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: Concussion, Hemorrhoids

Subject [redacted] was a 70-year-old white woman participating in Study 20110110 who had a concussion (reported term: observation for concussion) and hemorrhoids (reported term: worsening of hemorrhoids). Her medical history included hypercholesterolemia and hypokalemia. Concomitant medications included combination of bendroflumethiazide and potassium chloride, acetylsalicylic acid, lansoprazole, magnesium oxide, atorvastatin, atenolol, and unspecified diuretics. Previous treatment for hypercholesterolemia included atorvastatin.

The subject was in the parent study from 25 November one year ago* to 20 February [redacted] and received the last dose of evolocumab in the parent study on 23 January same year*. She was enrolled into Study 20110110 on 20 February same year* and received her first dose of evolocumab in Study 20110110 on that date.

Approximately 5-1/2 months later, on 19 August same year*, the subject fell from a bike and developed amnesia and pain in the neck. The subject was hospitalized on the same day. On 20 August same year*, a computerized tomogram of vertebral column was normal. Computerized tomography of head and cervical column disproved suspicion of bleeding or fracture. Additionally, during hospitalization, hypokalemia was diagnosed with a potassium level of 2.2 mmol/L. The investigator reported that her diuretic treatment had probably exacerbated the pre-existing hypokalemia. Treatment medication included potassium chloride. The investigator confirmed concussion as the final diagnosis. The event of concussion was reported as resolved on 21 August same year* and the subject was discharged. Concussion with amnesia due to the bike accident was confirmed per the discharge letter. Laboratory data disclosed low serum potassium, which was normalized.

On 03 February two years after*, the subject experienced worsening of hemorrhoids. The subject was hospitalized and received magnesium and lactulose. The event of hemorrhoids was reported as resolved on 07 February two years after*.

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As of the data cutoff date of [redacted], the subject was continuing in the study. She had received her last dose of evolocumab on 15 May same year*, following which evolocumab was discontinued at the subject's request.

The investigator reported that there was no reasonable possibility that the events of concussion and worsening of hemorrhoids were 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 280 mg Year 1 treatment: Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Osteoarthritis

Subject [redacted] was a 68-year-old white woman participating in Study 20110110 who developed osteoarthritis (reported term: worsening of osteoarthritis right knee). The subject's medical history included hypercholesterolemia and osteoarthritis. Concomitant medications while on study included rosuvastatin and combination of chondroitin sulfate, glucosamine sulfate, and methylsulfonylmethane. Previous treatment for hypercholesterolemia was not reported.

The subject was in the parent study from 24 November two years ago* to 16 February one year ago* and received the last dose of evolocumab in the parent study on 18 January one year ago*. After completing the first year of Study 20110110, in which she received standard of care treatment, the subject received the first dose of evolocumab on 13 March [redacted].

Approximately 4 months after the first dose of evolocumab, on 09 August same year*, the subject was hospitalized due to worsening of osteoarthritis in the right knee. The subject underwent a total right knee replacement. Treatment medication included paracetamol, ibuprofen, gabapentin, tramadol, oxycodone, zoplicone, rivaroxaban, and pantoprazole. The event of osteoarthritis resolved on 11 August same year*, and the subject was discharged from the hospital.

The subject's last dose of evolocumab prior to the event was on 31 July 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 the data cutoff date on [redacted].

The investigator reported that there was not a reasonable possibility that the event of osteoarthritis was related to the evolocumab. There was no co-suspect medication.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q2W 140 mg Year 1 treatment: Standard of care (SOC) Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SOC
Report: Angina pectoris

Subject [redacted] was a 67-year-old white man participating in Study 20110110 who developed angina pectoris (reported term: angina pectoris 1. time). The subject's medical history included hypercholesterolemia, arthralgia, back pain, hypertension, hypoacusis, inguinal hernia, inguinal hernia repair, orthostatic hypotension, and pain in extremity. The subject was an ex-smoker and had a family history of cardiac disorder. Concomitant medications included amlodipine, combination of bendroflumethiazide and potassium, and Vitamin E. Previous and current treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 20 October one year ago* to 26 January same year* and received the last dose of evolocumab in the parent study on 29 December one year ago*. The subject was randomized to Study 20110110 on 26 January [redacted] and assigned standard of care treatment. Approximately 10 months later, on 03 December same year*, the subject had a sudden onset of chest pain radiating to left arm and was hospitalized. The subject did not have similar symptoms before. Pain remained for approximately 10 to 15 minutes after glyceryl trinitrate was given to the subject in the ambulance. All relevant blood tests and coronary markers were normal; troponin level was not elevated. Electrocardiogram showed no signs of ischemia. Radiography of thoracic region and echocardiography were normal. Investigations showed no signs of myocardial infarction. The subject had suspected angina chest pain. Etiological and predisposing risk factors included age and sex of the subject, former cigarette user, hypertension, hypercholesterolemia, and family history of cardiac disease. A cardiac computerized tomography scan showed right dominant coronary artery system with significant (40%) proximal right coronary artery stenosis, the main branch had no changes. The left anterior descending artery had diffuse, pronounced changes, just after the second diagonal, estimated 70% stenosis, also pronounced changes distally. The circumflex artery had only mild diffuse changes. Small patent foramen ovale was noted; otherwise heart structure was normal. The subject was feeling well and the event of angina pectoris was reported as resolved on 04 December same year*. The subject was discharged from the hospital on the same day with the recommendation to use glyceryl trinitrate as needed.

*新薬承認情報提供時に置き換え

Standard of care simvastatin was continued. The subject withdrew consent and discontinued the study on 31 January one year after*.

The investigator reported that there was not a reasonable possibility that the event was related to any study procedure or study activity.

*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: Standard of care (SOC) Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SOC
Report: Lung neoplasm, Pulmonary embolism

Subject [redacted] was a 71-year-old white woman participating in Study 20110110 who developed a lung neoplasm (reported term: lung tumor) and pulmonary embolism. The subject's medical history included hypercholesterolemia. She was an ex-smoker (20 pack years). The subject did not have a family history of cancer or occupational exposure. Concomitant medications included acetylsalicylic acid, atenolol, hydroxyzine, phenoxymethylpenicillin, potassium, Vitamin E, combination of acetylsalicylic acid and magnesium oxide, combination of enalapril maleate and hydrochlorothiazide, and combination of bendroflumethiazide and potassium chloride. Previous treatment for hypercholesterolemia included simvastatin. Previous and current treatment for hypercholesterolemia included atorvastatin.

The subject was in the parent study from 01 November one year ago* to 06 February same year* and received the last dose of placebo in the parent study on 10 January same year*. The subject was randomized to Study 20110110 on 06 February [redacted] and assigned standard of care treatment. The subject had intermittent chest pain since 17 October same year* and was diagnosed with pleuritis. She was treated with phenoxymethylpenicillin and felt better. In November, she experienced more dyspnea. Approximately 9 months after randomization, on 03 November same year*, the subject was hospitalized with functional dyspnea. A high definition computerized tomogram with contrast revealed small pulmonary emboli in the segment artery, right side; in addition, a large centrally located lung tumor was seen on the right side. The subject was discharged from the hospital on 09 November same year*. On 14 November same year*, bronchoscopy revealed adenocarcinoma T4N3M1b. On the same date, the histopathological results taken during the endobronchial ultrasonography from stations 4R, 7 and 10 revealed metastases of adenocarcinoma in all preparations. The immune profile supported the diagnosis since the tumour cells were positive for thyroid transcription factor 1 (TTF1) and cytokeratin 7 (CK7). On the same date, the positron emission tomography scan showed lymph nodes positive and significantly increased fludeoxyglucose (FDG) uptake in the central infiltrate near the hilus. Significantly enlarged lymph nodes with FDG uptake were seen at station 4R which was right up against the tumour;

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also stations 7, 2R, 2L, and 1L and in a single periclavicular lymph node on the right side. Additionally significant increased FDG uptake was seen in the left adrenal which was enlarged. The conclusion was that the adenocarcinoma was stage T4N3M1b which was considered inoparable. The subject was diagnosed with pulmonary embolism and lung cancer (adenocarcinoma). Smoking was considered as a risk factor. Treatment included oxazepam, paracetamol, tinzaparin, and acetylsalicylic acid. The subject was started on dalteparin sodium for pulmonary embolism. The subject continued with antithrombotic therapy. The subject started chemotherapy for her lung neoplasm and received intravenous chemotherapy on 29 November same year* and on 21 December same year* and unknown chemotherapy tablets on 28 December same year*. On February one year after*, a lung scan was performed and showed no change in the small embolism or in the lung tumor. The subject continued on tinzaparin. The events of lung neoplasm and pulmonary embolism were reported as not resolved.

The subject discontinued the study due to the event of lung neoplasm with her last visit on 11 February one year after*.

The investigator reported that there was no reasonable possibility that the events lung neoplasm and pulmonary embolism were related to any study activity. The investigator considered that pulmonary embolism was secondary to the subject's lung cancer.

*新薬承認情報提供時に置き換え

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: Presyncope

Subject [redacted] was a 65-year-old white woman participating in Study 20110110 who developed presyncope (reported term: near syncope). The subject's medical history included hypercholesterolemia, hysterectomy, rectocele, osteoarthritis, vulvovaginal dryness, nasopharyngitis, and arthralgia. Concomitant medications included estradiol and paracetamol. Previous and current treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 14 November one year ago* to 20 February same year* and received the last dose of evolocumab in the parent study on 20 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 20 February [redacted].

Approximately 6 months later, on 26 September same year*, the subject experienced a transient attack of chest heaviness, dizziness, and a generalized discomfort while she was a passenger in a car. Upon admission to the hospital, the subject was stable; her blood pressure was 151/59 mmHg, temperature 37.9°C, pulse rate 56 beats per minute, respiration rate 20 breaths per minute, and oxygen saturation 95%. On physical examination, no hearing or vision disturbances were seen; no chest pain or radiating pain in any area; no nausea or vomiting, no heartburn; normal strength in all extremities, and normal respiration sounds. An electrocardiogram performed on 26 September same year* showed sinus rhythm without signs of ischemia or signs of acute myocardial infarct. Blood tests performed on 26 September same year* showed normal triiodothyronine and thyroxine levels and elevated thyroid-stimulating (TSH) hormone level of 6.31 mIU/L. TSH level was 3.96 mIU/L at baseline on 7 November one year ago*. The subject was treated with oxygen. The event of presyncope was reported as resolved on 27 September same year* and the subject was discharged from the hospital on the same date.

The subject's last dose of evolocumab prior to the event was on 03 September same year*. Evolocumab was continued. The subject received the last dose of evolocumab on 21 January one year after* and then discontinued from the study on 18 February one year after* due to withdrawal of full consent.

*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 presyncope was related to evolocumab.

Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q2W 70 mg Year 1 treatment: Standard of care
Report: Breast cancer

Subject [redacted] was a 64-year-old white woman participating in Study 20110110, who wad diagnosed with breast cancer (reported term: cancer right breast). The subject's medical history included hypercholesterolemia and hypertension. Concomitant medications included losartan, Vitamin E, and combination of bendroflumethiazide and potassium chloride. Previous and ongoing treatment for hypercholesterolemia included rosuvastatin.

The subject was in the parent study from 21 November one year ago* to 27 February same year* and received the last dose of evolocumab in the parent study on 30 January same year*. The subject was randomized to Study 20110110 on 27 February [redacted] and assigned standard of care treatment. Approximately 7 months after randomization, on 24 September same year*, the subject had a mammography that revealed a small tumor in the right breast. She had no symptoms and the tumor was not palpable. The subject was hospitalized on 03 October same year* and underwent a breast saving surgery. Nothing was found in the lymph nodes. On 17 October same year*, histology showed an invasive ductal carcinoma of 7 mm, free resection margin minimum 9 mm, receptor positive, normal human epidermal growth factor receptor 2 (HER2) expression. Reportedly, sentinel nodes (SN) 1 had micro-metastasis and SN2 was without metastases. Good cicatrization with no reaction was seen. The subject was referred to an oncologic specialist. Treatment included paracetamol. The event of breast cancer was reported to have resolved on 03 October same year* and the subject was discharged from the hospital on 04 October same year*.

The subject withdrew consent and discontinued the study on 25 February one year after*. The investigator reported that there was not a reasonable possibility that the event of breast cancer 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 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: Angina pectoris

Subject [redacted] was a 67-year-old white man participating in Study 20110110 who developed angina pectoris. The subject's medical history included hypercholesterolemia, ischemic heart disease and hypertension.

Concomitant medications included acetylsalicylic acid, trimetazidine, perindopril, alprazolam, glyceryl trinatrate, tetanus vaccine, heparin, tamsulosin, bisoprolol and clopidogrel.

Previous and current treatment for hypercholesterolemia was atorvastatin.

The subject was in the parent study from 18 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 9 months later, on 11 November one year after*, the subject developed angina pectoris and was hospitalized the following day. Admitting laboratory results were not considered abnormal and included creatine phosphokinase (CK) of 202 U/L, creatine phosphokinase MB (CK-MB) of 17 U/L and troponin I of 0.005 ng/ml. A coronarography performed on the same day revealed no significant coronary stenosis and an echocardiogram revealed no abnormalities. Treatment during hospitalization included clopidogrel, acetylsalicylic acid, trimetazidine, atorvastatin, bisoprolol, nitroglycerin and molsidomine. Following medical treatment, the subject did not complain of further chest pain. The outcome of the event was reported as resolved on 13 November one year after* and the subject was discharged from the hospital on the same date.

The last dose of evolocumab prior to the event was on 16 October one year after* and open label evolocumab was continued.

As of the data cutoff date of [redacted], the subject was continuing dosing, with the last dose before the cutoff on [redacted].

*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: Evolocumab SC Q4W 420 mg + Standard of care
Report: Inguinal hernia

Subject [redacted] was a 60-year-old white man participating in Study 20110110 who developed an inguinal hernia (reported term: both sided inguinal hernia). The subject's medical history included hypercholesterolemia, type 2 diabetes, asthma, atrial fibrillation/flutter, cardiac device/pacemaker, congestive heart failure, gastroesophageal reflux disease (GERD), hypertension, myocardial infarction, sleep apnea, and vertebrobasilar insufficiency. Concomitant medications included aceclofenac, gliclazide, clopidogrel, bisoprolol, hydrochlorothiazide, furosemide, potassium, trimetazidine, loratadine, salbutamol, metformin, insulin glargine, amlodipine, losartan, loratadine, carvedilol, acyclovir, rilmenidine, and enoxaparin sodium.

Previous and current treatment for hypercholesterolemia was atorvastatin.

The subject was in the parent study from 25 November two years ago* to 17 February one year ago* and received the last dose of evolocumab in the parent study on 20 January one year ago*. The subject was assigned to standard of care on 17 February one year ago* for the first year of Study 20110110, and received the first dose of evolocumab for the second year on 06 March [redacted].

A bilateral inguinal hernia was diagnosed on 20 November same year*. On 26 November same year* the subject was hospitalized, and elective herniorrhaphy was performed the same day. The inguinal hernia was not considered related to the study medication. The end date of the adverse event was 27 March one year after*, and the subject was discharged on that day without complications.

The last treatment prior to the event was on 06 March same year*. Evolocumab was discontinued on 22 April same year* due to the adverse event of inguinal hernia.

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*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Placebo SC Q4W Year 1 treatment: Standard of care Year 2-5 treatment: Evolocumab SC Q2W 420 mg + Standard of care
Report: Non-cardiac chest pain, vertebrobasilar insufficiency

Subject [redacted] was a 56-year-old white woman participating in Study 20110110 who developed non-cardiac chest pain (reported term: chest pain of extracardiac origin/non-cardiac/) and vertebrobasilar insufficiency. Her medical history included hypercholesterolemia, hyperuricemia, aortic valve stenosis, aortic valve incompetence, hypertension, gastroesophageal reflux disease, appendectomy, cholecystectomy, ovarian cystectomy, and limb operation (surgery for bilateral carpal tunnel syndrome). Concomitant medications while on study included irbesartan, nebivolol, rabeprazole, rilmenidine, bisoprolol, allopurinol, levofloxacin, azithromycin, clopidogrel, piracetam, salbutamol, pyridoxine, and combination of diastase, dimeticone, lipase, and protease. Previous and current treatment for hypercholesterolemia included rosuvastatin.

The subject was in the parent study from 02 December one year ago* to 24 February [redacted] and received the last dose of placebo in the parent study on 27 January same year*. The subject was assigned to standard of care treatment in year 1 of Study 20110110 from 24 February same year* to 28 March one year after*. The first dose of open label evolocumab was administered on 12 April one year after*.

On 01 March same year*, the subject developed chest pain, mainly after exercise. On 16 April same year*, the subject was admitted for elective coronarography with angina complaints. The symptoms were relieved by nitrate medication. Laboratory tests showed no significant abnormalities except for high blood lipid values. During treadmill exercise electrocardiogram, no repolarization abnormalities were noted. Holter monitoring revealed no significant abnormalities. The following day, on 17 April same year*, the coronarography revealed right dominant, intact coronary circulation and no stenosis was found. During her hospitalization, the subject was normotensive and free of angina symptoms. On 18 April same year*, the subject was discharged in satisfactory general condition. The event non-cardiac chest pain was reported as resolved on 31 March same year*.

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The investigator reported that there was no reasonable possibility that the event of non-cardiac chest pain was related to evolocumab.

On 23 April one year after*, the subject experienced vertigo, headache, disturbed spatial perception, lumbar and occipital pain and was diagnosed with vertebrobasilar insufficiency. The symptoms did not ameliorate with oral clopidogrel or piracetam, so she was subsequently hospitalized on 28 June one year after* and received piracetam, pyridoxine, magnesium, and salbutamol. The event was reported as resolved on 08 July one year after* and the subject was discharged from the hospital on the same day.

The subject was hospitalized again for vertebrobasilar insufficiency on 5 March two years after*. Piracetam and magnesium sulfate were administered from 5 March until 12 March two years after*. The event was not considered related to evolocumab and the subject continued in the study.

The last dose of evolocumab prior to the event was on 12 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 documented on [redacted]. The investigator reported that there was no reasonable possibility that the event vertebrobasilar insufficiency was related to evolocumab, and the history of hypercholesterolemia was reported as a predisposing factor for the event.

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Subject No: [redacted]
Treatment: Parent study: 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: Pain

Subject [redacted] was a 62-year-old white woman participating in Study 20110110 who developed pain (reported term: waist pain). The medical history included hypercholesterolemia, coronary artery disease osteoarthritis, spondylosis, scoliosis, intervertebral disc disorder, sciatica, obesity, hypertension, cerebral cyst, depression, and dizziness. Current treatment for hypercholesterolemia was atorvastatin.

The subject was in the parent study from 25 November one year ago* to 28 February same year* and received the last dose of evolocumab in the parent study on 06 February same year*. The subject received the first dose of evolocumab in Study 20110110 on 28 February [redacted].

On 17 March two years after*, the subject developed worsened waist pain. On 28 March two years after*, imaging of the lumbar spine showed small osseous deposits present at the edges of the vertebrae. The upper endplate of the 12th thoracic vertebra was compressed. The intervertebral spaces showed narrowing of varying degree. On 14 April two years after*, the subject was hospitalized for waist pain as she was showing no improvement with outpatient treatment and for a treatment of lower back pain radiating into the right lower limb. Treatment medications reported after the onset of the event included physiotherapy, massage, para vertebral steroid, dexamethasone, temazepam and lidocaine. The outcome of the event waist pain was reported as resolving and on 23 April two years after*, the subject was discharged from hospital.

The subject's last dose of investigational product prior to the event was not known. Open-label investigational product 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 not a reasonable possibility that the event was related to evolocumab or to the study procedures.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: 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: Angina pectoris

Subject [redacted] was a 77-year-old white woman participating in Study 20110110 who developed angina pectoris (reported term: stable angina). The subject's medical history included hypercholesterolemia, type V hyperlipidemia, essential hypertension, angina pectoris since 05 January two years ago*, myocardial ischemia, acute myocardial infarction in nine years ago*, atrial and ventricular premature depolarization, carotid artery stenosis (60% to 70%), transient cerebral ischemic attack in sixteen years ago* and cerebral infarction in two years ago*, gastroesophageal reflux disease, gastritis, asthma, chronic obstructive pulmonary disease, depression, impaired glucose tolerance, spinal osteoarthritis, osteoarthritis, megaloureter, mild chronic renal failure, and drug hypersensitivity (to angiotensin converting enzyme inhibitors causing cough). Concomitant medications included acetylsalicylic acid, metoprolol, nitroglycerin, pantoprazole, furosemide, valsartan, theophylline, mirtazapine, tiotropium, hydrochlorothiazide, alprazolam, and combination of aluminium, magnesium, and simethicone. Previous and ongoing treatment for hypercholesterolemia included simvastatin and ezetimibe.

The subject was in the parent study from 25 November one year ago* to 28 February same year* and received the last dose of evolocumab in the parent study on 06 February same year*. The subject received the first dose of evolocumab in Study 20110110 on 28 February [redacted].

Approximately 4 months later, on 19 June same year*, the subject developed angina pectoris and was admitted for further observation and monitoring. An electrocardiogram (ECG) at arrival showed 68 beats per minute (bpm), sinus rhythm, left R axis, in I, II aVL with mild ST-depression. Blood pressure was within normal range. A repeat ECG showed no changes from earlier and an acute myocardial event was excluded. Laboratory data included troponin T of < 0.03 ng/mL (normal range), sodium of 137 mM/L, potassium of 3.92 mM/L, chloride of 98 mM/L, glucose of 5.20 mM/L, glomerular filtration rate of 39 mL/min/L, blood urea nitrogen of 6.20 mM/L. On 20 June same year*, the subject received a scheduled evolocumab injection. On the same day, a repeat ECG showed no changes. Anteroposterior chest radiograph showed no abnormal lesion in the lungs and the heart was normal in size and location. The aorta had calcified walls (aortic sclerosis). Treatment medications included nitroglycerin spray. The event of angina pectoris

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was reported to have resolved on 22 June same year* and the subject was discharged from the hospital on the same date without chest pain.

The subject's last dose of evolocumab prior to the event was on 22 May 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 cutoff date on [redacted].

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

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent Study: 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: Arthralgia

Subject [redacted] was a 53-year-old white woman participating in Study 20110110 who developed arthralgia. The subject's medical history included hypercholesterolemia, hyperlipidemia, impaired glucose tolerance, gastroesophageal reflux disease, osteoporosis, osteoarthritis, intervertebral disc disorder, hypertension, myocardial infarction, angina pectoris, coronary artery disease, percutaneous coronary intervention, scoliosis, and tabagism. Concomitant medications included clopidogrel, trimetazidine, pantoprazole, alprazolam, and betaxolol. Previous and current treatment for hypercholesterolemia included atorvastatin.

The subject was in the parent study from 25 November one year ago* to 15 February same year* and received the last dose of placebo in the parent study on 20 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 15 February [redacted].

Approximately 7 months and 2 weeks later, on 01 October same year*, the subject was hospitalized due to worsened backache and was diagnosed with arthralgia. Treatment for the event included Ritex solution (acetic acid medication for arthralgia), massage, gymnastics, and physiotherapy. The subject's joint pain was reported to be somewhat better. No diagnostic or investigational findings were reported at the time of event. The event of arthralgia was reported as resolved on 12 October same year* and the subject was discharged from the hospital on the same date.

The subject's last dose of evolocumab prior to the event was on 26 September same year*. 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 not a reasonable possibility that the event of arthralgia 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 420 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: Abdominal pain, Upper abdominal pain, Acute cholecystitis, Procedural nausea, Procedural vomiting, Urticaria

Subject [redacted] was a 59-year-old white woman participating in Study 20110110 who developed abdominal pain (reported term: worsening abdominal pain), upper abdominal pain (reported term: severe pain right upper quadrant), acute cholecystitis, procedural nausea (reported term: nausea post op recovery at home), procedural vomiting (reported term: vomiting-post op recovery at home), and urticaria (reported term: hives). The subject's medical history included hypercholesterolemia, cardiomegaly, cardiomyopathy, hyperlipidemia, hypertension, defibrillator, congestive heart failure, coronary artery disease with coronary artery stenting, peripheral vascular disease, Raynaud's syndrome, Vitamin D deficiency, appendectomy, stent placement in the left leg, pain, allergy (to penicillin, tetanus immunoglobulin, rocuronium bromide, and metronidazole [hives]), and tobacco use. Concomitant medications included Vitamin E, paracetamol, acetylsalicylic acid, furosemide, lisinopril with hydrochlorothiazide, oxycodone, metoprolol, naproxen, Vitamin D, and potassium chloride. Previous treatment for hypercholesterolemia was not provided; current treatment included simvastatin.

The subject was in the parent study from 22 November one year ago* to 17 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 17 February [redacted]. Approximately 1 year and 7 months later, on 26 September one year after* the subject was hospitalized with worsening abdominal pain described as like a tight cramping, somewhat dull in the right upper quadrant, worst in the upper epigastrium. The pain did not radiate and there was no chest pain or shortness of breath. There was a burning sensation that worsened after eating. The subject had a positive Murphy's sign on examination. Upon admission the subject's vital signs revealed blood pressure of 167/81 mmHg and oral temperature of 98 degrees Fahrenheit. Laboratory tests included glomerular filtration rate of 53 mL/min, peripheral pulse rate of 72/minute, neutrophil count of 9.91 x 10^9/L, respiratory rate of 18/minute and white blood cell (WBC) count of 13 x 10^9/L A computerized tomography of the abdomen showed a small 1 mm stone in the gallbladder neck.

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There was a small area of low attenuation in the left hepatic lobe adjacent to the falciform ligament measuring 1.5 x 1.0 cm that might represent an area of differential perfusion or focal fatty infiltration.

On 26 September one year after* the subject developed acute cholecystitis. On the same day, the subject was treated with metronidazole at a dose of 500 mg intravenously every 8 hours. On 27 September one year after*, the subject underwent a laparoscopic cholecystectomy. She tolerated the procedure well and left the operating room in a satisfactory condition. Additional treatment included magnesium hydroxide and levofloxacin. The events of abdominal pain and acute cholecystitis were reported to have resolved on 27 September one year after*.

On 28 September one year after*, the subject's hospitalization was extended due to hives that presented after metronidazole treatment and metronidazole was discontinued on the same date. Treatment included diphenhydramine.

On 29 September one year after* there was no pain in the incisional area, there was no nausea, and urticaria was still noted with generalized itchiness. The outcome of the event of urticaria was reported as resolved on 29 September one year after* and the subject was discharged from the hospital on the same date.

On 30 September one year after* the gall bladder showed a cyst measuring 0.6 x 0.6 cm located in the fundus. The cystic duct was also obscured by a calculus. There were three black calculi measured 0.3 cm in greatest dimension. There was a moderate amount of green brown viscous bile.

A few days later, on 02 October one year after*, the subject developed worsening abdominal pain with vomiting and nausea and she was re-hospitalized on the next day, 03 October one year after*. The subject's abdomen was soft, tender with normal bowel sounds. There was a positive Murphy's sign. The subject was tachycardic, but otherwise hemodynamically stable. The subject was unable to eat, because of persistent vomiting. There was no diarrhea or constipation and pain was 8/10. Unspecified intravenous fluids and electrolyte replacement with potassium chloride, magnesium sulfate and sodium phosphate, as well as morphine for pain, and ondansetron were administered. The subject's pain was initially 6/10 and reduced to 2/10 within 1 hour. Additional treatment included magnesium sulfate, macrogol, and aluminium hydroxide/magnesium hydroxide. The subject's abdomen was soft with bowel sounds and there were small loose movements. The subject was also treated with paracetamol and oxycodone hydrochloride,

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oxycodone terephthalate with paracetamol for pain. The subject's pain was 9/10 and it reduced to 5/10 after she received morphine once.

On 03 October one year after*, vital signs revealed blood pressure of 143/81 mmHg and peripheral pulse rate of 103/minute. An ultrasound of the abdomen showed hypoechoic area in the left lobe of the liver, obscuration of the head and tail of the pancreas, and a complex area of fluid collection in the gallbladder fosa.

Additional treatment included enoxaparin. The events of upper abdominal pain, procedural nausea, and procedural vomiting were reported to have resolved on 04 October one year after* and the subject was discharged from the hospital on the same date. At the time of discharge the subject was afebrile with vital signs within normal limits, ambulating, and tolerating intake.

The subject's last dose of evolocumab prior to the events was on 30 August one year after*. Evolocumab was temporarily withheld until the subject recovered; dosing was re-started on 22 October 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 date on [redacted]. The investigator reported that there was not a reasonable possibility that the events of abdominal pain, upper abdominal pain, acute cholecystitis, procedural nausea, procedural vomiting, and urticaria were related to evolocumab.

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Subject No: [redacted]
Treatment: Parent Study: Evolocumab SC Q2W 140 mg Year 1 treatment: Standard of care (SOC) Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SOC
Report: Thyroid neoplasm

Subject [redacted] was a 65-year-old white woman participating in Study 20110110 who was diagnosed with a thyroid neoplasm (reported term: thyroid nodule). The subject's medical history included hypercholesterolemia. Concomitant medications included alendronate sodium, calcium, clonazepam, diclofenac, famotidine, magnesium, olanzapine, oxybutinin, Vitamin E, and venlafaxine. Previous and ongoing treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 24 October one year ago* to 31 January same year* and received the last dose of evolocumab in the parent study on 03 January same year*. The subject was randomized to Study 20110110 on 31 January [redacted] and assigned standard of care treatment.

Approximately 1 year and 1 month later, on 21 February one year after*, the subject was diagnosed with a thyroid neoplasm. Subsequently, on 08 May one year after*, the subject was hospitalized and underwent a thyroidectomy. After surgery, the subject developed hypothyroidism and was started on levothyroxine and calcium was continued. No relevant laboratory results were provided. The event of thyroid neoplasm was reported as resolved on 08 May one year after* and the subject was discharged from the hospital on 09 May one year after*.

After completing the first year of Study 20110110, the subject began year 2. The subject received the first dose of evolocumab in Study 20110110 on 27 February 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 date on [redacted].

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

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Subject No: [redacted]
Treatment: Parent study: Study 20101155, Evolocumab SC Q2W 105 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: Benign prostatic hyperplasia

Subject [redacted] was a 57-year-old white man participating in Study 20110110 who was diagnosed with benign prostatic hyperplasia (reported term: benign prostatic hypertrophy). The subject's medical history included hypercholesterolemia, hyperlipidemia, myocardial infarction, transient ischemic attack, hypertension, rhinitis, drug hypersensitivity (to carbamazepine), hearing loss, acute renal failure, osteoarthritis, knee arthroplasty, gout, back pain, depression, and eczema. Concomitant medications included Vitamin E, acetylsalicylic acid, escitalopram, metoprolol, paracetamol, ibuprofen, meloxicam, and allopurinol. Previous treatment for hypercholesterolemia included nicotinic acid; current treatment included atorvastatin and ezetimibe.

The subject was in the parent study from 20 July same year* to 28 October same year* and received the last dose of evolocumab in the parent study on 30 September same year*. The subject received the first dose of evolocumab in Study 20110110 on 28 October [redacted]. Approximately 3 months later, on 21 January one year after*, the subject was diagnosed with benign prostatic hypertrophy. On 23 March one year after*, the subject was hospitalized for an elective transurethral resection of the prostate. Additional treatment included silodosin and ciprofloxacin. The event of benign prostatic hyperplasia was reported to have resolved on 23 March one year after* and the subject was discharged from the hospital on 24 March one year after*.

The subject's last dose of evolocumab prior to the event of benign prostatic hyperplasia was on 20 January 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 cutoff date on [redacted]. The investigator reported that there was no reasonable possibility that the event of benign prostatic hyperplasia was related to evolocumab.

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Subject No: [redacted]
Treatments: 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: Rib fracture, Pneumonia

Subject [redacted] was a 61-year-old white man participating in Study 20110110 who had a rib fracture (reported term: multiple rib fractures S/P trauma) and pneumonia (reported term: healthcare associated pneumonia). The subject's medical history included hypercholesterolemia, dyslipidemia, coronary artery disease, hypertension, osteoarthritis, myocardial infarction, sleep apnea syndrome, tonsillectomy, appendectomy, pain, carpal tunnel decompression, back pain, angioplasty, disability, and obesity. Concomitant medications included Vitamin E, acetylsalicylic acid, glyceryl trinitrate, paracetamol, tramadol, ergocalciferol, gabapentin, metoprolol, chlorphenamine/paracetamol/phenylephrine, and baclofen. Previous treatment for hypercholesterolemia included simvastatin, ezetimibe and fish oil; current treatment included simvastatin and fish oil.

The subject was in the parent study from 21 July same year* to 13 October same year* and received the last dose of evolocumab in the parent study on 15 September same year*. The subject received the first dose of evolocumab in Study 20110110 on 13 October [redacted]. Approximately 1 year and 7 months later, on 16 May two years after*, the subject was hospitalized due to an accident while driving an all-terrain vehicle. On admission blood pressure was 122/66 mmHg, pulse 64 beats/min, respiratory rate 16 breaths/min and oxygen saturation 98% on room air, and Glasgow coma scale was 15. The chest radiograph showed right rib fractures 1 - 7 and right scapula fracture; left foot radiograph showed possible cuneiform fracture of the left second toe with no evidence of ankle fracture. Computerized tomography (CT) of chest showed left 1st rib fracture, right 1st through 7th rib fractures and a body fracture of the scapula on the right; no evidence of pneumothorax; mediastinum was normal; no sternal fracture or other injuries were noted. Treatment included ondansetron, fentanyl, bacitracin, pantoprazole, methocarbamol, lidocaine, ibuprofen, enoxaparin, docusate with senna, docusate, hydrocodone with acetaminophen, bisacodyl, oxycodone and lactulose. The subject was discharged from the hospital on 20 May two years after*. On follow-up, the subject met all rehabilitation goals including ambulating distance, up and down stairs and was able to participate in activities of daily living. Treatment

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included hydrocodone with acetaminophen, tramadol and docusate sodium. The event of multiple rib fractures was reported as resolved on 20 May two years after*.

On 06 June two years after*, the subject developed a cough, fever, flu sensation, yellow sputum, and chills. On 10 June two years after*, chest radiograph revealed right lateral pleural thickening and small retrocardiac infiltrate. The same day, the subject was hospitalized and diagnosed with pneumonia. Treatment included ceftriaxone. Laboratory results showed chloride 101 meq/L, creatinine 1.2 mg/dL, blood sugar 116 mg/dL, potassium 3.8 mg/dL, sodium 135 meq/L, blood urea nitrogen (BUN) 19 mg/dL, carbon dioxide (CO_2) 21 meq/L, hematocrit 37.6%, hemoglobin 12.7g/dL, lymphocytes 5%, monocytes 3%, neutrophils 91%, oxygen saturation on room air 92-98%, platelets 234 X 10^3/µL, red blood cells (RBC) 4.6 X 10^{12}/L, white blood cells (WBC) 23.4 X 10^3/µL. Baseline WBC was 6.24 x 10^3/µ/L on 11 July same year*. On an unknown date, antibiotics were changed to piperacillin/tazobactam, levofloxacin, and vancomycin. Chest radiograph revealed left lower lobe infiltrate. Microbiology test for methicillin-resistant *Staphylococcus aureus* was negative. Additional treatment for the event included oxycodone hydrochloride/oxycodone terephthalate/paracetamol; diphenhydramine/paracetamol; hydrocodone/paracetamol; enoxaparin, *Lactobacillus acidophilus*, lidocaine, diphenhydramine, oxycodone, sodium chloride, lorazepam, and ketorolac. The event healthcare-related pneumonia was reported as resolved on 13 June two years after*.

The subject's last dose of evolocumab prior to the event of rib fracture was on 24 April two years after*, and prior to the event of pneumonia was on 29 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 events of rib fracture and pneumonia were related to evolocumab.

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Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q2W 140 mg Year 1 treatment: Standard of care (SOC) Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SOC
Report: Bronchitis

Subject [redacted] was a 59-year-old white man participating in Study 20110110 who developed bronchitis. His medical history included hypercholesterolemia, chronic obstructive pulmonary disease, depression, coronary artery disease, hypertension, type 2 diabetes mellitus, cerebrovascular accident, dyspepsia, herpes zoster, coronary artery bypass graft, left bundle branch block, congestive cardiac failure, hyperlipidemia, chronic kidney disease, obesity, benign prostatic hyperplasia, cerebellar stroke, myocardial infarction, decreased ejection fraction, ischemic cardiomyopathy, peripheral neuropathy, hypokalemia, tobacco and alcohol use, and family history of arterial hypertension, atherosclerotic coronary artery disease, nasopharyngitis, and myocardial infarction. Concomitant medications included combination of aluminum hydroxide and magnesium, potassium, mometasone, combination of acetaminophen and hydrocodone, clonidine, amlodipine, fluticasone, escitalopram, bupropion, insulin detemir, insulin aspart, hydralazine, clopidogrel, lisinopril, famotidine, cefalexin, combination of hydrocodone and acetaminophen, carvedilol, isosorbide, acetylsalicylic acid, and Vitamin E. Previous and ongoing treatment for hypercholesterolemia included atorvastatin.

The subject was in the parent Study 20101155 from 14 September two years ago* to 19 December two years ago* and received the last dose of evolocumab on 21 November two years ago*. Subsequently, the subject was randomized to Study 20110110 on 19 December two years ago* and assigned standard of care treatment. After completing the first year of study, the subject received the first dose of evolocumab in Study 20110110 on 21 January [redacted]. Approximately 1.5 months later, on 02 March same year*, the subject presented to the emergency department with a 3-day history of increasing cough and congestion with a brief, initial sore throat, and a fever the previous day. He reported tighter breathing than usual, with coughing of non-purulent sputum. He reported vomiting that morning, and overall decreased appetite and decreased energy. He denied having any chest pain or swelling, and had not had any change in his breathing at night, or had not had any recent medication changes. Vital signs included temperature of 37.0°C, blood pressure 134/73 mm Hg, pulse rate of 76 bpm, respiratory rate 20 breaths/min, and oxygenation 92% on room air. Laboratory values revealed glucose 352 mg/dL, creatinine 1.2 mg/dL, blood

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urea nitrogen (BUN) normal at 21 mg/dL. A chest radiograph showed cardiomegaly and a small amount of fluid in the minor fissure. A posterioranterior (PA) and lateral chest radiograph revealed cardiomegaly with mild vascular engorgement. The subject was empirically treated with ceftriaxone and azithromycin. He was assessed with hypoxia, congestion, and bronchitis, and since the subject required oxygen and continued treatment, he was hospitalized. Further laboratory data revealed an elevated WBC at 19,000/µL, neutrophils 87%, hemoglobin 14.7 g/dL, hematocrit 43.3%, mean cell volume 89.3 fl, platelets 154,000/µL, chloride borderline at 100 mg/L, potassium 3.9 mEq/L and total bilirubin 2 mg/dL. The rest of the liver function tests were normal. Furosemide and potassium were initially held so the subject could become better hydrated; all other medications were continued as usual. Additional treatment included deep venous thrombosis prophylaxis with enoxaparin, intravenous furosemide, pantoprazole, albuterol, acetaminophen, ondansetron, zolpidem, and oxygen. On 03 March same year*, laboratory tests revealed WBC 16.4 thou/µL, neutrophils 83%, hemoglobin 14.8 g/dL, hematocrit 43.2%, mean cell volume 89.3 fL, platelet count 155,000/µL, blood glucose 240 mg/dL, BUN 30 mg/dL, creatinine 1.2 mg/dL, potassium 3.3 mEq/L, and chloride 98 to 99 mEq/L. The event of bronchitis was reported as resolved on 06 March same year*.

The last dose of evolocumab prior to the event was on 04 February same year*. The last dose of evolocumab prior to the data cutoff date of [redacted] was on [redacted]. The investigator stated that there was not a reasonable possibility that the event of bronchitis was related to evolocumab. As of the data cutoff date, the subject was continuing in the study.

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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: Migraine

Subject [redacted] was a 59-year-old white man participating in Study 20110110 who experienced a migraine (reported term: migraine headache). The subject's medical history included hypercholesterolemia, coronary artery disease, hypothyroidism, anxiety, peripheral arterial occlusive disease, hypertension, intermittent claudication, ophthalmic migraines (migraine with aura), and hypersensitivity. Concomitant medications included metoprolol, diltiazem, bisoprolol, acetylsalicylic acid, levothyroxine, alprazolam, cilostazol, gabapentin, amlodipine, and loratadine. Previous treatment for hypercholesterolemia included pravastatin.

The subject was in the parent study from 14 September same year* to 21 December same year* and received the last dose of evolocumab in the parent study on 21 November same year*. The subject received the first dose of evolocumab in Study 20110110 on 21 December [redacted]. Approximately 7 and half months later, on 08 August one year after*, the subject presented to the hospital complaining of headache for 1 week. The subject had mild lightheadedness and dizziness for 2 days and he also reported change in his vision and partial visual loss. Upon admission, he had some lightheadedness and dizziness, no jaw claudication, no temporal pain, and no weakness in his arms or legs. The subject's body temperature was 98°F, heart rate 58 beats per minute, respiratory rate 18 breaths per minute, blood pressure 148/96 mmHg, and oxygen saturation 99%. A computerized tomogram of the brain was stable and normal. A magnetic resonance imaging of the brain showed smooth opened nasopharyngeal mucosal space, and a mass measuring 19 x 25 x 10 x 22 mm, extending into the left lateral pharyngeal recess, most likely retention cyst benign mixed tumor and secondly, no infarct. A carotid duplex ultrasound showed moderate carotid stenosis within the right internal carotid origin; stenosis estimates appeared to be between 40% and 59% similar, but less vaso-occlusive plaque was seen within the left internal carotid origin with stenosis estimated less than or equal to 39%; common carotid artery flow demonstrated no significant turbulence or hemodynamic flow changes bilaterally; vertebral flow patterns were antegrade bilaterally. During his hospital stay, the subject was asymptomatic and did not have any other episodes of slurred speech. The event of migraine was reported as

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resolved on 10 August one year after* and the subject was discharged from the hospital on the same day with pain medication and his regular medication.

The last dose of evolocumab prior to the event and in the study was on 18 January one year after*. The subject withdrew consent and discontinued the study on 09 January two years after*. The investigator reported that there was no reasonable possibility that the event of migraine was related to evolocumab.

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Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q2W 105 mg Year 1 treatment: Standard of care
Report: Post procedural hemorrhage

Subject [redacted] was a 72-year-old white man participating in Study 20110110 who experienced post procedural hemorrhage (reported term: post operative bleed). The subject's medical history included hypercholesterolemia, flank pain, hypertension, type 2 diabetes mellitus, transurethral prostatectomy, coronary artery bypass, coronary angioplasty, arteriosclerosis coronary artery, multiple fractures, shoulder surgery, myocardial infarction, hydronephrosis, hemorrhagic anemia, urinary retention, peripheral vascular disorder, hyperlipidemia, and pulmonary embolism. Concomitant medications included acetylsalicylic acid, allopurinol, aripiprazole, ascorbic acid, cyanocobalamin, escitalopram oxalate, glipizide, metformin, multivitamins, nadolol, ramipril, sildenafil citrate, Vitamin E, and warfarin. Previous and ongoing treatment for hypercholesterolemia included atorvastatin.

The subject was in the parent study from 23 September one year ago* to 03 January same year* and received the last dose of evolocumab in the parent study on 05 December one year ago*. The subject was randomized to Study 20110110 on 03 January [redacted] and assigned standard of care treatment. On 18 June same year*, the subject was hospitalized for an elective endocystoscopy, right retrograde pyelogram, and placement of right double J ureteral stent under fluoroscopic. Examination of the abdomen revealed right flank discomfort. Physical examination was grossly within normal limits and did not reveal any acute distress. The investigator reported that the subject tolerated the procedure well and there was no blood loss and no complications. However, the subject developed a post-procedural hemorrhage. Hemoglobin (Hgb) level dropped and international normalized ratio (INR) was elevated. It was reported that the subject had a likely retroperitoneal bleed and was borderline hypotensive. The subject was transferred to the Intensive Care Unit and evaluated for postoperative cardiac care and retroperitoneal peri-duodenal hematoma. The subject had significant status improvement with continued clinical support. On an unspecified date during hospitalization, laboratory tests revealed Hgb of 12.8 g/dL, prothrombin time greater than 180 seconds, INR greater than 19, partial thromboplastin time of 124 seconds, carbon dioxide of 32 mmoL/L, blood urea nitrogen of 28 mg/dL, creatinine of 2.5 mg/dL, glucose of 111 mg/dL, alanine aminotransferase of 14 U/L, and alkaline aminotransferase of 63 U/L.

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Computerized tomography scan showed evidence of a marked right hydroureter with periureteral inflammatory change. There was no evidence of radio-opaque calculi. Wall thickening and debris were apparent within the right renal pelvis. Treatment included transfusion of 6 units of packed red blood cells and 7 units of fresh frozen plasma. Warfarin and glipizide were stopped on 18 June same year*. The event of post procedural hemorrhage was reported as resolved on 25 June same year* and the subject was discharged from the hospital on that day.

The subject withdrew consent and discontinued the study on 09 January one year after*. The investigator reported that there was not a reasonable possibility that the event of post procedural hemorrhage was related to any study activity.

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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: Atrial thrombosis

Subject [redacted] was a 77-year-old white man participating in Study 20110110 who developed atrial thrombosis (reported term: left atrial clot). The subject's medical history included hypercholesterolemia, aortic stenosis, hypertension, gout, allergic rhinitis, and coronary artery disease. Concomitant medications included testosterone, desloratadine, allopurinol, potassium, combination of loratadine and pseudoephedrine, clopidogrel, carvedilol, furosemide, lisinopril, doxazosin, and multivitamins. Previous treatment for hypercholesterolemia included rosuvastatin.

The subject was in the parent study from 01 November one year ago* to 08 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 08 February [redacted].

Approximately 7 months and 2 weeks later, on 25 September one year after*, the subject was hospitalized due to aortic stenosis. A transesophageal echocardiogram was performed and found ejection fraction from 25% to 20% with a large left atrial clot in the left atrium. The left ventricular function was severely decreased and right ventricular function was moderately to severely decreased. Aortic valve was thickened, calcified, and moderately to severely restricted. Severe aortic stenosis was reported. The subject was admitted for intravenous anticoagulation with heparin because of his chronic kidney disease. Treatment included warfarin. Laboratory tests revealed white blood cell count of 5.8 x 10^9/L, hemoglobin of 12.8 g/dL, hematocrit of 38.5%, platelet count of 219000/mm^3, international normalized ratio of 1.9, sodium of 141 mEq/L, potassium of 4.5 mEq/L, chloride of 104 mEq/L, carbon dioxide of 30 mm Hg, glucose of 109 mg/dL, urea of 40 mg/dL, creatinine of 2.3 mg/dL, calcium of 9 mg/dL, glomerular filtration rate of 27.6 mL/min, creatinine clearance of 26.9 mL/min, albumin of 3.4 g/dL, total protein of 6.9 g/dL, alkaline phosphatase of 67 IU/L, aspartate aminotransferase of 22 IU/L, alanine aminotransferase of 31 IU/L, bilirubin of 0.6 mg/dL, and urinalysis revealed 2+ protein and bacteria traces. The investigator reported aortic stenosis, non-ischemic cardiomyopathy,

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ejection fraction of 25%, left atrial clot, chronic kidney disease, atrial fibrillation, and obstructive sleep apnea as final diagnoses. Discharge medications included allopurinol, carvedilol, doxazosin mesilate, furosemide, potassium, lisinopril, combination of loratadine and pseudoephedrine, esomeprazole, fluticasone, multiple vitamins, and testosterone. Warfarin was continued. The subject was discharged from the hospital on 01 October one year after*. At the time of the data cutoff date of [redacted], the event of atrial thrombosis was not resolved.

The last dose of evolocumab prior to the event of atrial thrombosis was on 18 September 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 cutoff date on [redacted]. The investigator reported that there was no reasonable possibility that the event of left atrial clot was related to evolocumab.

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Subject No: [redacted]
Treatments: 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: Pulmonary granuloma, Pancreatitis

Subject [redacted] was a 76-year-old white woman participating in Study 20110110 who developed a pulmonary granuloma (reported term: granuloma of right upper lung lobe) and pancreatitis. The subject's medical history included hypercholesterolemia, hypertension, back surgery, hysterectomy, transient ischemic attack, carpal tunnel syndrome, meniscus injury, trigger finger, drug hypersensitivity, right upper lobe lung mass (first noted in June one year ago*), depression, hyperlipidemia, insomnia, urinary incontinence, gastroesophageal reflux disease, and cystitis. The subject's family history included cancer and aneurysm. Concomitant medications included escitalopram, metoprolol, ramelteon, amlodipine/hydrochlorothiazide/olmesartan, medoxomil, rabeprazole, solifenacin, and acetylsalicylic acid. Previous and ongoing treatment for hypercholesterolemia included ezetimibe and simvastatin.

The subject was in the parent study from 16 November one year ago* to 08 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 08 February [redacted].

Approximately 1 year and 2 months later, on 01 April one year after*, a positron emission tomography (PET) scan was performed and the subject was diagnosed with large right upper lobe lung mass. The subject was admitted to the hospital on the same day for biopsy and subsequent thoracotomy with right upper lobe wedge resection. On the same day, right anterolateral thoracotomy with excisional biopsy of the right upper lobe of the lung, lymph nodes biopsy (x 2) and intercostal nerve block were performed under general endotracheal anesthesia. The right middle lobe and the right lower lobe of lung were free of any pathology. Station 9 lymph node x 2 were removed. The subject tolerated the procedure well and was transferred to the cardiovascular intensive care unit in stable condition. The final pathology diagnosis of the right upper lobe mass wedge biopsy was necrotizing granulomatous inflammation. Acid-fast bacillus (AFB) and Grocott's methenamine silver stain (GMS) stains performed on block 1B and 1C were negative. The lymph node biopsy showed one benign lymph node. The biopsy was negative

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for malignancy. No other relevant laboratory test results were reported. On 13 March one year after*, tissue culture (source: biopsy) showed no white blood cells and no organism. Tissue culture showed no growth after 24 and 48 hours of incubation. The event of pulmonary granuloma resolved on 03 April 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 pulmonary granuloma was on 06 March one year after*. The event of pulmonary granuloma was considered resolved on 23 March two years after*.

On 20 March two years after*, the subject was diagnosed with pancreatitis and was hospitalized on an unknown date. Lipid regulating medications were temporarily discontinued. The subject's last dose of evolocumab prior to the event of pancreatitis was on 12 March two years after*. Pancreatitis was considered resolved on 23 March two years after*. No further details were available at the time of this report.

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 granuloma right upper lung lobe and pancreatitis were related to evolocumab.

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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: Palpitations

Subject [redacted] was a 44-year-old black man participating in Study 20110110 who developed palpitations (reported term: heart palpitations). The subject's medical history included hypercholesterolemia, coronary artery disease, hyperlipidemia, hypertension, cardiac disorder, stent placement, and family history of diabetes mellitus, hypertension, and prostate cancer. The subject was a non-smoker and an alcohol user. Concomitant medications included fexofenadine, acetylsalicylic acid, lorazepam, multivitamins, and lisinopril. Previous and ongoing treatment for hypercholesterolemia included general nutrients and rosuvastatin.

The subject was in the parent study from 22 November one year ago* to 14 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 14 February [redacted].

Approximately 2 months later, on 15 April same year*, the subject experienced palpitations. Three days later, on 18 April same year*, the subject presented to the emergency department with worsened palpitations; there was no radiating pain; the character of the symptoms was pressure, moderate degree at onset and at maximum, and no exacerbating factor; associated symptom included shortness of breath, but no chills, fever, nausea or vomiting. The subject had 3 episodes of generalized palpitations while exercising and was first worked up at his workplace. An electrocardiogram showed a wide complex accelerated junctional rhythm with heart rate of 70 beats per minute and no P waves; chest radiography was normal. The subject was converted back to sinus rhythm and was admitted for further evaluation and care under telemetry monitoring with cardiology consultation. Blood test showed cell blood count (CBC) with normal differential, prothrombin time 12.9 sec, international normalized ratio (INR) 1.0, activated partial thromboplastin time 28.2 sec, sodium 141 mmol/L, potassium 3.7 mmol/L, carbon dioxide 30 mmol/L, glucose 102 mg/dL, neutrophils 36.8%, lymphocytes 50.0%, calcium 9.2 mg/dL, total creatine phosphokinase (CPK) 579 U/L, creatine kinase-muscle and bone (CK-MB) 4.2 ng/mL, serial troponin less than 0.01 ng/mL and negative toxicology screen. Baseline thyroid stimulating hormone (TSH) was 1.27 mu/L on 15 November one year ago*.

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On 19 April same year*, the subject remained clinically stable with normal cardiac markers; laboratory test showed serial troponin less than 0.01 ng/mL, cholesterol 111mg/dL, high density lipoprotein (HDL) 49 mg/dL, low density lipoprotein (LDL) 39 mg/dL, LDL/HDL ratio 0.8, cholesterol/HDL ratio 2.3, very low density lipoprotein (VLDL) 23 mg/dL and triglycerides 116 mg/dL; a two-dimensional echocardiogram (2D ECHO) showed normal ejection fraction and no acute findings. The final diagnosis was junctional rhythm thought to be benign. The subject was given glyceryl trinitrate, enoxaparin for deep vein thrombosis (DVT) prophylaxis. The event resolved on 19 April same year*, and the subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event of palpitations was on 10 April same year*. As of the data cut-off 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 palpitations was related to evolocumab.

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Subject No: [redacted]
Treatments: Parent study: Study 20101155, Evolocumab SC Q4W 420 mg Year 1 treatment: Standard of care only Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Lumbar spinal stenosis, Lumbar radiculopathy

Subject [redacted] was a 73-year-old white woman participating in Study 20110110 who developed lumbar spinal stenosis (reported term: spinal stenosis of lumbar region) and lumbar radiculopathy (reported term: low back pain recurrent left lumbar radiculopathy). The subject's medical history included hypercholesterolemia, diabetes, scoliosis, low back pain, back surgery, physiotherapy, chiropractor visits, kinesitherapy, spinal stimulators, and therapeutic procedure not otherwise specified. Concomitant medications included lisinopril, omeprazole, montelukast, insulin aspart, insulin detemir, macrogol, oxybutynin, azelastine, levosalbutamol, loratadine/pseudoephredine, and Vitamin D. Previous and ongoing treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 16 September two years ago* to 09 December two years ago* and received the last dose of evolocumab in the parent study on 10 November two years ago*. The subject was randomized to Study 20110110 on 09 December two years ago* and assigned standard of care treatment. After completing the first year of the study, the subject received her first dose of evolocumab on 04 January [redacted]. While the subject was receiving standard of care, on 12 July one year ago*, a magnetic resonance imaging of her lumbar spine revealed a left lateral recess stenosis at L4-L5. On unspecified dates, she had undergone 4 previous surgeries due to chronic lumbar pain; however, her left leg pain and numbness were gradually worsening.

Approximately 4 months after the first dose of evolocumab, on 22 May same year*, the subject was hospitalized due to lumbar spinal stenosis. Unspecific imaging test revealed a left lateral recess stenosis at L4-L5. On the same day, the subject underwent a surgery for spinal stenosis; re-exploration of the left L4-L5 lumbar fusion, re-exploration of the left L4-L5 lumbar laminectomy for nerve root decompression, posterolateral arthrodesis L4-L5, and Vitoss allograft. A fusion was explored and the subject was noted to have pseudoarthrosis at the L4-L5 level. The L5 screw was also noted to be a little more loose than expected. The previous defect was delineated and then a repeat laminectomy was performed on the left side at the

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L4-L5 level with dissection of epidural fibrosis. There were no intraoperative complications. The investigator reported recurrent left L4-L5 lateral recess stenosis as the postoperative diagnosis. The event of lumbar spinal stenosis was reported as resolved on 23 May same year* and the subject was discharged from the hospital on the same day. The subject's last dose of evolocumab prior to the event of lumbar spinal stenosis was on 20 May same year*. Evolocumab was continued.

After the subject underwent a lumbar laminectomy on 22 May same year*, her pain worsened. Two months later, on 10 July same year*, a computerized tomography with lumbar myelogram showed a screw extending into the recess space showing severe stenosis. Approximately 7 months after the first dose of evolocumab, on 22 July same year*, the subject was hospitalized for further evaluation and treatment due to an increase in pain in the left leg. The subject underwent an exploration of lumbar spinal fusion, removal of instrumentation (L2 through L5) with re-instrumentation using Xia-3 pedicle screws (L3 through S1), posteroanteral arthrosis at L3, L4, L5, S1 and combined interbody posterolateral arthrodesis at L4-L5 with interbody peek at L4-L5. There were no intraoperative or postoperative complications. The subject started physical therapy and tramadol. Discharge medication included morphine and ondansetron. The event of lumbar radiculopathy was reported as resolved on 25 July same year* and the subject was discharged from the hospital on the same day. The subject's last dose of evolocumab before the event was on 19 July 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 cutoff date on [redacted].

The investigator reported that there was no reasonable possibility that the events of low back pain recurrent left lumbar radiculopathy and lumbar spinal stenosis were related to evolocumab.

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Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q2W 105 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care (SOC) Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SOC
Report: Myocardial Infarction

Subject [redacted] was a 58-year-old white man participating in Study 20110110 who experienced ventricular fibrillation and respiratory arrest. The subject's medical history included dyslipidemia, hypertension, atrial fibrillation, type 2 diabetes mellitus, chronic obstructive pulmonary disease, tricuspid regurgitation, mild congestive cardiac failure, coronary artery disease, ischemic cardiomyopathy, angina, myocardial infarction twice in four years ago*, coronary artery bypass graft in thirteen years ago*, and percutaneous coronary intervention. The subject had an automatic implantable cardiac defibrillator (ICD) placement in one year ago*. The subject was a concurrent tobacco user and had allergy to acetaminophen/tramadol. The subject had a family history of premature coronary heart disease. Concomitant medications included Vitamin E, acetyl salicylic acid, glimepiride, metoprolol, metformin, and lisinopril. Previous and ongoing treatment for hypercholesterolemia included pravastatin.

The subject was in the parent study from 08 November one year ago* to 14 February same year* and received the last dose of evolocumab in the parent study on 17 January same year*. The subject was randomized to Study 20110110 on 16 February same year* and received the first dose of evolocumab on 16 February [redacted].

Approximately 2 years after receiving the first dose of evolocumab, on the morning of 17 February two years after*, the subject experienced shocks at home and was taken to the emergency room (ER) through emergency medical services (EMS) in cardiorespiratory arrest, with ventricular fibrillation. The subject was treated with amiodarone, lidocaine, magnesium, epinephrine, and norepinephrine. Pulse returned after cardiopulmonary resuscitation (CPR) maneuvers into atrial fibrillation (AF) with right bundle branch block (RBBB). Blood pressure was 76/55 mmHg, respiratory rate was 18 breaths per minute, and cardiac troponin I was 0.226 ng/mL. The subject remained unconscious. Therefore, hypothermia was initiated. A transthoracic echocardiogram (TTE) was performed, which showed a worsening ejection fraction with an estimated left ventricular ejection fraction of 20% with septal hypokinesis and dilated right ventricle (RV). A left ventricular thrombus was also noted for which the subject was

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anticoagulated. ECG showed ST elevation myocardial infarction and the subject was taken to the catheterization lab where he was found to have a right coronary artery (RCA) thrombus. The same day, the subject underwent percutaneous coronary intervention to the RCA with 4 bare metal stents. He was started on ticagrelor, acetyl salicylic acid, and atorvastatin. The subject continued with post arrest care and hypothermia with normalization of hemodynamics and optimization of ventilator settings. Computed tomography performed on the same day showed no evidence of significant intracranial injury. The subject was also found to have criteria for sepsis on admission, probably due to aspiration pneumonia. The subject was initially started on broad spectrum antibiotics with vancomycin and a combination of piperacillin and tazobactam. Tracheal blood cultures were performed and were negative on admission. Tracheal aspirate grew pansensitive *Staphylococcus aureus* species and the subject was transitioned to a combination of amoxicillin and clavulanate.

The events of ventricular fibrillation and respiratory arrest were reported as resolved on 17 February two years after* and 18 February two years after*, respectively. The subject was discharged from the hospital in stable condition on 21 February two years after*.

The subject's last dose of evolocumab prior to the event was on 14 February two years 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 events of ventricular fibrillation and respiratory arrest were related to the investigational product.

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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: Pneumonia, Chronic obstructive pulmonary disease

Subject [redacted] was a 74-year-old white woman participating in Study 20110110 who developed pneumonia (reported term: community acquired pneumonia) and chronic obstructive pulmonary disease (reported term: acute chronic obstructive pulmonary disease exacerbation). The subject's medical history included hypercholesterolemia, chronic obstructive pulmonary disease, asthma, unstable angina, myocardial infarction, hypertension, coronary artery disease, hyperlipidemia, angioplasty right carotid artery, percutaneous coronary intervention, stent placement, and allergy to prednisone. She was a former smoker. Concomitant medications included oxygen, salmeterol, acetylsalicylic acid, glyceryl trinitrate, metoprolol, fluticasone, ramipril, hydrochlorothiazide, telmisartan, salbutamol, montelukast, atorvastatin, ticagrelor, and ipratropium. Previous and ongoing treatment for hypercholesterolemia included ezetimibe and rosuvastatin.

The subject was in the parent study from 13 October one year ago* to 19 January same year* and received the last dose of placebo in the parent study on 22 December one year ago*. The subject received her first dose of evolocumab in Study 20110110 on 19 January [redacted].

Approximately 1 year and 7 months later, on 18 August one year after*, she developed increasing shortness of breath and left-sided chest pain radiating to her left shoulder. On 19 August one year after*, she was hospitalized for further evaluation and management of pneumonia of the right lower lobe, chronic obstructive pulmonary disease exacerbation, and chest pain. The subject reported that lately she was using oxygen all the time, not just at night, and was still short of breath; her symptoms were progressively getting worse; she had dyspnea on lying down and left-sided chest pain constantly, 5/10 in intensity, sharp in nature, radiating to the left shoulder, and associated with palpitation. Physical examination showed temperature 36.6°C, heart rate 71 beats per minute, respiratory rate 18 breaths per minute, blood pressure 125/59 mmHg, and oxygen saturation 91%. Laboratory tests showed brain natriuretic peptide 105 pg/mL, white blood cell count 6.3 x 10^9/mL, hemoglobin 11.8 g/dL, hematocrit 36%, mean cell volume 91 fL,

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platelet count 204 x 10^9/mL, sodium 143 mmol/L, potassium 3.8 mmol/L, chloride 106 mmol/L, bicarbonate 29 mmol/L, glucose 107 mg/dL, blood urea nitrogen 23 mmol/L, creatinine 1.0 mg/dL, calcium 9.2 mg/dL, and troponin 0.03 ng/mL. Laboratory tests results showed troponin 0.03, 0.02, and 0.04 ng/mL, cholesterol 135 mg/dL, triglycerides 62 mg/dL, low-density lipoprotein (LDL) 80 mg/dL, high-density lipoprotein (HDL) 74 mg/dL. An electrocardiogram showed normal sinus rhythm and no acute ST changes. Chest radiography showed right lower lobe infiltrate. Echocardiogram was normal, stress test was equivocal, and cardiac enzymes were negative. Treatment included antibiotics, methylprednisolone, nebulizer, salbutamol, ipratropium, ticagrelor, metoprolol, atorvastatin, oxygen, and levofloxacin.

On 20 August one year after*, a 2D echocardiogram showed ejection fraction preserved at 60%, diastolic dysfunction, mild aortic stenosis, and aortic insufficiency. Troponin I levels were 0.02 and 0.04 ng/mL. On 21 August one year after*, white blood cell count was 15.1 x 10^3/µL, her chest radiograph showed right hemi-diaphragm with right basilar atelectasis, and a CT of chest showed acute pneumonia.

On 21 August one year after*, a computed tomography (CT) angiogram showed no pulmonary embolus and anterior peripheral left upper lobe ground-glass opacifications, which could have been acute or chronic. On this day, laboratory tests showed a WBC of 15.1 x 10^3/µL and a chest radiograph showed elevated right hemi-diaphragm with right basilar atelectasis and a chest CT scan showed acute pneumonia. On 21 August one year after*, the Cardiolite stress test showed the following: small focus of reversibly reduced activity in the distal lateral apex may indicate minimal ischemia; larger non-reversible abnormality in the inferobasal area consistent with myocardial infarction; on wall motion study the ventricle was in normal size, it contracted uniformly with an ejection fraction of 48% following both stress and rest.

On 22 August one year after*, laboratory tests results showed white blood cell count 10.3 x 10^9/mL, hemoglobin 12 g/dL, platelet count 219 x 10^9/mL, fasting blood sugar 134 mg/dL, brain natriuretic peptide 105 pg/mL. On 22 August one year after*, the sputum culture was negative. On 23 August one year after*, a left cardiac catheterization showed severe proximal left anterior descending (LAD) stenosis at a previously placed LAD stent. After successful intervention of LAD stent with drug-eluting stent placement, a stent was placed at origin and proximal portion of the right coronary artery. On 24 August one year after*, an electrocardiogram showed normal sinus rhythm, ST

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and T-wave abnormality, considered inferior ischemia; non-specific T-wave abnormality replaced inverted T waves in anterior leads.

On 24 August one year after*, the subject was discharged from the hospital. Chronic obstructive pulmonary disease was reported to be resolved on 24 August one year after*; pneumonia on 28 August one year after*. The subject's last dose of evolocumab prior to the events was on 02 August one year after*.

As of the data cutoff date [redacted], her last dose of evolocumab was on 13 March two years after*, and she was continuing in the study.

The investigator reported that there was no reasonable possibility that the events of pneumonia and chronic obstructive pulmonary disease exacerbation were related to evolocumab, and there were no co-suspect medications.

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