumab in the parent study on 26 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 23 February [redacted].

Approximately 1 year and 2 weeks later, on 10 March one year after*, the subject developed chronic sinusitis. On 31 May one year after*, the subject underwent an elective ear, nose and throat surgery to resolve her chronic sinusitis symptoms. Preoperative diagnoses included bilateral chronic sinusitis-pansinusitis, and inferior turbinate hypertrophy. More specifically, the subject had bilateral maxillary chronic sinusitis with polyps, bilateral ethmoid chronic sinusitis with polyps, bilateral frontal chronic sinusitis, bilateral sphenoid chronic sinusitis with polyps, and bilateral inferior turbinate hypertrophy.

The subject underwent an endoscopic sinus surgery using image-guided (bilateral) computer navigation which included bilateral maxillary antrostomy, bilateral total ethmoidectomy, bilateral

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frontal sinusotomy, bilateral sphenoidotomy, bilateral inferior turbinate reduction, balloon sinuplasty and submucous resection. A Propel intersect implant was placed to medialize the middle turbinate. Treatment included lidocaine with epinephrine, nitrous oxide, propofol, rocuronium, fentanyl, glycopyrronium, midazolam, neostigmine, ocular lubricant gentamicin, dexamethasone, ondansetron, prednisone, oxymetazoline, levofloxacin, and analgesics. The event of chronic sinusitis was reported as resolving. The subject was discharged from the hospital on 01 June one year after* and reportedly returned to work. The subject's last dose of evolocumab prior to the event of chronic sinusitis was on 23 February one year after*. Evolocumab was continued.

On 24 February two years after*, the subject developed cellulitis of the left (L) groin. Approximately 4 days later on 28 February two years after*, the subject developed chest pain and upper respiratory infection. On 03 March two years after*, the subject presented to the emergency room with chest pain and increasing erythema in her left groin area. The subject also had increasing shortness of breath, productive cough with yellow/green sputum, chest pain, sore throat, and nasal congestion. The subject described her chest pain as feeling of central non radiating chest tightness. On 03 March two years after*, electrocardiography (EKG) showed sinus rhythm at 66 beats per minute. Treatment included combination of sulfamethoxazole and trimethoprim. The subject reported that one month ago, she had undergone hair removal in her groin area and had an ingrown hair that became infected. The subject had been having some pustular greenish drainage from her groin area. Other lesions with approximately 1 cm in diameter developed on her legs, upper extremities and under the left breast. Significant erythema was present on the groins bilaterally, extending to the abdominal wall and on left breast. There was greenish/yellow discharge from both the groin wounds. These symptoms were consistent with cellulitis.

On 03 March two years after*, laboratory investigations showed troponin I < 0.01 ng/mL, and white blood cell count (WBC) 13.2 to 15.3 x 10^9/L. The chest PA (posterior anterior) and lateral radiograph showed no active process. Treatment after the onset of event included vancomycin. The outcome of the event upper respiratory tract infection was considered resolved on 06 March two years after*, and the event of cellulitis (L) groin was considered resolved on 23 April two years after*. However, the event of chest pain was reported as ongoing and the subject remained in the hospital.

The subject's last dose of investigational product prior to the event was on 17 February two years after*. The investigational drug was continued. 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].

The investigator reported that there was no reasonable possibility that the events of chronic sinusitis, cellulitis (L) groin, chest pain, and upper respiratory infection were related to evolocumab.

Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q4W 420 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: Deep vein thrombosis

Subject [redacted] was a 57-year-old white woman participating in Study 20110110 who developed deep vein thrombosis (reported term: deep venous thrombosis of the left leg). The subject's medical history included hypercholesterolemia, hypertension, and chronic back pain. The subject was slightly overweight and had a sedentary lifestyle. There was no family history of clots. Concomitant medications included hydrochlorothiazide, lisinopril, celecoxib, pregabalin, acetylsalicylic acid, metoprolol, sertraline, loperamide, tramadol, pantoprazole, metaxalone, and omeprazole. Previous and ongoing treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 14 October one year ago* to 09 January same year* and received the last dose of evolocumab in the parent study on 09 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 09 January [redacted]. Approximately 1 year and 9 months later, on 28 September one year after*, the subject had severe pain in her left leg, like a cramp that was not getting any better; it was getting hard and edematous in the lower extremity, and she was hospitalized. An ultrasound of the lower extremity showed evidence of a deep vein thrombosis (DVT) in the saphenous, popliteal, and femoral veins. Laboratory tests showed a sedimentation rate of 32 mm/hour, functional antithrombin III 86%, antithrombin III antigen (AG) 87%, protein C 126%, protein S total 129%, and protein S free 86%. A chest radiograph of the lungs performed on 29 September one year after* was clear. Laboratory tests on 30 September one year after* showed an international normalized ratio (INR) of 1.52. The subject was started on enoxaparin and warfarin. She was doing well without any major issues; the pain and swelling of the leg improved, although she still had some cramps with ambulation.

On 01 October one year after*, the subject's INR was 2.30 and the subject was discharged while she was still being treated with warfarin, and the treatment was planned for 6 weeks. She continued her medications for hypertension and hypercholesterolemia. The subject was advised that because of her sedentary state, she should be on acetylsalicylic acid. It was reported that the subject may have some venous insufficiency, which could put her at risk for a clot. The event deep vein thrombosis was reported to have resolved on 31 December one year after*.

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The subject's last dose of evolocumab prior to the event was on 23 September one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject continued in the study, and the last dose of evolocumab was on the cutoff date of [redacted]. The investigator reported that there was no reasonable possibility that the event of deep vein thrombosis was related to evolocumab, and there were no co-suspect medications.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: 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: Non-cardiac chest pain, Urinary incontinence, Contrast media allergy, Fluid retention, Chest pain, Abdominal pain

Subject [redacted] was a 56-year-old white woman participating in Study 20110110 who developed non-cardiac chest pain (2 events), urinary incontinence, allergy to contrast media (reported term: acute allergic reaction to IVP dye), fluid retention, chest pain (reported term: atypical chest pain) and abdominal pain (reported term: worsening abdominal pain). The subject's medical history included hypercholesterolemia, myocardial infarction, coronary artery disease, coronary artery bypass, stent placements, permanent pacemaker insertion, diabetes mellitus, obesity, panic attacks, hyperlipidemia, gastroesophageal reflux disease, irritable bowel syndrome, stress urinary incontinence, hypertension, hypothyroidism, anxiety disorder, ischemic cardiomyopathy, implantable cardioverter defibrillator insertion, stable angina pectoris, ejection fraction 50%, chronic abdominal pain, and allergy to penicillin, eptifibatide (integrilin), nuts, dust, and cats. Concomitant medications included isosorbide, acetylsalicylic acid, lisinopril, clopidogrel, levothyroxine, alprazolam, furosemide, metoprolol, paracetamol, influenza vaccine, multivitamin combinations, morphine, ketorolac, docusate, antibacterials for systemic use, bumetanide, exenatide, dexlansoprazole, cyclobenzaprine, glyceryl trinitrate, magnesium sulfate, Vitamin D, diphenhydramine, and methylprednisolone. Previous and ongoing treatment for hypercholesterolemia included atorvastatin and rosuvastatin.

The subject was in the parent study from 16 November one year ago* to 22 February same year* and received the last dose of evolocumab in the parent study on 26 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 22 February [redacted].

Three days later, on 25 February same year*, the subject woke up with chest pain, nausea, and vomiting, and was hospitalized. Laboratory test results showed troponin I < 0.04 ng/mL. An electrocardiogram showed a T wave abnormality. Treatment included glyceryl trinitrate and hydrocodone. On 25 February same year*, the event non-cardiac chest pain was reported as resolved and the subject was discharged after myocardial infarction was ruled out. The subject's last dose of evolocumab prior to the event was on 22 February same year*. Evolocumab was continued.

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Approximately 6 months after the first dose of evolocumab, on 27 August same year*, the subject was admitted to the hospital for elective retropubic sling procedure for urinary incontinence. During the surgery, cystoscopy was performed after the sling had been placed, and showed normal bladder mucosa. The event urinary incontinence was reported as resolved on 28 August same year* and the subject was discharged from the hospital. The subject's last dose of evolocumab prior to the event was on 08 August same year*. Evolocumab was continued.

Approximately 1 year after the first dose of evolocumab, on 26 February one year after*, the subject developed an acute allergic reaction and was hospitalized. The subject was to undergo an abdominal CT scan because of abdominal pain. She had a reaction to the intravenous contrast, which caused erythema on her face, tightening of her throat, and some chest discomfort, and was hospitalized due to chest pain. The subject denied any headaches, fever, chills, nausea, vomiting, or diarrhea. Her vital signs were as follows: blood pressure 114/55 mmHg, pulse 66 beats per minute (bpm), temperature 97.9 F, and respiration rate of 18 breaths per minute. The abdominal CAT scan only revealed fatty liver. Laboratory tests showed the following results: troponin I < 0.04 ng/mL, alkaline phosphatase 119 U/L, and total bilirubin 1.0 mg/dL. An electrocardiogram did not show any acute changes. The subject's cardiac enzymes were all negative; cardiac issues were ruled out. The subject was diagnosed to have an acute allergic reaction to the intravenous dye. Treatment included hydrocortisone, diphenhydramine, and nitroglycerin. The subject was feeling well; she did not have any further problem with tightness of her throat or chest, and there was no rash. The event acute allergic reaction was reported to have resolved on 27 February one year after* and the subject was discharged from the hospital. The subject's last dose of evolocumab prior to the event was on 20 February one year after*. Evolocumab was continued.

Approximately 1 year and 4 months after the first dose, on 18 June one year after*, the subject developed fluid retention. On 03 July one year after*, the subject was evaluated by a primary physician since she had swelling in the lower extremities (on and off) and some mild shortness of breath. On the same day, the subject was hospitalized with questionable atypical chest pain associated with some shortness of breath. Upon admission, her vital signs were as follows: blood pressure 113/54 mmHg, pulse rate 67 bpm, respiratory rate 18 breaths per minute, and body temperature 96.4 F. The subject's cardiac enzymes were negative. The chest radiograph was negative and showed no pneumonia or congestion. On 04 July one year after*, laboratory data showed creatine phosphokinase MB of 0.6, 0.7, 0.8 ng/mL and troponin I < 0.04 ng/mL (performed 3 times). An echocardiogram showed ejection fraction of 40% to 45%. Treatment included bumetanide and

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nitroglycerin. After administration of the intravenous diuretic, the subject's swelling improved. The swelling of the lower extremities resolved. The investigator reported that fluid retention was probably multifactorial. The events fluid retention and atypical chest pain were reported to have resolved on 05 July one year after* and the subject was discharged from the hospital along with instructions on taking her medication and physical activity. The subject's last dose of evolocumab prior to the event was on 12 June one year after*. Evolocumab was continued.

On 11 December one year after*, the subject was diagnosed with worsening of abdominal pain and non-cardiac chest pain which resulted in the hospitalization on the same day. On presentation to the hospital, the subject did not have detectable abdominal peristaltic movements and experienced nausea and vomiting. The subject was unable to tolerate anything orally. Computed tomography (CT) scan of abdomen and pelvis revealed fatty liver infiltration. Laboratory value for troponin was negative. Treatment medications after the onset of the event included morphine sulfate, glyceryl trinitrate, magnesium citrate, ondansetron, and hydromorphone. Peristalsis returned after rehydration. On 13 December one year after*, the subject`s vital signs were: blood pressure of 139/60 mmHg, heart rate 85 bpm, respiratory rate 16 breaths per minute, body temperature 98.1°F and oxygen saturation 95%. The events of worsening abdominal pain and non-cardiac chest pain were reported as resolved on 13 December one year after* and the subject was discharged from the hospital on the same day.

The subject's last dose of investigational product prior to the event was on 30 October 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 cutoff date on [redacted].

The investigator reported that there was no reasonable possibility that the events of non-cardiac chest pain, urinary incontinence, allergy to contrast media, fluid retention, chest pain and worsening abdominal pain were related to evolocumab.

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Subject No: [redacted]
Treatment: 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: Cellulitis

Subject [redacted] was a 63-year-old black woman participating in Study 20110110 who developed cellulitis. The subject's medical history included hypercholesterolemia, hypertension, hypothyroidism, osteoarthritis, type 2 diabetes mellitus, tonsillectomy, hysterectomy, right knee arthroscopic surgery, ingrown toenail, obesity, and allergy to penicillin. Concomitant medications included sitagliptin, levothyroxine, valsartan, triamterene, naproxen, combination of bisoprolol and hydrochlorthiazide, metformin, and combination of hydrocodone and paracetamol. Previous and ongoing treatment for hypercholesterolemia included rosuvastatin.

The subject was in the parent study from 26 August same year* to 05 December same year* and received the last dose of evolocumab in the parent study on 04 November same year*. The subject received the first dose of evolocumab in Study 20110110 on 05 December [redacted].

Approximately 1 year and 5 months later, on 20 May two years after*, the subject developed swelling and rash on the left knee, which increased and spread across the leg. On 04 June two years after*, the subject presented to the emergency department and was hospitalized to exclude deep vein thrombosis. On the same day; the subject was diagnosed with cellulitis. During hospitalization, the subject was treated with doxycycline, nystatin, and enoxaparin. On 07 June two years after*, the event of cellulitis was reported as resolved, and the subject was discharged from the hospital on the same date. The investigator reported that the subject did not have a previous history of cellulitis, nor etiological or predisposing risk factors associated with the event.

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 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 cellulitis was related to evolocumab.

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Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q2W 70 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care (SOC) Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SOC
Report: Intervertebral disc disorder, Intervertebral disc injury

Subject [redacted] was a 47-year-old black man participating in Study 20110110 who experienced an intervertebral disc disorder (reported term: cervical neck lesion C4-6) and intervertebral disc injury (reported term: discal injury). The subject's medical history included hypercholesterolemia, chronic cardiac failure, diabetes mellitus type 2, diabetic neuropathy, drug hypersensitivity (enalapril), hypertension, spinal fusion surgery. Concomitant medications included clopidogrel, furosemide, insulin glargine, isosorbide, methocarbamol, metoprolol, nifedipine, potassium, Vitamin E, and combination of hydrocodone and paracetamol. Previous and ongoing treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 28 September one year ago* to 04 January same year* and received the last dose of evolocumab in the parent study on 07 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 04 January [redacted].

Approximately 7 months later, on 07 August same year*, the subject was hospitalized for spinal fusion surgery. The subject had undergone multiple surgeries for cervical disc fusion since 2005. He started having pain in August same year* (date not specified). The subject underwent spinal fusion surgery on 09 August same year*. He was feeling better and was advised a collar to decrease neck movements. The event of spinal fusion surgery was reported as resolved on 09 August same year* and the subject was discharged from the hospital.

Approximately 1 year and 4 months after the first dose, on 07 May one year after*, the subject was hospitalized for planned low back surgery. The underlying cause for the event of low back surgery was fused vertebra (cervical fusion C5-7). Treatment included anterior cervical disc fusion surgery. The event of surgery was reported as resolved on 08 May 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 of spinal fusion surgery was on 18 July same year*, and the last dose of evolocumab prior to the event of surgery was on 01 May one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the

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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 events of cervical fusion C4-6 and low back surgery were related to evolocumab.

Subject No: [redacted]
Treatment: Parent study: Study 20101155, Evolocumab SC Q2W 140 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2 to 5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Costochondritis, Pleurisy, Pneumonia

Subject [redacted] was a 72-year-old white woman participating in Study 20110110 who developed costochondritis, pleurisy (reported term: pleuritis), and pneumonia. The subject's medical history included hypercholesterolemia, chronic obstructive pulmonary disease, bronchitis, hypertension, abdominal aortic aneurysm, depression, palpitation presumably supraventricular tachycardia, dyslipidemia, right carotid artery stent placement, 2 dilation and curettages, 2 hysterectomies, coccygectomy, right carotid endarterectomy, former smoker, alcoholic, and allergy to codeine. Concomitant medications included Vitamin E, oxygen, fluoxetine, Vitamin D_3, atropine/diphenoxylate, alendronate, alprazolam, acetylsalicylic acid, ramipril, atropine, tiotropium, and amlodipine. Previous and ongoing treatment for hypercholesterolemia included atorvastatin.

The subject was in the parent study from 03 November one year ago* to 07 February same year* and received the last dose of evolocumab in the parent study on 12 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 07 February [redacted].

Approximately 3 months later, on 08 May same year*, the subject presented to the hospital with acute onset of shortness of breath with some diaphoresis and chest pain in the left precordial area. The pain was sharp/stabbing with 8/10 intensity that lasted about 10 to 15 seconds and kept coming back. The subject also complained of a dry cough and nausea but denied fever, vomiting, diarrhea, or abdominal pain. The subject was hospitalized on the same day with costochondritis and pleurisy. On admission, the subject's vital signs included temperature of 36.6°C, pulse rate of 72 beats per minute (bpm), respiratory rate of 18 breaths per minute, and oxygen saturation of 92 to 94% on 3 liters. Laboratory tests results on the same day revealed no significant abnormalities. Venous blood gases revealed pH 7.49, carbon dioxide 27, and lactic acid of 35 mg/dL. On the same day, a computerized tomography (CT) angiogram of the chest was normal, a chest radiograph revealed no acute process, and an electrocardiogram (ECG) revealed normal sinus rhythm with some left ventricular hypertrophy and nonspecific T-wave inversions on the inferior leads; B-type natriuretic peptide (BNP) was less than 5 ng/mL and troponin I was less than 0.05 ng/mL.

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On 09 May same year*, an ultrasound of the abdomen done for size of known abdominal aortic aneurysm revealed interval increase in maximal anteroposterior (AP) diameter of the infrarenal abdominal aortic aneurysm from 3.1 cm to 4 cm. A nuclear medicine (NM) myocardial perfusion with Lexiscan (regadenoson) stress test revealed no evidence of myocardium at risk; there was no evidence of myocardial infarction. Global ejection fraction was 75%. The next day, on 10 May same year*, the subject's vital signs included temperature of 36.8°C, heart rate of 70 bpm, blood pressure of 121/74 mmHg, respiratory rate of 18 breaths per minute, oxygen saturation of 97% on room air, with walking 90% and 93% on 2 liters. Treatment for the events included amlodipine with atorvastatin, levofloxacin, levosalbutamol, ipratropium, metoprolol, pantoprazole, enoxaparin, and paracetamol. The outcome of the events of costochondritis and pleurisy was reported as resolved on 10 May same year*, and the subject was discharged from the hospital on the same day in a stable condition. Evolocumab was continued. The investigator stated that the subject did not have previous events similar to the reported events.

Approximately 1 year and 2 months after the first dose of evolocumab in Study 20110110, on 08 April one year after*, the subject underwent a chest radiograph that revealed pneumonia. On 06 April one year after*, she developed fever and cough that was worse on 07 April one year after*. She was treated with levofloxacin and an inhaler. Other treatment included metoprolol. She increased her oral fluids and had some urinary frequency, but she thought that was the reason.

On the morning of 10 April one year after*, the subject began coughing up blood. She had developed some pain in her ear the day before that was still present on admission. She also had a fever that reached 102°F. She was up-to-date on her flu shot and pneumonia vaccine. She did have some substernal chest pressure, which she reported occurred when she arrived at the emergency department. She denied any radiation. The subject was short of breath without nausea or vomiting. On the same day, the subject was hospitalized with acute respiratory failure for which she was treated with steroids. Physical examination showed the lungs clear to auscultation bilaterally, with decreased breath sounds in the bases, skin warm and dry, the rest of the systems were normal. The subject's vital signs revealed a body temperature of 38.4°C, heart rate of 94 bpm, respiratory rate of 24 breaths per minute, blood pressure of 176/84 mmHg, and oxygen saturation that went from 88 to 93% on 4 litres oxygen via a nasal cannula.

Laboratory tests were unremarkable. Chest radiograph showed increased markings in both lower lobes consistent with atelectasis versus infiltrate. ECG showed sinus rhythm with no acute abnormalities. Results were pending for the CT angiogram of the chest. The diagnosis was bilateral lower lobe pneumonia which was treated with ceftriaxone and azithromycin. The

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subject had some scant hemoptysis likely due to pneumonia and she was placed on enoxaparin for deep vein thrombosis prophylaxis.

The subject improved gradually and was put on a tapering dose of prednisone. The subject was on home oxygen and she improved symptomatically, but she complained of diarrhea. A *Clostridium difficile* test was negative. The subject was treated with vancomycin, but her diarrhea did not improve. A CT scan of the abdomen showed infrarenal aortic aneurysm with thrombus. Vascular surgery was consulted and recommended no anticoagulation and no further intervention. A colonoscopy revealed sigmoid polyp and she had a polypectomy; the pathology results were pending. She was to follow up within 2 weeks with the gastroenterologist. After discontinuation of famotidine and enoxaparin, the subject's diarrhea improved. The subject's electrolytes were monitored and she had been afebrile and her WBC count was normal.

On 20 April one year after*, the subject was awake and oriented. She denied any abdominal pain, diarrhea, nausea or vomiting. Her vital signs showed a temperature of 36.9°C, heart rate of 73 bpm, respiratory rate of 18 breaths per minute, blood pressure of 143/79 mmHg, oxygen saturation of 92% on 2 liters. She was medically stable. The subject was discharged home on 20 April one year after* on her regular outpatient medication plus Vitamin D_3 and prednisone for 9 more days. The event of pneumonia was reported to have resolved on 28 April one year after*.

The subject's last dose of evolocumab prior to the events of costochondritis and pleurisy was on 01 May same year*, and the last dose of evolocumab prior to the event of pneumonia was on 02 April one year after*. Evolocumab was continued.

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]. The investigator reported that there was no reasonable possibility that the events of costochondritis, pleuritis, and pneumonia were related to evolocumab.

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

Subject [redacted] was a 52-year-old white man participating in Study 20110110 who was diagnosed with prostate cancer. The subject's medical history included hypercholesterolemia, hypertension, ankylosing spondylitis, alcohol use (3 per day, usually beer or wine), inguinal hernia repair, elevated prostatic-specific antigen (PSA) levels between 2.50 to 4.30 ng/mL; and a family history of colon cancer and hypertension. Concomitant medications included omeprazole, naproxen, felodipine, guaifenesin with dextromethorphan, cetirizine, mometasone, fluticasone, and acetaminophen/hydrocodone. Previous and ongoing treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 15 November one year ago* to 21 February same year* and received the last dose of placebo in the parent study on 24 January same year*. The subject received the first of evolocumab in Study 20110110 on 21 February [redacted]. On the same day, the subject had an abnormal prostate exam. On 16 April same year*, the subject had an elevated PSA level of 4.2. Subsequently, on 23 April same year*, a transrectal ultrasound-prostate-guided needle biopsy revealed adenocarcinoma, Gleason score of 3+4 with the largest amount of the core being 30%. The prostate gland measured 22 g on ultrasound, and therefore the tumor was clinically staged as T2a. Approximately 2 months and 1 week after the first dose of evolocumab, on 01 May same year*, the diagnosis of prostate cancer was confirmed. On 13 July same year*, the subject was hospitalized for a robotic assisted laparoscopic radical prostatectomy with bilateral nerve preservation. Surgery was uneventful with a smooth recovery. On 14 July same year*, the subject was discharged from the hospital on ciprofloxacin and hydrocodone/paracetamol. The event of prostate cancer was reported to have resolved on 13 July same year*.

The subject's last dose of evolocumab prior to the event was on 17 April same year*. Evolocumab was continued. As of the data cutoff date of [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 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 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: Non-cardiac chest pain

Subject [redacted] was a 56-year-old white man participating in Study 20110110 who developed non-cardiac chest pain. The subject's medical history included sleep apnea, chronic obstructive pulmonary disease, gastroesophageal acid reflux, hypercholesterolemia, angina pectoris, cardiac arrest, cardiac catheterization, myocardial infarction, and stent insertion. Concomitant medications included acetylsalicylic acid, amlodipine, clopidogrel, furosemide, glyceryl trinitrate, levothyroxine, melatonin, metformin, metoprolol, multivitamins, potassium, tramadol, and guaifenesin/dextromethorphan. Previous and ongoing treatment for hypercholesterolemia included ezetimibe and simvastatin.

The subject was in the parent study from 02 November one year ago* to 10 February same year* and received the last dose of evolocumab in the parent study on 11 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 10 February [redacted].

Approximately 1 year and 7 months later, on 10 September one year after*, the subject was hospitalized due to chest pain. The subject presented with worsening of chronic pain and was ashen and diaphoretic. Laboratory tests revealed troponin I of 0 ng/mL and brain natriuretic peptide of 54.5 pg/mL. Chest radiograph revealed no evidence of acute intrathoracic disease. Chest pain was considered to be gastrointestinal tract or obesity-related. On 11 September one year after*, laboratory tests revealed troponin I of 0.012 ng/mL, blood creatine phosphokinase 183 IU/L, and creatine kinase muscle-brain (MB) of 3.26 ng/mL. The subject underwent catheterization with diagnostic angiography which showed a widely patent left anterior descending stent, no obstructive coronary artery disease, normal left ventricular function with ejection fraction greater than 60%, moderately elevated left ventricular end-diastolic pressure, and some diastolic dysfunction with left ventricular end-diastolic volume of 19 mL that could cause some degree of discomfort. There were no coronary findings that could explain his chest pain syndrome. An electrocardiogram (ECG) was abnormal (no details provided). The investigator reported chest pain, coronary artery disease, and abnormal ECG as per hospital diagnosis; and hypertension, hyperlipidemia, palpitations, hypothyroidism, chronic pain, diabetes, sleep apnea, and asthma as secondary diagnosis. A diet with low fat and low salt was recommended. Treatment

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included morphine, ondansetron, oxycocet, glyceryl trinitrate, and paracetamol. Discharge medications included acetylsalicylic acid, amlodipine, clopidogrel, combination of ezetimibe and simvastatin, furosemide, levothyroxine, melatonin, metformin, metoprolol, multivitamins, potassium, tramadol, and bilevel positive airway pressure (BiPaP). The event was reported as resolved on 11 September one year after* and the subject was discharged from the hospital on the same date.

The subject's last dose of evolocumab prior to the event of non-cardiac chest pain was on 23 August one year after*. Evolocumab was continued. As of the data cutoff date of [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 non-cardiac chest pain was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study Evolocumab SC Q4W 420 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: Angina pectoris

Subject [redacted] was a 59-year-old white man participating in Study 20110110 who developed angina pectoris (reported term: worsening angina). His medical history included hypercholesterolemia, coronary heart disease, ischemic cardiomyopathy (ejection fraction 40%), hyperuricemia, arterial hypertension, ACE inhibitor intolerance (cough), sleep apnea syndrome (with CPAP use since April 2008), paroxysmal atrial fibrillation, and coronary artery bypass in twenty- five years ago*,twelve years ago* and four years ago*. Concomitant medications while on study included glyceryl trinitrate, acetylsalicylic acid, allopurinol, isosorbide dinitrate, valsartan, diclofenac, bisoprolol, eplerenone, furosemide, clindamycin, cortisone, enoxaparin sodium, colecalciferol, diclofenac, phenprocoumon, molsidomine, loperamide, montelukast sodium, and *Saccharomyces boulardii*. Previous and current treatment for hypercholesterolemia included rosuvastatin and ezetimibe.

The subject was enrolled into the parent study from 02 November one year ago* to 25 January same year*, and received the last dose of evolocumab in the parent study on 02 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 03 May [redacted].

Approximately 2 years after the first dose of evolocumab, on 16 October one year after*, the subject experienced an episode of atrial fibrillation. The results of an electrocardiogram (ECG) revealed low-frequency continuous arrhythmia with atrial fibrillation (heart rate 75/min), left axis deviation, slow R progression with R-S reversal in V5/V6, negative T wave in 1 and aVL, ST segment depressions in leads 1 and 11 (0.1 mV), V5 and V6 (0.1 mV) and ST segment elevations in aVR & V1 (0.1 mV). Normal sinus rhythm was restored with electrical cardioversion and laboratory tests revealed troponin T 0.008 ng/mL, uric acid 8.9 mg/dL, hemoglobin 15.1 g/dL, hematocrit 44%, platelets 181 x 10^9/L. Enoxaparin sodium was prescribed for anticoagulation therapy and the bisoprolol dose was increased. Two weeks later, on 27 October one year after*, the subject experienced chest pain and pressure and was subsequently admitted to the hospital on 29 October one year after* for an acute coronary syndrome. The following day, a cardiac catheterization showed that the arterial bypasses were patent; at the point of LIMA/RAD insertion, there was a

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50% stenosis not requiring intervention; the RAD was represented as retrograde up to the middle third; the venous bypasses were occluded; and left ventriculography showed a global medium-grade impairment of left ventricular function (ejection fraction 40%) with impaired contractility close to the base. Atrial fibrillation was detected. After a transesophageal echocardiogram excluded a thrombus, electrical cardioversion was performed and normal sinus rhythm was restored. The bisoprolol dose was again increased and anticoagulation was initiated with phenprocoumon. Additional treatments for the event included molsidomine and enoxaprin. The event acute coronary syndrome was reported as not resolved; the subject was discharged from the hospital on 31 October one year after*. The last dose of evolocumab product prior to event onset was on 17 October one year after*. Open label evolocumab was continued. 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 documented on [redacted].

The investigator stated that there was no reasonable possibility that the event acute coronary syndrome was related to investigational product.

*新薬承認情報提供時に置き換え

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: 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 fluvastatin. Previous and current treatment for hypercholesterolemia included fluvastatin, rosuvastatin and ezetimibe.

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 2½ years after the first dose of evolocumab, On 04 March two years after*, computed tomography (CT) of neck, larynx, jaw, 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, N2 gland and skeletal metastasis. On 26 March two years after*, magnetic resonance imaging (MRI) was performed that showed cervical, thoracal 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 as treatment for the event. Investigational product was temporarily 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].

The investigator stated that there was no reasonable possibility that the event malignant lung neoplasm was related to investigational product.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q4W 350 mg Year 1 treatment: Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Splenic artery aneurysm

Subject [redacted] was a 58-year-old white man participating in Study 20110110 who developed a splenic artery aneurysm (reported term: aneurysm arteria lienalis). His medical history included hypercholesterolemia, hypertension, lower limb fracture, and pneumonia. Concomitant medications included Vitamin E, paracetamol, and enalapril. Previous and current treatments for hypercholesterolemia included rosuvastatin and ezetimibe.

The subject was in the parent study from 14 November one year ago* to 08 February same year* and received the last dose of evolocumab in the parent study on 09 January same year*. The subject was randomized to Study 20110110 on 08 February [redacted] and assigned standard of care treatment.

On 29 January one year after*, a computerized tomography of the aorta revealed an aneurysm arteriae lienalis. Subsequently, on 11 March one year after*, the subject was hospitalized in order to undergo an aneurysm coiling. The event was reported as resolved on 12 March one year after* and the subject was discharged on that date.

After completing 1 year in the study, the subject received the first dose of evolocumab on 21 March one year after*. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff on [redacted].

The investigator reported that there was no reasonable possibility that the event of splenic artery aneurysm was related to any study activity.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q4W 350 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: Musculoskeletal pain

Subject [redacted] was a 66-year-old white woman participating in Study 20110110 who developed musculoskeletal pain (reported term: worsening pain right shoulder). Her medical history included hypercholesterolemia. Concomitant medications included atorvastatin, ezetimibe, esomeprazole, carbasalate, salmeterol, fluticasone, tiotropium, omeprazole, lubricating eye ointment (Duratears), and temazepam. Previous and current treatments for hypercholesterolemia included atorvastatin and ezetimibe.

The subject was in the parent study from 30 December one year ago* to 23 March same year* and received the last dose of evolocumab in the parent study on 24 February same year*. The subject received the first dose of evolocumab in the Study 20110110 on 23 March [redacted].

Approximately 1 month later, on 24 April same year*, the subject developed worsening pain in the right shoulder. The subject was hospitalized on 21 March one year after* and underwent tendon repair and removal of calcifications and bone splinters on the same date. Treatment included celecoxib. The event was reported as resolved on 22 March one year after* and the subject was discharged on the same date.

The last dose of evolocumab prior to the event was on 20 April same year*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study, and the last dose of evolocumab prior to the data cutoff date was on [redacted].

The investigator reported that there was no reasonable possibility that the event musculoskeletal pain was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q4W 350 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: Lumbar hernia

Subject [redacted] was a 25-year-old white woman participating in Study 20110110 who developed a lumbar hernia (reported term: hernia lumbalis). The subject's medical history included hypercholesterolemia. Concomitant medications included ethinylestradiol, azithromycin, nitrofurantoin, omeprazole, and diclofenac. Previous and current treatment for hypercholesterolemia included atorvastatin and ezetimibe.

The subject was in the parent study from 05 January same year* to 29 March same year* and received the last dose of evolocumab in the parent study on 05 March same year*. The subject received the first dose of evolocumab in Study 20110110 on 29 March [redacted].

Approximately 1 year and 4 months later, on 04 July one year after*, the subject had lower back pain and developed lumbar hernia; treatment included paracetamol. Laboratory results and diagnostics showed herniated nucleus pulposus L5-S1. On 01 October one year after*, the subject was hospitalized and underwent surgery (unspecified). The event resolved on 01 October one year after*, and the subject was discharged from the hospital on 02 October one year after*.

The subject's last dose of evolocumab prior to the event was on 26 April one year after*. As of the data cutoff date of [redacted], the last dose of evolocumab was administered on 16 August one year after*. The subject requested to end administration of evolocumab and withdrew consent from the study on 03 December one year after*.

The investigator reported that there was no reasonable possibility that the event lumbar hernia was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study Evolocumab SC Q4W 350 mg Year 1 treatment: Standard of care Year 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Rib fracture, Hypothermia

Subject [redacted] was a 42-year-old white man participating in Study 20110110 who experienced a rib fracture (reported term: costa fracture) and hypothermia (reported term: hypotermia). His medical history included hypercholesterolemia and arthralgia. Concomitant medications included methylprednisolone, phenoxymethylpenicillin, tramadol, paracetamol, ibuprofen, and acetaminophen. Previous and current treatment for hypercholesterolemia included rosuvastatin and ezetimibe.

The subject was enrolled into the parent study and received the first dose of evolocumab on 19 December two years ago* and last dose on 14 February one year ago*. The subject was assigned standard of care on 14 March one year ago* and received the first dose of evolocumab with standard of care on 10 April [redacted].

Approximately 9 months after receiving the first dose of open-label evolocumab, on 19 January one year after*, the subject experienced a fall while snowboarding, hit his face and was immobilized in the snow, in -14° C weather, for more than 2 hours while waiting for rescue personnel. When the rescue team transported the subject to the ambulance, he was hypothermic. The subject was admitted to the hospital on the same day. Computed tomography (CT) scan revealed no bleeds and no vital organ damage and radiography scan revealed fractures of 4 costal ribs. Treatment medications after the onset of the event included paracetamol, ibuprofen, and nalbuphine. The outcome of the event hypothermia was reported as resolved on 19 January one year after* and the outcome of the event rib fracture was recovering. The subject was discharged from the hospital the following day; he remained in the study and treatment with evolocumab was continued. The events were not considered related to evolocumab.

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].

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The investigator stated that there was no reasonable possibility that the events of rib fracture, and hypothermia were related to the investigational product.