Subject No: [redacted]
Treatment: Parent study: Ezetimibe PO QD 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 30-year-old white man participating in Study 20110110 who developed appendicitis. The subject's medical history included hypercholesterolemia, arterial hypertension, and bronchial asthma. Concomitant medications included ramipril and combination of budesonide and formoterol. The subject did not receive previous treatment for hypercholesterolemia.

The subject was in the parent study from 11 October one year ago* to 03 January same year* and received the last dose of ezetimibe in the parent study on 03 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 05 January [redacted].

Approximately 11 months later, on 11 December same year*, the subject visited the emergency room with abdominal pain and subsequently was hospitalized with a diagnosis of appendicitis. White blood cell count was 5.27 x 10^3/µL on 08 December same year*. Laboratory data on 11 December same year* showed C-reactive protein of 1.17 mg/dL, white blood cell (WBC) count of 13.9 x 10^3/µL, hemoglobin of 17.4 g/dL, hematocrit of 49.3%, red blood cell (RBC) count of 5.37 x 10^6/µL, platelet count of 225 x 10^3/µL, cholesterol of 170 mg/dL, triglycerides of 240 mg/dL, urea of 18.2 mg/dL, creatinine of 0.80 mg/dL, uric acid of 7.29 mg/dL, estimated glomerular filtration rate of > 60 mL/min/1.73 m^2, sodium of 136 mmol/L, potassium of 4.37 mmol/L, and chloride of 97.6 mmol/L. On the same date, 11 December same year*, the subject underwent an appendectomy. Treatment included combination of amoxicillin and clavulanate; paracetamol; and ibuprofen. No predisposing risk factors or any etiology associated with the event were reported. The event of appendicitis resolved on 11 December same year*, and the subject was discharged from the hospital on 13 December same year*.

The subject's last dose of evolocumab prior to the event was on 08 December 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 not a reasonable possibility that the event of appendicitis 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 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: Pelvic fracture

Subject [redacted] was a 44-year-old white man participating in Study 20110110 who had a pelvic fracture. The subject's medical history included hypercholesterolemia, hypertension, sleep apnea syndrome, and tetanus immunization. Concomitant medications included bisoprolol, perindopril, zolpidem, and combination of ascorbic acid, caffeine, and glucuronamide (Guronsan). The subject received no previous treatment for hypercholesterolemia.

The subject was in the parent study from 12 October one year ago* to 15 January same year* and received the last dose of evolocumab in the parent study on 21 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 18 January [redacted]. Approximately 10 months and 3 weeks later, on 06 December same year*, the subject suffered a pelvic fracture in a car accident while driving under the influence of alcohol. On admission to the hospital, he stated that he had no loss of consciousness and mainly complained of pain in his neck and right ankle. On physical examination, he was awake and oriented. Vital signs included a blood pressure of 150/70 mmHg, a heart rate of 76 beats per minute, temperature of 36.1°C, and an oxygen saturation of 99%. Laboratory evaluations showed an ethanol level of 2.13 g/dL. Radiography of the pelvis showed fracture of ischium branch right pubis and bilateral acetabular roof. Radiography of the right leg and ankle showed no intraarticular effusion. An electrocardiogram revealed regular sinus rhythm of 63 beats per minute. Treatment for the event included paracetamol; combination of amoxicillin and clavulanate; tramadol; sodium chloride; povidone iodine; and lidocaine. Additionally, a peripheral catheter was placed for perfusion, cardiac monitoring was done for 1 day, dry bandage was applied, and bed rest was recommended. The subject was discharged from hospital on 10 December same year*. The event of pelvic fracture was considered as resolved on 03 June one year after*. The subject was slowly recovering at home with lasting chronic pain.

The subject's last dose of evolocumab prior to the event was on 21 November same year*. The last dose of evolocumab was on 12 June one year after*. On 10 July one year after* the investigator decided to discontinue treatment. As of data cutoff date of [redacted], the subject is still continuing in the study.

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The investigator reported that there was not a reasonable possibility that the event of pelvic fracture was related to evolocumab. No co-suspect medication was identified by the investigator.

Subject No: [redacted]
Treatment: Parent study: Ezetimibe PO QD Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Impaired gastric emptying

Subject [redacted] was a 31-year-old white woman participating in Study 20110110 who had impaired gastric emptying (reported term: gastroparesis). The subject's medical history included hypercholesterolemia, *Clostridium difficile* infection, chronic back pain, and panic attacks. Concomitant medications included combination of oxycodone hydrochloride, oxycodone terephthalate and paracetamol, alprazolam, metronidazole, and domperidone. The subject received no previous treatment for hypercholesterolemia.

The subject was in the parent study from 21 September same year* to 14 December same year* and received the last dose of ezetimibe in the parent study on 14 December same year*. The subject received her first dose of evolocumab in Study 20110110 on 14 December [redacted].

Approximately 10 months later, on 13 October one year after*, she began to notice a gradual weight loss. Seventeen days later, on 30 October one year after*, the subject was diagnosed with impaired gastric emptying. Her study day 1 weight on 21 September same year* was 84 pounds (38.4 kg). On 29 August one year after*, baseline fasting blood glucose was 5.1 mmol/L and hemoglobin was 124 g/L.

Approximately 4 months after diagnosis, on 07 February two years after*, she was hospitalized for weight loss secondary to impaired gastric emptying. At the time of admission, her weight was 71 pounds (32.3 kg). The subject reported that domperidone did not alleviate her nausea and vomiting after ingesting food or liquid. The diagnoses were severe malnutrition, impaired gastric emptying, iron deficiency anemia, and hyperkalemia. Potassium levels were 3.7 mEq/L and 4.1 mEq/L on 29 August and 13 December one year after*, respectively. On 04 February two years after* her potassium level was 4.3 mEq/L and on 05 February 2013, the subject's laboratory tests showed hemoglobin 106 g/L, hematocrit 0.32 L/L, red blood cell (RBC) count 9.36 x 10^{12}/L, prothrombin time 17.4 seconds, international normalized ratio (INR) 1.6, albumin 29 g/L, phosphorus 1.83 mmol/L, iron 2 µmol/L, and transferrin saturation 0.05. The subject received 1 dose of intravenous saccharated iron oxide.

On 12 February two years after*, a percutaneous endoscopic gastrojejunal feeding tube was placed in the second portion of the duodenum with concomitant administration of propofol, midazolam

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hydrochloride, and fentanyl. After the procedure, she did not present evidence of re-feeding syndrome.

On 15 February two years after*, laboratory tests showed glucose 3.8 mmol/L, albumin 26 g/L, total protein 53 g/L, calcium 2.09 mmol/L, phosphorus 1.53 mmol/L, aspartate aminotransferase (AST) 51 U/L, and alanine aminotransferase (ALT) 96 U/L. On 16 February two years after*, repeated laboratory tests showed albumin 29 g/L, total protein 55 g/L, and ALT 47 U/L. On 21 February two years after*, laboratory results were potassium 5.1 mmol/L, albumin 32 g/L, and total protein 59 g/L. On 26 February two years after*, albumin was 33 g/L.

On 29 May two years after*, laboratory data showed total bilirubin 0.2 mg/dL, direct bilirubin <0.1 mg/dL, alkaline phosphatase 44 U/L, alanine aminotransferase (ALT) 12 U/L, aspartate aminotransferase (AST) 16 U/L, lactate dehydrogenase 121 U/L, blood urea nitrogen 16 mg/dL, creatinine 0.6 mg/dL, glucose 87 mg/dL, total protein 6.9 g/dL, and albumin 3.9 g/dL.

On 01 March two years after*, the subject was discharged from the hospital with the J-tube and continued to receive feedings at home. Hydromorphone was prescribed for pain control at the gastrostomy site. The event of impaired gastric emptying remained ongoing as of the analysis data cutoff date.

The subject's last dose of evolocumab prior to the event was on 17 October one year after*. As of the data cutoff date of [redacted], the subject had received the last dose of evolocumab on [redacted]. Evolocumab remained withheld. The investigator stated that when the J-tube has been removed and the subjects weight has increased, restarting blinded investigational product will be revisited.

The investigator reported that there was not a reasonable possibility that the event of impaired gastric emptying was related to evolocumab. The investigator reported that no concomitant medications were considered to be co-suspect.

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Subject No: [redacted]
Treatments: Parent Study: Ezetimibe PO QD 10 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Infective bursitis

Subject [redacted] was a 65-year-old white woman participating in Study 20110110 who developed infective bursitis (reported term: infection in left burse trochanterica). The subject's medical history included hypercholesterolemia, rheumatoid arthritis, excoriation, drug hypersensitivity, lymphoma, cholelithiasis, hip arthroplasty in five years ago*, and meningioma surgery. No current concomitant medications were reported. Previous treatment for hypercholesterolemia included ezetimibe.

The subject was in the parent study from 26 October one year ago* to 18 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 18 January [redacted].
Approximately 2 years and 2 months later, on 13 March two years after*, the subject developed pain in the region of the previously replaced hip. She was diagnosed with an infection in the left trochanteric bursa. The subject was hospitalized the same day, and underwent soft tissue surgical revision, and received phenoxymethylpenicillin, flucloxacillin, morphine and paracetamol. Hemocultures were negative. The infection was reported resolved on 31 March two years after*. Additionally, it was reported that there were no aetiology or predisposing risk factors associated with the event. Also, it was confirmed that the subject did not undergo any recent surgeries or modification of left hip replacement.

The subject's last dose of the investigational product prior to the event was on 12 February two years after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study and no additional evolocumab dosing had been documented.

The investigator reported that there was not a reasonable possibility that the event of left bursa trochanteric was related to investigational product.

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Subject No: [redacted]
Treatment: Parent study: Placebo SC Q4W Year 1 treatment: Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Chest pain

Subject [redacted] was a 45-year-old black woman participating in Study 20110110 who developed chest pain. Medical history included dyslipidemia, obesity, seasonal allergy, tendonitis, smoking, and tubal ligation. Concomitant medications included atenolol and hydrochlorothiazide. Previous and current treatment for dyslipidemia was not provided.

The subject was in the parent study from 29 July same year* to 21 October same year* and received placebo. The subject was randomized to standard of care in Study 20110110 on 21 October [redacted].

Approximately 7 months later, on 01 June one year after*, the subject was hospitalized for chest pain. The discomfort occurred at rest and not necessarily with exertion and was 3 to 4 minutes in duration, described as squeezing pain which radiated to the throat and associated with shortness of breath. Chest radiography showed no acute pulmonary abnormality. Electrocardiogram (EKG) showed sinus rhythm, no acute changes noted except for some T-wave inversion in III and aVF flattening in lead II. The subject was treated with acetylsalicylic acid and nitroglycerin with relief. The admitting diagnosis was unstable angina. Troponin was 0.302 ng/mL and 0.230 ng/ml. On 04 June one year after*, she underwent left cardiac catheterization, coronary angiogram and left ventricular angiogram of the right femoral artery, due to non-Q-wave myocardial infarction. Reports showed multivessel disease, 2 lesions in the codominant circumflex, 90% proximally and 70% in the mid portion. The subject also had an eccentric 50% lesion in the mid LAD; 70% proximal stenosis in the small right codominant. The subject underwent successful direct stenting of the circumflex lesions. LV angiogram showed normal left ventricular size and systolic function with ejection fraction of 50 to 55. The event of chest pain was considered resolved by 05 June one year after*.

The subject was receiving standard of care lipid lowering treatment prior to the event and received the first dose of evolocumab in Study 20110110 on 16 November 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].

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The investigator reported that there was not a reasonable possibility that the event chest pain was related to the study procedures.

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: Coronary artery disease

Subject [redacted] was a 49-year-old black woman participating in Study 20110110 who developed coronary artery disease. The subject's medical history included hypercholesterolemia, hypertension, dyslipidemia, cholelithiasis with cholecystectomy, esophageal stenosis, esophageal dilation procedure, asthma, Hodgkin's disease, radiotherapy, chemotherapy, bone marrow transplant, and disease recurrence (Hodgkin's disease at left clavicle). The subject had hypersensitivity to lisinopril and a family history of hypertension, cancer, and cerebrovascular accident. Concomitant medications included acetylsalicylic acid, amplodipine, simvastatin, salbutamol, fluticasone, ciprofloxacin, Robitussin (codeine/guaifenesin/pseudoephedrine), combination of amoxicillin and clavulinic acid, and Vitamin E. Previous treatment for hypercholesterolemia was not reported.

The subject was in the parent study from 18 August same year* to 09 November same year* and received the last dose of evolocumab in the parent study on 12 October [redacted]. The subject received the first dose of evolocumab in Study 20110110 on 09 November same year*. Baseline blood pressure on 11 August same year* was 113/79 mmHg. Baseline calculated LDL-cholesterol was 160.5 mg/dL on 18 August same year*. On 17 November same year*, a transthoracic echocardiography showed that the systolic function was mildly to moderately reduced, estimated ejection fraction was in the range of 40% to 45%, with mild diffuse hypokinesis, severe hypokinesis of the inferior myocardium and mild mitral regurgitation. Myocardial perfusion showed large areas of inferoseptal and inferobasal ischemia to a heart rate of 146 beats per minute (bpm).

Approximately 2 weeks later, on 23 November same year*, the subject felt tired and had chest pain. On 30 November same year*, the subject was hospitalized. Stress test was positive for inferior basal reversible ischemia. Left heart catheterization, left ventriculogram, and angiography showed 70% stenosis at the bifurcation point in both the anterior descending and left circumflex artery. The right coronary artery had a subtotal of 99% proximal occlusion with late filling of a distal posteriolateral (PL) and posterior descending artery (PDA) branches. Computerized

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tomography of the chest showed a partially calcified mass along the right cardiac, likely reflecting calcified lymph nodes, likely related to radiation fibrosis within the paramediastinal right lung. The subject was diagnosed with coronary artery disease.

On 01 December same year*, echocardiogram revealed an ejection fraction of 45%. Pericardial biopsy showed fibrous tissue with mild chronic inflammation and metaplastic ossification; no evidence of malignancy was observed. Electrocardiogram revealed sinus tachycardia, incomplete right bundle branch block, and abnormal QRS-T angle. On 01 December same year*, the subject underwent cardiac surgery for 4 coronary artery bypass grafts. Treatment medications included paracetamol, metoprolol, ibuprofen, oxycodone, furosemide, ondansetron, oxycodone, simvastatin, fentanyl, heparin, aspirin, docusate, a combination of aluminum hydroxide gel and magnesium carbonate, amlodipine, verapamil, oxymetazoline, famotidine, and ciprofloxacin. On 10 December same year*, the subject was discharged in good clinical condition. On 31 January one year after* a myocardial perfusion test showed normal results. The event of angina pectoris was reported as ongoing on 29 January one year after*.

The subject's last dose of evolocumab prior to the event of angina pectoris was on 09 November same year* (the first dose). Evolocumab was temporarily withheld, and reinitiated on 01 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 no reasonable possibility that the event of angina pectoris was related to evolocumab. The investigator considered the event related to chemotherapy for Hodgkin's disease. Additional risk factors included hypertension, dyslipidemia and family history of premature coronary artery disease (CAD).

*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 Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Intestinal obstruction, Syncope, Toxicity to various agents

Subject [redacted] was a 66-year-old white woman participating in Study 20110110 who developed, at different timepoints, intestinal obstruction (reported term: bowel obstruction), syncope, and toxicity to various agents (reported terms: drug induced toxicity, lithium toxicity, tremors due to lithium toxicity). The subject's medical history included hypercholesterolemia, dyslipidemia, sarcoidosis, hypothyroidism, fibromyalgia, irritable bowel disease, restless leg syndrome, asthma, bipolar disorder since twenty-one years ago*, essential hypertension, appendectomy, hysterectomy, cholecystectomy, carpal tunnel release, gastroesophageal reflux disease, finger trigger release, bilateral knee arthroplasty, salpingo-oophorectomy, hernia repair, varicose vein surgery, pacemaker insertion on 30 January three years after*, and drug allergy to meperidine and sulfa antibiotics. Social history included former smoking (quit 29 years ago) and occasional alcoholic use (1 shot of liquor per week). The subject's family history included a father with diabetes. Concomitant medications included ropinirole, pregabalin, levothyroxine, ubidecarenone, glucosamine, cyanocobalamin, colecalciferol, acetylsalicylic acid, meloxicam, lamotrigine, and lithium, aluminum-magnesium hydroxide, hydrocodone, magnesium oxide, multivitamin, naproxen, paracetamol, meloxicam, combination of chondroitin and glucosamine, and Vitamin E. No previous or ongoing treatments for hypercholesterolemia were reported.

The subject was in the parent study from 16 September same year* to 08 December same year* and received the last dose of evolocumab in the parent study on 11 November same year*. The subject received the first dose of evolocumab in Study 20110110 on 08 December [redacted].

Approximately 5 and a half months later, on 23 May one year after*, the subject developed abdominal cramping and vomiting. On 24 May one year after*, the subject was hospitalized due to intestinal obstruction. The event intestinal obstruction was thought to be secondary to adhesions from the hysterectomy. On 25 May one year after*, a bowel resection was performed and the event of intestinal obstruction was reported as resolved. The subject was discharged from the hospital on 07 June one year after*.

The subject's last dose of evolocumab prior to the event of Intestinal obstruction was on 27 April one year after*. Evolocumab was continued.

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Approximately 1 year and 11 months after first dose in Study 20110110, on 1 November two years after*, the subject experienced syncope. On 08 January three years after*, the subject went to the emergency room with complaints of the syncopal event, recurrent and progressive dizziness for the past 2 months, and unsteady gait for several weeks. She was admitted to the hospital. On the same day, laboratory data revealed only a slightly lithium level 1.2 and 1.4 mEq/L. Additionally, electrocardiography showed sinus bradycardia, possible sinus arrhythmia, and old septal infarct; computerized tomography (CT) and MRI scan of the head showed no significant acute findings, carotid Doppler showed no hemodynamically significant lesions; transthoracic echocardiography (TTE) did not report any important abnormality. On 09 January three years after*, 24-hour Holter was consistent with sick sinus syndrome. Average daily heart rate 52 was ranging from 28 to 83. There were several pauses of up to 2.34 seconds present. There were premature supraventricular ectopic beats and rare premature ventricular ectopic beats. On 10 January three years after*, the subject was discharged from the hospital. On 30 January three years after*, the subject underwent successful dual-chamber pacemaker insertion. The syncope was reported resolved on 30 January three years after*.

The subject's last dose of investigational product prior to the event of syncope was on 11 October two years after*. Evolocumab was continued.

Approximately 2 years and 3 months after first Study 20110110 evolocumab dose, on 13 February three years after*, the subject presented to emergency room with tremors, rigidity, dizziness, myoclonic jerks and unsteady gait, nausea, and vomiting and was hospitalized.

She was taking lithium for bipolar disorder and reportedly had been noncompliant with the medication, occasionally missing doses and then taking extra doses. Urinalysis revealed a lithium level of 2.3 mEq/L. The subject stated that her lithium dose was increased from 300 mg to 600 mg twice a day. The subject was diagnosed with lithium toxicity. Urine drug and toxicology result showed no presence of other drugs.

On 18 February three years after*, after psychiatric consultation, suicidal ideation was ruled out and overdosing was considered accidental. Treatment reported after the onset of the event included calcium carbonate, clonazepam, lorazepam, pramipexole dihydrochloride, labetalol hydrochloride, acetylsalicylic acid, paracetamol, magnesium hydroxide, ondansetron, and enoxaparin sodium. The outcome of the event lithium toxicity was reported as resolved on 18 February three years after* and the subject was discharged from the hospital on same day.

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The subject's last dose of evolocumab prior to the event of toxicity to various agents was on 11 February three 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 not a reasonable possibility that the events intestinal obstruction, syncope, and lithium toxicity were related to open label investigational product.

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

Subject [redacted] was a 73-year-old white man participating in Study 20110110 who had squamous cell carcinoma (reported term: lesion on top of head [squamous cell carcinoma]). The subject's medical history included hypercholesterolemia, back pain, hepatitis A, insomnia, lethargy, removal of bladder calculus, and transurethral prostatectomy. The subject did not have a family history of skin cancer. Concomitant medications included ginkgo biloba, linoleic acid, multivitamin (combination of ascorbic acid, calcium pantothenate, ergocalciferol, nicotinamide, pyridoxine hydrochloride, retinol, riboflavin, and thiamine hydrochloride). The subject did not receive any previous treatment for hypercholesterolemia.

The subject was in the parent study from 23 August same year* to 30 November same year* and received the last dose of evolocumab in the parent study on 03 November same year*. The subject received the first dose of evolocumab in Study 20110110 on 30 November [redacted]. Approximately 5 months later, on 01 May one year after*, the subject was diagnosed with squamous cell carcinoma. Lesions on the left hand and top of head were removed. On 08 November one year after*, curettage plus electrodessication (ED) on the scalp were performed. Re-evaluation of left hand was carried out. Five days later, on 13 November one year after*, biopsy of left dorsal hand showed squamous cell dermal carcinoma (0.7 cm), hypertrophic actinic keratosis, and hyperkeratotic plaques. The event of squamous cell carcinoma was reported as resolved on 02 October one year after*.

The subject's last dose of evolocumab prior to the event was on 17 April 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 not a reasonable possibility that the event of squamous cell carcinoma was related to evolocumab.

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Subject No: [redacted]
Treatments: Parent study: Ezetimibe PO QD Year 1 treatment: Evolocumab SC Q4W 420 mg + standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + standard of care
Report: Breast cancer

Subject [redacted] was a 63-year-old white woman participating in Study 20110110 who was diagnosed with breast cancer. The subject's medical history included hypercholesterolemia, hyperlipidemia, menopause, depression, osteoarthritis. Family history included breast cancer in aunt and cousin. Concomitant medications included Vitamin E, multivitamins (ascorbic acid, calcium pantothenate, ergocalciferol, nicotinamide, pyridoxine hydrochloride, retinol, riboflavin, thiamine hydrochloride), Vitamin C (ascorbic acid), taurine, *Verbena officinalis* herb, and magnesium. Previous treatment for hypercholesterolemia was not provided.

The subject received her first dose of evolocumab on 01 December [redacted]. Approximately 1.5 years later, she had nodules noted in a mammogram on 13 June two years after*. Approximately 1.5 months later, on 25 July two years after*, she was diagnosed with breast cancer. Biopsy of the right breast showed infiltrating ductal carcinoma; intermediate combined histologic grade (2+ tubules, 2+ pleomorphism, and 2+ mitoses); tumor size at least 5 mm; lymphovascular invasion not identified; ductal carcinoma in situ, intermediate nuclear grade, with coarse calcification and comedonecrosis; breast cancer prognosis profile was estrogen receptor (ER) 100% strong positive, progesterone receptor (PR) 40% positive, Ki-67 30% positive, human epidermal growth factor receptor 2 (HER2)/ncu pending. Biopsy of the left breast showed infiltrating carcinoma with lobular features; intermediate combined histologic grade (2+ tubules, 2+ pleomorphism, and 2+ mitoses); tumor size at least 6 mm; lymphovascular invasion not identified; breast cancer prognosis profile was ER 100% strong positive; PR 70% strong positive; Ki-67 40% positive; HER2/ncu pending. The subject was scheduled for bilateral mastectomy on 15 August two years after*.

As of the data cutoff date of [redacted], the event of breast cancer was reported as not resolved. The subject requested to stop evolocumab administration, and evolocumab was discontinued after the last dose before the event (on 22 March one year after*). As of the data cutoff date, the subject was continuing in the study.

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The investigator reported that there was no reasonable possibility that the event of breast cancer was 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: Pneumonia

Subject [redacted] was a 55-year-old black woman participating in Study 20110110 who developed pneumonia. The subject's medical history included hypercholesterolemia, sciatica, rash, postmenopause, tonsillectomy, and tubal ligation. Concomitant medications included Vitamin E, naproxen, and furosemide. The subject did not receive previous treatment for hypercholesterolemia.

The subject was in the parent study from 12 August same year* to 09 November same year* and received the last dose of evolocumab in the parent study on 19 October same year*. The subject received her first dose of evolocumab on 09 November [redacted]. Approximately 6 months and 3 weeks later, on 28 May one year after*, she reported that she began experiencing symptoms of pneumonia. Two days later, on 30 May one year after*, she was hospitalized for chest pain, and pneumonia was diagnosed. Treatment for the event included amoxicillin, levofloxacin, codeine with promethazine, salbutamol, and prednisone. The subject was discharged from the hospital on 03 June one year after*. The event of pneumonia was resolved on 05 September one year after*.

The subject's last dose prior to the event was on 23 May one year after*. As of the data cutoff date of [redacted], her last dose of evolocumab was on 26 March three years after*; she was continuing in the study.

The investigator reported that there was not a reasonable possibility that the event of pneumonia 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 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: B-cell lymphoma

Subject [redacted] was a 52-year-old white man participating in Study 20110110 who was diagnosed with B-cell lymphoma (reported term: large B-cell lymphoma). The subject's medical history included hypercholesterolemia, sleep apnea syndrome, and tobacco use. Concomitant medication included Vitamin E, doxycycline monohydrate, and codeine/guaifenesin. The subject did not receive any previous treatment for hypercholesterolemia.

The subject was in the parent study from 26 August same year* to 02 December same year* and received the last dose of placebo in the parent study on 04 November same year*. The subject received the first dose of evolocumab on 02 December [redacted]. Baseline albumin was 4.4 g/dL and lactate dehydrogenase (LDH) was 166 U/L on 26 August same year*. Approximately 1 year and 4 months later, on 01 April two years after*, the subject developed a cough. On 17 May two years after*, chest radiography showed 2 mass-like densities in the right lower lobe. The subject had increased levels of alkaline phosphate, lactate dehydrogenase, red cell distribution width, neutrophil count, C-reactive protein, and decreased levels of albumin, hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, and lymphocyte count. A computerized tomogram of the chest showed 2 masses in the right lower lobe consistent with neoplasm, hilar and probable mediastinal lymphadenopathy, and multiple large masses in the spleen with mesenteric and para aortic lymphadenopathy. Pelvis represented lung primary with metastases below the diaphragm. On 22 May two years after*, computerized tomogram of abdomen, pelvis and chest showed right lower lobe pulmonary masses; splenic masses were again seen with retroperitoneal lymphadenopathy in the upper abdomen; other evidence of abdominal or pelvic malignancy was not seen. On 03 June two years after*, lung biopsy showed large B cell lymphoma. On 07 June two years after*, the subject had a repeat episode of cough that was treated with doxycycline monohydrate and codeine/guaifenesin.

The subject's last dose of evolocumab prior to the event was on 17 May two years after*, which was also his last dose in the study. Evolocumab was withheld as of 17 May two years after* and was re-started on

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27 February three years after*. The last dose prior to the data cut-off date of [redacted] was administered on [redacted]. The investigator reported that there was no reasonable possibility that the event B-cell lymphoma was related to evolocumab.

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Subject No: [redacted]
Treatments: 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: Benign adenoma

Subject [redacted] was a 68-year-old white woman participating in Study 20110110 who was diagnosed with a benign adenoma (reported term: villous adenoma benign). The subject's medical history included hypercholesterolemia, chronic sinusitis, gastric ulcer, glaucoma, osteoarthritis, prolonged activated partial thromboplastin time (PTT), urinary tract infection, upper respiratory tract infection, and uterine leiomyoma. Concomitant medications included calcium with Vitamin D, omeprazole, bimatoprost, montelukast, amiodarone, trimethobenzamide, hydrochlorothiazide, and losartan. Ongoing treatment for hypercholesterolemia included atorvastatin.

The subject was in the parent study from 12 July same year* to 18 October same year* and received the last dose of evolocumab in the parent study on 19 September same year*. The subject received the first dose of evolocumab in Study 20110110 on 18 October [redacted].

Approximately 27 months and 2 weeks later, on 30 January three years after*, the subject was reported to have a benign villous adenoma. The subject had a laparoscopic hemicolectomy and prophylactic plasma transfusion due to the medical history of a prolonged PTT since puberty. The benign adenoma was reported resolved on 5 April three years after*.

The subject's last dose of investigational product prior to the events was administered on 08 January three years after*. Investigational product was continued. As of the cutoff date of [redacted], the last dose of evolocumab was on 05 March three years after*.

The investigator reported that there was not a reasonable possibility that the event benign villous adenoma was related to investigational product.

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Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q4W 420 mg Year 1 treatment: Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Chest pain, Hypoglycemia, Dyspnea, Cholecystitis

Subject [redacted] was a 58-year-old white man participating in Study 20110110 who developed dyspnea (reported term: shortness of breath), chest pain, hypoglycemia, and cholecystitis. The subject's medical history included hypercholesterolemia, type 2 diabetes mellitus, hyperlipidemia, prostate cancer, knee operation, and family history of diabetes mellitus. The subject was a smoker and alcohol user. Concomitant medications included metformin, glibenclamide, Vitamin E, and atorvastatin.

The subject was in the parent study from 12 July one year ago* to 07 October one year ago* and received the last dose of evolocumab in the parent study on 08 September one year ago*. After completing 1 year of standard of care treatment on Study 20110110, the subject received the first dose of evolocumab on 08 November [redacted].

Approximately 4 months and 2 weeks later, on 27 March one year after*, the subject developed chest pain and dyspnea while climbing stairs. Upon arrival to the emergency room, subject's electrocardiogram and cardiac enzymes were normal. Laboratory data disclosed glycosylated hemoglobin (HgA1c) of 9.0 g/L, white blood cell (WBC) count of 13.8 x 10^9/L, glucose of 88 mg/dL; troponin I was not detected. The subject was admitted to the hospital on the same day with hypoglycemia, chest pain and dypnea. On an unspecified date during hospitalization, glucose was 180 mmol/L. Baseline values on 07 October one year ago* included blood pressure of 116/73 mmHg, fasting glucose of 130 mg/dL, calculated LDL cholesterol of 135, and a body mass index (BMI) of 38.818.

Prior to the onset of events, the subject had been working for 12 to 15 hours without eating. The subject was observed on telemetry and did not receive treatment for the events. The events of chest pain, hypoglycemia, and dyspnea were reported as resolved on 27 March one year after*, and the subject was discharged on 29 March one year after*.

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On 02 April one year after*, the subject presented to the emergency department with complaints of abdominal pain and diarrhea. At admission, pain was mostly midepigastric; nausea, vomiting, fever and chills were denied; recent weight loss was noted. Abdomen was soft, diffusely tender with exquisite pain in the right upper quadrant. Abdominal ultrasound showed that the gallbladder contained a large stone in the gallbladder neck with gallbladder wall thickening; the liver was normal in size and showed no evidence of any mass lesions or bile duct dilatation; the pancreas was not visualized secondary to overlying bowel gas; the visualized portions of the kidneys and the spleen appeared within normal limits; the abdominal aorta was not seen secondary to overlying bowel gas; inferior vena cava (IVC) was unremarkable. The subject was diagnosed with cholelithiasis with gallbladder wall thickening and positive sonographic Murphy's sign. On 03 April one year after*, vital signs showed temperature of 97.9°C, heart rate of 65 beats per minute, respiratory rate of 18/minute, blood pressure 129/77 mmHg and pulse oximetry of 98%. Laboratory tests showed glucose of 167 mg/dL and sodium of 134 mmol/L. There was no obstructive jaundice; lipase was slightly elevated at 62 IU/L, and white blood cell (WBC) count was 112 x 10^6/L; urinalysis was negative. Hepatobiliary iminodiacetic acid (HIDA) scan was consistent with cholecystitis. On 05 April one year after*, the subject underwent laparoscopic cholecystectomy. Treatment for the event included hydromorphone, levofloxacin, metronidazole, insulin, and normal sodium chloride. The event of cholecystitis was reported as resolved on 08 April one year after*, and the subject was discharged from the hospital.

The subject's last dose of evolocumab prior to the events of chest pain, hypoglycemia, dyspnea, and cholecystitis was on 19 March one year after*. As of the data cut-off date [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cut-off date on [redacted]. The investigator reported that there was no reasonable possibility that the events chest pain, hypoglycemia, dyspnea, and cholecystitis were related to evolocumab.

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Subject No: [redacted]
Treatment: 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: Hepatotoxicity

Subject [redacted] was a 38-year-old white woman participating in Study 20110110 who experienced hepatotoxicity (reported term: liver toxicity). The subject's medical history included hypercholesterolemia, hypertension, gastritis and obesity. The subject had a negative history for recent surgery or anesthesia, no family history of liver disease, and a negative history of alcohol or drug use and no known exposure to liver toxins. Concomitant medications included Vitamin E, lisinopril, metformin, ranitidine, valsartan, and hydrochlorothiazide. Previous treatment for hypercholesterolemia was not reported.

The subject was in the parent study from 01 August same year* to 24 October same year* and received the last dose of evolocumab in the parent study on 27 September same year*. The subject received the first dose of evolocumab in Study 20110110 on 24 October [redacted]. On the same day, laboratory tests obtained prior to the first dose of evolocumab revealed alanine aminotransferase (ALT) 52 U/L, aspartate aminotransferase (AST) 32 U/L, uric acid 7.6 mg/dL and glucose 110 mg/dL. Baseline values obtained on 01 August same year* included AST 70 U/L, AST 42 U/L, and total bilirubin 0.2 mg/dL. On 16 January one year after*, laboratory tests revealed ALT 48 U/L, AST 27 U/L, uric acid 7.0 mg/dL and glucose 112 mg/dL. On 11 April one year after*, the subject had symptoms of nausea, mild epigastric pain after eating, and vomiting. These symptoms continued, along with upper abdominal distention, gas, and poor appetite. The subject was feeling better on some days followed by a worsening of symptoms. On 17 April one year after*, laboratory tests showed: ALT 147 U/L, AST 90 U/L, uric acid 8.1 mg/dL, glucose 124 mg/dL and positive results for hepatitis A. On 25 April one year after*, ALT was 169 U/L and AST was 118 U/L. On 24 May one year after*, repeated laboratory tests revealed ALT 189 U/L, AST 136 U/L, uric acid 9.6 mg/dL and glucose 119 mg/dL. Test for *Helicobacter pylori* was positive.

Approximately 7 months after the first dose of evolocumab, on 31 May one year after*, the subject was still symptomatic with poor appetite, upper abdominal bloating and discomfort and foot pain. Clinical laboratory investigations showed: ALT >5 x upper normal limit; positive results for Hepatitis A virus total antibodies and Epstein Barr virus IgG, and negative results for Hepatitis A virus IgM, Epstein-Barr virus IgM, Hepatitis C virus, Hepatitis B surface antigen and Hepatitis B

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core total antibodies. No additional titers were done. The investigator determined that these findings constituted a medically important event of hepatotoxicity. The subject was not hospitalized. Treatment medication included combination of amoxicillin trihydrate, clarithromycin, and lansoprazole. The subject started feeling better and liver function tests improved after one week of therapy. Treatment with evolocumab was withheld at visit 28, 32, and 36 of the study.

On 19 June one year after*, laboratory test showed ALT 100 U/L, AST 62 U/L, uric acid 8.5 mg/dL and glucose 122 gm/dL. On 06 July one year after*, laboratory data showed ALT 71 U/L, AST 42 U/L, total bilirubin 0.2 mg/dL, direct bilirubin < 0.1 mg/dL, alkaline phosphatase 96 U/L, lactose dehydrogenase 145 U/L, uric acid 7.8 mg/dL, albumin 3.6 gm/dL, and glucose 110 gm/dL.

On an unspecified date, laboratory tests showed a dramatic drop in the AST and ALT levels. The investigator reported that subject showed marked improvement of symptoms and had resumed a normal diet; liver function test results were also improved. The subject agreed to continue to receive study medication and evolocumab was restarted on 06 August one year after* (visit 40). Repeated follow-up laboratory results showed: AST 67 U/L and ALT 100 U/L on 27 September one year after*; AST 67 U/L and ALT 124 U/L on 08 October 2012; AST (range) 59 to 34 U/L, and ALT (range) 118 to 53 U/L from 31 October one year after* to 20 December one year after* and AST 37 U/L and ALT 52 U/L on 17 January two years after*. Subsequent liver function tests showed consistent improvement 8 months after the first dose of evolocumab.

The event of hepatotoxicity was reported to have resolved on 06 July one year after*.

On 15 April two years after*, liver function tests were normal. During the visit on 13 May two years after*, no laboratory tests were performed and the subject had no complaints.

On 20 November two years after*, it was reported that the subject had failed to present for a scheduled visit in June two years after*. Multiple attempts to contact the subject, then her husband and friends, were unsuccessful. It was reported that the subject told her husband that she did not want to continue in the study and did not want to come for a final visit. Additionally, it was reported that the subject was fine and was working full time.

The subject's last dose of evolocumab prior to the event of hepatotoxicity was on 17 April one year after* after which the evolocumab was withheld and again started on 06 June one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the last dose of evolocumab was on 13 May two years after*. The investigator reported that there was no reasonable possibility that the event

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of hepatotoxicity was related to evolocumab. The investigator reported obesity as a risk factor for the event of hepatotoxicity.

Subject No: [redacted]
Treatment: Parent Study: Placebo SC Q2W Year 1 treatment: Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg+ Standard of care
Report: Appendicitis

Subject [redacted] was a 58-year-old white woman participating in Study 20110110 who developed appendicitis (reported term: acute appendicitis). The subject's medical history included hypercholesterolemia.

Concomitant medications included levothyroxine, atenolol, chlortalidone, meloxicam, potassium, cyclobenzaprine, ranitidine, dexlansoprazole, ciprofloxacin, amoxicillin, fish oil, cefoxitin, morphine, ondansetron, sucralfate, oseltamivir phosphate and multivitamins. Previous treatment for hypercholesterolemia was not reported.

The subject received placebo in the parent study from 31 August same year* to 14 December same year*. The subject was randomized to Study 20110110 on 14 December [redacted] and assigned standard of care treatment.

Approximately 6 months and 2 weeks after the randomization, on 26 June one year after*, the subject presented to the emergency room with complaints of right lower quadrant abdominal pain, episode of vomiting and tender guarded abdomen. Abdominal computerized tomography revealed acute appendicitis. On the same day, the subject was admitted to the hospital and underwent appendectomy. No laboratory tests were performed. The event was reported as resolved on 26 June one year after* and the subject was discharged from the hospital on next day.

The event of appendicitis was reported during the first part of the study in which the subject received standard of care treatment. After the completion of 1 year in the study, she received the first dose of evolocumab on 21 January two years after*.

As of the data cutoff date of [redacted], the subject was continuing in the study and the subject 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 any study activity or procedure.

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Subject No: [redacted]
Treatment: 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: Lower limb fracture

Subject [redacted] was a 34-year-old white man participating in Study 20110110 who experienced a lower limb fracture (reported term: fractured tibia/fibula). The subject's medical history included hypercholesterolemia, back pain, hemorrhoids, lactose intolerance, insomnia, sleep apnoea syndrome and anxiety. Concomitant medications included Vitamin E, hydrocodone, clonazepam, prazosin, trazodone, citalopram, and cyclobenzaprine. Previous treatment for hypercholesterolemia was not reported.

The subject was in the parent study 19 September one year ago* to 28 December one year ago* and received the last dose of evolocumab in the parent study on 29 November one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 10 April [redacted]. Approximately 1 month and 2 weeks later, on 23 May same year*, the subject fractured a lower limb in a motorcycle accident. On the same day, the subject was hospitalized and underwent surgery. Treatment medication included hydrocodone. The subject was discharged from the hospital on 27 May same year*. The subject missed his week-8 study visit. The event of lower limb fracture was reported to have resolved on 01 January one year after*.

The subject's last dose of evolocumab prior to the event was on 09 May 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 cutoff date was on [redacted]. The investigator reported that there was no reasonable possibility that the event of lower limb fracture was related to evolocumab.

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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: Alcohol withdrawal syndrome, Hyponatremia, Syncope

Subject [redacted] was a 58-year-old white man participating in Study 20110110 who had alcohol withdrawal syndrome, hyponatremia, and syncope (reported term: fainting). The subject's medical history included hypercholesterolemia, insomnia, appendectomy, alcohol dependence, post-traumatic stress disorder, major depression, chronic urinary tract infections, headaches, hypomagnesemia, hypertension, gastroesophageal reflux disease, previous knee and ankle surgeries and osteoarthritis. Concomitant medications included naproxen, mefenamic acid, ibuprofen, and paracetamol. Previous treatment for hypercholesterolemia was not provided.

The subject was in the parent study from 26 September one year ago* to 03 January same year* and received the last dose of placebo in the parent study on 05 December one year ago*. The subject received his first dose of evolocumab in Study 20110110 on 14 February [redacted].

Approximately 1 month later, on 10 March same year*, he checked himself into a rehabilitation center for alcoholism. The subject developed alcohol withdrawal syndrome on 11 March same year*. Two days later, on 13 March same year*, he had severe electrolyte imbalance, hyponatremia, and fainting. Treatment included multivitamins (ascorbic acid, calcium pantothenate, ergocalciferol, nicotinamide, pyridoxine hydrochloride, retinol, riboflavin, and thiamine hydrochloride), Vitamin B12, zolpidem, venlafaxine, prazosin, and chlordiazepoxide. The events of alcohol withdrawal syndrome, hyponatremia, and syncope were reported as resolved on 13 April same year* and the subject was discharged on that same date.

The subject's first and last dose of evolocumab before the events was on 14 February same year*. Evolocumab was discontinued. The investigator decided to withdraw the subject from the study because of alcoholism. As of the data cutoff date of [redacted], the subject`s last dose of evolocumab prior to the cutoff was on [redacted].

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The investigator reported that there was no reasonable possibility that the events of alcohol withdrawal syndrome, hyponatremia, and fainting were related to evolocumab.

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

Subject [redacted] was a 57-year-old black woman participating in Study 20110110 who developed nephrolithiasis and pyelonephritis. The subject's medical history included hypercholesterolemia, urinary tract infection from same year*, and left sided back and rib pain. Concomitant medications included cyclobenzaprine, naproxen, mometasone, and fluticasone. Previous treatment for hypercholesterolemia included ezetimibe.

The subject was in the parent study from 16 August same year* to 08 November same year*. The subject received the first dose of investigational product on 08 November [redacted].

Approximately 2 years and 4 months later on 14 March three years after*, the subject presented to emergency room with complaints of nausea, vomiting, abdominal discomfort, dysuria, and symptoms of urinary frequency, and was admitted to the hospital. At the time of hospital admission, the subject was diagnosed with pyelonephritis. On the same day, on 14 March three years after*, a computed tomography scan of kidney showed 15 x 13 mm calculus in right kidney, lower pole right renal 3 x 1 mm calculus, and upper pole left renal calyceal 2-mm calculus. On an unknown date, abdominal radiograph showed staghorn calculus and severe right hydronephrosis. Treatment medication reported after the onset of event included ceftriaxone sodium. The investigator reported that there were no predisposing factors associated with the events. The outcome of the event kidney infection was reported as resolved on 18 March three years after*, and the subject was discharged from the hospital on the same day. The outcome of the event kidney stones was reported as resolving.

The subject's last dose of investigational product prior to the events was administered on 25 February three years after*. Investigational product was continued. As of the cutoff date of [redacted], the last dose of evolocumab was on 25 March three years after*.

The investigator reported that there was not a reasonable possibility that the events kidney infection and kidney stones were related to investigational product.

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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: Non-cardiac chest pain

Subject [redacted] was a 72-year-old white woman participating in Study 20110110, who developed non-cardiac chest pain. The subject's medical history included hypercholesterolemia, annual esophagogastroduodenoscopy, constipation and left shoulder bursitis. Concomitant medications included Vitamin E, paracetamol, pantoprazole, metoprolol, diclofenac, sucralfate, and lubiprostone. Previous treatment for hypercholesterolemia was not reported.

The subject was in the parent study from 30 August same year* to 06 December same year* and received the last dose of evolocumab in the parent study on 08 November same year*. The subject received the first dose of evolocumab in Study 20110110 on 06 December [redacted]. On the same day, baseline blood pressure was 118/72 mmHg and calculated LDL cholesterol was 168.5 mg/dL. Approximately 11 months later, on 15 November one year after*, the subject complained of chest pain. The subject was hospitalized and examined by a cardiologist, who suspected that pain was due to esophageal causes. The pain lasted for 2 hours and 30 minutes and was associated with shortness of breath and diaphoresis. The subject remained stable. The event of chest pain was reported as resolved on 17 November one year after* and the subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event was not known. 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.

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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: Bursitis, Non-cardiac chest pain

Subject [redacted] was a 48-year-old white woman participating in Study 20110110 who developed bursitis (reported term: bursitis of left shoulder), and non-cardiac chest pain. The subject's medical history included hypercholesterolemia, dyspnea, gastroesophageal reflux disease, constipation, irritable bowel syndrome, hypothyroidism, menopause, fibromyalgia, dry mouth, fatigue, dysphagia, bladder discomfort, insomnia, osteoarthritis, back pain, depression, anxiety, obesity, peripheral edema, nocturia, headache, and muscle spasms. The subject did not have history of left shoulder bursitis or etiological or predisposing factors associated with the event. Concomitant medications included Vitamin E, loratadine, fluticasone, levothyroxine, multivitamins, omeprazole, tocopherol, pentosan polysulfate sodium, lubiprostone, dicycloverine, promethazine, calcium with Vitamin D, estradiol, methocarbamol, gabapentin, venlafaxine, mirtazapine, bupropion, salbutamol, buspirone, lurasidone, temazepam, hydroxyzine, trazodone, and melatonin. Previous treatment for hypercholesterolemia was not reported.

The subject was in the parent study from 08 September same year* to 01 December same year* and received the last dose of placebo in the parent study on 03 November same year*. The subject received the first dose evolocumab in Study 20110110 on 01 December [redacted]. On the same day, baseline blood pressure was 110/86 mmHg and calculated LDL cholesterol was 148.5 mg/dL. Approximately 1 year later, on 17 December one year after*, the subject developed pain in the left side of her arm and atypical chest pain. On 19 December one year after*, the subject presented to the emergency room and was hospitalized. Echocardiogram was normal with ejection fraction of 60% to 65%. Electrocardiogram and radiograph of the left shoulder were also normal. Coronary computed tomography angiogram showed no evidence of pulmonary embolism. Laboratory tests showed blood myocardial-specific isoenzyme of creatine phosphokinase (CK-MB) of 3.5 ng/mL, and troponin < 0.02 ng/mL. Later the same day, repeated laboratory tests showed blood CK-MB of 2.1 ng/mL, and troponin < 0.02 ng/mL. The subject was diagnosed with bursitis. Treatment for the event included methylprednisolone, morphine,

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hydrocodone and celecoxib. The subject was discharged from the hospital on 21 December one year after*. The event of bursitis was reported as resolved on 21 January two years after*.

On 13 July two years after*, the subject presented to the emergency department with chest pain and pain in the epigastric area radiating to the arm and neck. Baseline electrocardiogram and cardiac enzymes were negative. The subject was diagnosed with non-cardiac chest pain and hospitalized for observation. The event of non-cardiac chest pain was reported as resolved on 16 July two years 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 bursitis was on 27 November one year after*, and the last dose prior to the event of non-cardiac chest pain was on 11 July 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 bursitis and non-cardiac chest pain were related to evolocumab.

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Subject No: [redacted]
Treatments: 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: Non-cardiac chest pain

Subject [redacted] was a 53-year-old white woman participating in Study 20110110 who developed non-cardiac chest pain. The subject's medical history included hypercholesterolemia, hypertension, obesity, palpitations, spinal column stenosis, insomnia, constipation, dry eye, muscle spasms, swelling, seasonal allergy, fibromyalgia, depression,asthma, gastric banding, and cardiac catheterization. Concomitant medications included Vitamin E, metaxalone, furosemide, systane lubricant, cetrizine, multivitamins, metoprolol, calcium with Vitamin D, paracetamol/hydrocodone, magnesium, salbutamol, Vitamin D, docusate sodium, aripiprazole, zolpidem, hydrochlorothiazide, salmeterol/fluticasone, fentanyl, duloxetine, and topiramate. Previous treatment for hypercholesterolemia was not reported.

The subject was in the parent study from 21 September one year ago* to 04 January same year* and received the last dose of evolocumab in the parent study on 02 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 04 January [redacted]. On the same day, baseline blood pressure was 120/82 mmHg and calculated LDL cholesterol was 159.5 mg/dL. Approximately 5 months later, on 21 June same year*, the subject was hospitalized due to intermittent chest pain for 2 weeks. Cardiac enzymes were negative and an electrocardiogram revealed minor terminal T-wave inversion. The following day, on 22 June same year*, an echocardiogram showed left ventricular ejection fraction of 58% and right ventricular ejection fraction of 50%. A stress test was normal. The subject was diagnosed with gastrointestinal related non-cardiac chest pain. Treatment included glyceryl trinitrate, acetylsalicylic acid, enoxaparin, and pantoprazole. The event of was reported as resolved on 22 June 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 non-cardiac chest pain was on 20 June 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 non-cardiac chest pain was related to evolocumab.

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Subject No: [redacted]
Treatment: Parent Study: Evolocumab SC Q2W 105 mg Year 1 treatment: Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg+ Standard of care
Report: Postmenopausal hemorrhage, Uterine leiomyoma

Subject [redacted] was a 56-year-old white woman participating in Study 20110110 who had postmenopausal hemorrhage (reported term: post-menopausal bleeding) and uterine leiomyoma (reported term: uterine submucous fibroid). The subject's medical history included hypercholesterolemia. The subject's had no history of fibroids.

Concomitant medications included ciprofloxacin, metronidazole, lidocaine, vasopressin, and Vitamin E. Previous treatment for hypercholesterolemia was not reported.

The subject received evolocumab in the parent study from 31 August same year* to 06 December same year*. The subject was randomized to Study 20110110 on 06 December [redacted] and assigned standard of care treatment.

Approximately 3 months and 3 weeks after the randomization, on 21 March one year after*, the subject developed postmenopausal bleeding with known submucousal fibroid. On the same day, ultrasound was performed and a fibroid was identified. On 25 May one year after*, subject's serum human chorionic gonadotropin was negative. Approximately 2 months later, on 30 July one year after*, the subject was hospitalized to undergo a planned vaginal hysterectomy. The event of postmenopausal hemorrhage and uterine leiomyoma were reported as resolved on 30 July one year after* and the subject was discharged from the hospital on the next day.

After the completion of 1 year in the study, she received first dose of evolocumab on 04 January two years after*. As of the data cutoff date of [redacted], the subject was continuing in the study and received last dose of evolocumab prior to the data cutoff date on [redacted]. The investigator reported that there was no reasonable possibility that the event was related to any study activity or procedure.

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Subject No: [redacted]
Treatments: 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: Menorrhagia

Subject [redacted] was a 41-year-old white woman participating in Study 20110110 who developed menorrhagia. The subject's medical history included hypercholesterolemia, anxiety and depressive disorders, asthma, smoking, cholelithiasis, insomnia and previous tubal ligation. Concomitant medications included Vitamin E, lorazepam, salbutamol, zolpidem, hydrocodone, erythromycin, paracetamol, doxycycline, hydromorphone, ketoprofen, ipratropium, azithromycin, prednisone, medinite, ketorolac tromethamine, tramadol, ondansetron, droperidol, lidocaine hydrochloride, sucralfate, aluminum w/magnesium hydroxide/simeticone, oxycodone, cyclobenzaprine, cefuroxime axetil, spirulina spp., clonazepam, bupivacaine, clindamycin, fentanyl, flebobag ring lact (lactated Ringer's solution), midazolam, hydroxyzine embonate, and naproxen. The subject had not received any previous treatment for hypercholesterolemia.

The subject was in the parent study from 14 September same year* to 20 December same year* and received the last dose of evolocumab in the parent study on 22 November same year*. The subject received the first dose of evolocumab in study 20110110 on 20 December [redacted].

On 06 November two years after*, the subject experienced menorrhagia and was admitted to the hospital 14 days later. The subject reported that her menstrual cycle occurred every 3 weeks for 4 to 5 days. Her vital signs were normal. A Da Vinci total laparascopic hysterectomy and cystoscopy was performed, uterus and cervix specimens were collected and sent to pathology (results not available). The event was reported as resolved on 20 November two years after* and the subject was discharged from the hospital on the following day (21 November two years after*).

The subject's last dose of the evolocumab before the event was 22 October 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 date on [redacted].

The investigator did not report any co-suspect medications and no risk factors for the abnormal bleeding and determined that there was not a reasonable possibility that the event menorrhagia 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: Standard of care only Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Costochondritis, Biliary dyskinesia, Pneumonia

Subject [redacted] was a 31-year-old white man participating in Study 20110110 who had costochondritis, biliary dyskinesia (reported term: biliary dyskinesis), and pneumonia (reported term: pneumonia, healthcare associated). His medical history included hypercholesterolemia, costochondritis, celiac sprue, steatosis, obesity, microcytosis, embolism and thrombosis of deep vessels of distal lower extremity, deep phlebitis - leg, elbow tendonitis, arthritis of elbow, annular tear of lumbar disc, circadian rhythm sleep disorder shift work type, and acute costochondritis. Concomitant medications included Vitamin E, multivitamin with Vitamin E (tocopherol, ascorbic acid, calcium pantothenate, ergocalciferol, nicotinamide, pyridoxine hydrochloride, retinol, riboflavin, and thiamine hydrochloride), baclofen, diclofenac, sertraline, tramadol, hydromorphone, gabapentin, paracetamol, prednisone, diazepam, ondansetron, hydrocodone, omeprazole, and naproxen. The subject did not receive any previous treatment for hypercholesterolemia.

The subject was in the parent study from 16 September two years ago* to 12 December two years ago* and received the last dose of evolocumab in the parent study on 14 November two years ago*. The subject received the first dose of evolocumab on 07 January [redacted].

Approximately 2 months later, on 08 March same year*, the subject developed costochondritis and was hospitalized on the same date. Signs and symptoms associated with the event included chest discomfort radiating to his right arm, associated with nausea and lightheadedness, some shortness of breath, and pain 5/10 lasting 30 minutes and relieved at rest. Electrocardiogram (EKG), computerized tomogram (CT scan), stress test, and blood work showed no abnormal findings. On an unspecified date, a CT of chest was negative for pulmonary embolus. Chest radiogram, myocardial perfusion scan, and troponin were negative. D-dimer was 561 ng/mL and EKG showed normal sinus rhythm. The treatment included naproxen. The subject was discharged from the hospital on 09 March same year* and the event was reported to have resolved on 14 April same year*.

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The subject received the last dose of evolocumab prior to the event of costochondritis on 04 March same year*. Evolocumab was continued. The investigator reported that there was no reasonable possibility that the event costochondritis was related to evolocumab.

Approximately 5 months after receiving the first dose of evolocumab, on 28 May same year*, the subject's alanine aminotransferase (ALT) was 69 U/L and aspartate aminotransferase (AST) was 41 U/L. Previous ALT was 60 U/L and AST was 31 U/L on 16 September two years ago*. Around 30 May same year*, the subject developed abdominal pain. Subsequently, on 18 June same year*, a hepatobiliary scan was positive for biliary dyskinesia. The subject did not have a prior history of biliary dyskinesia. On that same day, cholecystectomy was carried out; the subject was not hospitalized for the event. Treatment for the event included intravenous normal saline, diphenhydramine, hydromorphone, and droperidol. Risk factors associated with the event included obesity. The event biliary dyskinesia was reported to have resolved on 18 June same year*.

The last dose of investigational product prior to the event of biliary dyskinesia was on 28 May same year*. Evolocumab was continued. The investigator reported that there was no reasonable possibility that the event biliary dyskinesia was related to evolocumab.

Approximately 8 months after receiving the first dose of evolocumab, on 30 August same year*, the subject was hospitalized to undergo foot surgery. At the time of admission, the subject presented with dyspnea. He had right foot plantar fasciitis with heel spur, cavus foot, and peroneus brevis tendon tear and underwent plantar fasciotomy with heel spur excision, elevation 1st metatarsal osteotomy, calcaneal osteotomy, and tenodesis of the peroneus brevis to the peroneus longus. Postoperatively, his pain was controlled with intravenous as well as oral narcotics. He underwent physical and occupational therapy. The investigator noted that due to the subject's chronic pain and opioid tolerance, he required a high amount of oral narcotics. He also developed fever postoperatively, which was associated with hypoxia.

On 01 September same year*, the subject was diagnosed to have healthcare-associated pneumonia. Chest radiography showed some faint increase in density in the right mid lung area representing some atelectasis versus infiltrate. Urinalysis showed no evidence of urinary tract infection. Blood culture was negative. The subject was treated for healthcare-associated pneumonia with intravenous levofloxacin, and with enoxaparin during hospitalization for deep vein thrombosis prophylaxis. The subject improved with antibiotics and he was afebrile for more than 24 hours

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prior to discharge. The subject was discharged home in a stable state on 02 September same year*. The event was reported to have resolved on 06 September same year*.

The last dose of evolocumab prior to the event was on 15 August same year*. Evolocumab was continued. The investigator reported that there was not a reasonable possibility that the event of pneumonia was related to evolocumab.

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].

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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: Aortic stenosis, Coronary artery stenosis

Subject [redacted] was a 76-year-old white man participating in Study 20110110 who developed aortic stenosis (reported term: worsening aortic stenosis) and coronary artery stenosis (reported term: worsening left anterior descending narrowing). The subject's medical history included hypercholesterolemia, dyslipidemia, coronary artery disease, cardiac failure, hypertension, myocardial infarction, aortic stenosis (since 23 September three years ago*), coronary artery stenosis, dyspnea, intermittent claudication, peripheral vascular disorder, stent placement, asthma, and headache. Concomitant medications included acetylsalicylic acid, ramipril, multivitamins, cyanocobalamin, fish oil, salbutamol, combination of budesonide and formoterol, ibuprofen, and paracetamol. Previous treatment for hypercholesterolemia included rosuvastatin.

The subject was in the parent study from 29 November one year ago* to 06 March same year* and received the last dose of evolocumab in the parent study on 09 February same year*. On 06 March [redacted], the subject received the first dose of evolocumab in Study 20110110.

Approximately 1 year later, on 26 March one year after*, stress echocardiogram revealed the aortic stenosis, and the event was reported as worsening of a pre-existing condition. On 03 May one year after*, a di echo report revealed moderate to severe aortic stenosis. On 09 May one year after*, percutaneous coronary intervention revealed significant obstructive disease in the proximal left anterior descending. On that same date, cardiac catheterization revealed moderate to severe left anterior descending proximal disease. The subject was diagnosed with worsening of a pre-existing condition of left anterior descending narrowing. On 23 July one year after* post-catheterization, the subject underwent ultrasound/Doppler examination of the carotid arteries, which revealed mid-moderate bilateral segmental mixed calcified atheromatous carotid artery disease with less than 50% stenosis of the internal carotid artery bilaterally with greater than 50% stenosis of the left external carotid artery. On 05 September one year after*, the subject underwent a coronary artery bypass graft and an elective aortic valve replacement, and the events of aortic stenosis and coronary artery stenosis were reported as resolved on the same day.

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The subject's last dose of evolocumab prior to the event of aortic stenosis was on 04 March one year after*, and prior to the event of coronary artery stenosis was on 07 May 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 on 01 April two years after*.

The investigator reported that there was no reasonable possibility that the events of aortic stenosis and coronary artery stenosis 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 Q2W 70 mg Year 1 treatment: Evolocumab SC 420 mg QM + SOC Years 2-5 treatment: Evolocumab SC 420 mg QM + SOC
Report: Mitral valve incompetence

Subject [redacted] was a 71-year-old white man participating in Study 20110110 who developed mitral valve incompetence (reported term: severe mitral regurgitation). The subject's medical history included hypercholesterolemia and mitral valve prolapse since October 2009. Concomitant medications included acetylsalicylic acid, Vitamin E, metoprolol, acetylsalicylic acid, colecalciferol, oxycocet, influenza vaccine, and rosuvastatin. Previous and ongoing treatment for hypercholesterolemia included rosuvastatin.

The subject received evolocumab in the parent study from 18 July one year ago* to 24 October one year ago* and received the last dose of evolocumab in the parent study on 26 September one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 04 January [redacted].

On 20 November one year after*, severe mitral regurgitation was diagnosed by echocardiography. On 25 February two years after*, the subject was hospitalized for surgical mitral valve repair. The next day the cardiac valve mitral leaflet specimen revealed mere fibrosis with thickening. On 28 February two years after*, laboratory testing revealed hemoglobin of 89 g/L, hematocrit of 0.257 L/L, leucocyte cell count of 13.4 x 10^9/L, red blood cell count of 3.02 x 10^{12}/L, platelet count of 65 x 10^9/L; neutrophil count of 10.3 x 10^9/L, and monocyte count of 1.9 x 10^9/L. Laboratory test results collected from 28 February to 04 March two years after* demonstrated similar results with only minor changes. The subject was treated for the event with metoprolol, oxycodone, and ferrous fumarate. The subject was discharged on 04 March two years after*. The outcome of the event was reported as recovering.

The subject's last dose of evolocumab was on 04 February two years after*, and study drug was withheld for an unknown period of time. As of the data cutoff date of [redacted], the subject was continuing in the study.

The investigator reported there was not a reasonable possibility that the event of severe mitral regurgitation was related to study drug or device.

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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: Hepatic lesion, Metastases to lung; Metastases to lymph nodes

Subject [redacted] was a 65-year-old Asian man participating in Study 20110110 who was diagnosed with a hepatic lesion (reported term: worsening of hepatic lesion), metastases to the lung (reported term: intrathoracic pulmonary metastatic disease), and metastases to lymph nodes (reported term: right paracardiac lymph node metastases). The subject's medical history included hypercholesterolemia, chronic hepatitis B carrier, antrectomcy/vagotomy for peptic ulcer disease, enlarged prostate, and elevated prostate-specific antigen. Concomitant medications included dutasteride, omeprazole, and tamsulosin. Previous treatment for hypercholesterolemia was not reported. Current treatment for hypercholesterolemia was simvastatin.

The subject was in the parent study from 15 September one year ago* to 07 December one year ago* and received the last dose of evolocumab in the parent study on 09 November one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 04 January [redacted]. Approximately 1 year and 2 months later, on 28 February one year after*, the subject developed right upper quadrant pain.

On 06 March one year after*, an abdominal ultrasound showed that the liver was mildly enlarged and there was increased echogenicity consistent with fatty infiltration. There was an ill-defined rounded heterogeneous mass within the right lobe of the liver measuring 9.0 x 6.6 x 6.5 cm. The spleen, aorta, biliary tree, and kidneys were within normal limits. The pancreas was not well visualized due to overlying bowel gas. Limited evaluation of the pelvis demonstrated a significantly enlarged prostate gland with a measurement of 187 mL. On 28 March one year after*, laboratory tests showed alkaline phosphatase of 135 U/L, alanine aminotransferase of 12 U/L, aspartate aminotransferase of 25 U/L, lactate dehydrogenase of 315 U/L, creatinine of 1.2 mg/dL, glucose of 110 mg/dL, and albumin of 3.9 g/dL. Evolocumab was continued.

On 16 April one year after*, the computerized tomogram (CT) scan showed a large lesion spanning segment 8 and measuring 8.1 cm transverse, 8.5 cm anteroposterior, and 9 cm in the axial plane. The mass showed little, if any, enhancement. Central attenuation was low, suggesting

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liquid or necrosis. The mass did not have the appearance of a large benign hemangioma. No additional focal hepatic abnormalities were identified. The lower lungs included within the field of view and were clear with the exception of minor scarring or atelectasis at the right lung base. There were no pleural effusions. The spleen, kidneys, pancreas, and gallbladder were normal in appearance. There were surgical clips adjacent to the stomach likely related to partial gastrectomy. There were occasional small para-aortic and paracaval lymph nodes; the largest showed a diameter of 9 mm. The urinary bladder was distended and there was marked prostatic enlargement. The prostate showed a diameter of approximately 6.5 cm and indented the bladder base. The pelvic structures were otherwise unremarkable. .

On 25 April one year after*, the subject was diagnosed with cholangiocarcinoma.

The subject was admitted to the hospital on 06 June one year after* and underwent portal vein embolization on 07 June one year after* in order to induce regenerative hypertrophy with the hope that an extended right hepatectomy could be offered. The subject tolerated the procedure well. The subject was discharged on 07 June one year after*.

On 23 July one year after*, CT of the thorax depicted bilateral intrapulmonary nodules radiologically highly suspicious for intrathoracic pulmonary metastatic disease, and right paracardiac lymph nodes suggesting lymph node metastases. The CT of abdomen and pelvis revealed that the hypo-enhancing mass in the right liver had increased in size since the prior study; in addition, this mass had now penetrated the diaphragm and a directly contiguous mass was seen in the anterolateral pleural space on the right. It was also noted the tumor was infiltrating into the muscle layers and was intimate with the periosteum of the posterior aspect of the sixth rib, which was accounting for the subject's pain. This characterized the tumor as unresectable. On 24 July one year after*, the subject was diagnosed to have intrathoracic pulmonary metastatic disease and right paracardiac lymph nose metastases. The event of hepatic lesion was considered as resolved on 25 July one year after*.

On 06 August one year after*, the subject returned to the clinic for abdominal and chest pain, for which he was already taking a combination of oxycodone hydrochloride, oxycodone terephthalate, and paracetamol. Further radiation therapy was advised to achieve some local control or pain relief.

The investigator reported that the subject died on 05 September one year after* due to progressive metastatic carcinoma.

The last dose of evolocumab prior to the event was on 24 April one year after*, and the subject discontinued from the study at that point. The investigator reported that there was not a

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reasonable possibility that the events of hepatic lesion, metastases to lung, and metastases to lymph nodes were related to evolocumab. The investigator reported no predisposing factors associated with the events.