Subject No: [redacted]
Treatment: Placebo QM SC (plus diet)
Report: Road traffic accident, multiple fractures

Subject [redacted] was a 68-year-old Asian man participating in Study 20110109 who had multiple fractures due to a road traffic accident (reported terms: motor vehicle accident, multiple fractures). The subject's medical history included hypercholesterolemia, hypertension, chronic mild bilateral shoulder pain, hernia repair, tuberculosis, vitamin B12 deficiency, and right bundle branch block. Concomitant medications reported included combination of paracetamol and codeine phosphate, naproxen, vitamin E, and vitamin B12 (cyanocobalamin). The subject had no reported previous treatment for hypercholesterolemia.

The subject received the first dose of placebo on 23 May [redacted]. Approximately 7 months later, on 21 December same year*, the subject was struck by a motor vehicle and was hospitalized.

Diagnostic imaging of left elbow, forearm, and wrist showed a grossly comminuted intra-articular fracture of the distal radius impacted with dorsal displacement of distal fragments by approximately 1.3 cm. There was also a displaced fracture across the base of the ulnar styloid. Imaging of right tibia, fibula, ankle, and foot showed comminuted fractures involving the proximal third and mid shaft regions of the tibia. There was a comminuted, mildly displaced fracture of the fibular mid shaft. There was also an undisplaced, transversely oriented fracture at the lateral malleolus.

On 22 December same year*, a computerized tomogram (CT) of wrist showed an extensively comminuted distal radial transmetaphyseal fracture with the main component extending through the metaphysis. There was a 3/4 shaft width radial displacement of the metaphysis in relation to the proximal diaphysis, with moderate dorsal impaction and 1/4 shaft width dorsal displacement. There was intra-articular extension of the fracture with involvement of both the scaphoid and lunate facets as well as extension into distal radioulnar joint. A non-displaced fracture was noted through the ulnar styloid base. The subject was diagnosed with right segmental tibia fracture and left distal radius fracture and underwent a right tibia intramedullary nail fixation and left distal radius open reduction, internal fixation operation. During the surgical procedure, the subject received intravenous cefazolin sodium.

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During the postoperative phase, the subject had difficulty mobilizing due to multi-extremity trauma and difficulty with urinary retention. On 14 January one year after*, he was transferred to the Rehabilitation Center and subsequently discharged. The event of motor vehicle accident was reported to have resolved on 12 April one year after*. Both the events of tibia and radius fracture were reported to have resolved on 15 March one year after*. The investigator reported that intramedullary rod was in place.

The subject's last dose of placebo prior to the event was on 03 December same year*. Dose administration was interrupted, and was reinitiated 26 April one year after* (week 48), which was the last dose given. The investigator reported that there was not a reasonable possibility that the events motor vehicle accident or multiple fractures were related to placebo. The subject completed the study on 22 May one year after*.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 80 mg)
Report: Myocardial infarction

Subject [redacted] was a 67-year-old white man participating in Study 20110109 who developed myocardial infarction (reported term: myocardial infarction of back side of heart left ventricle). The subject's medical history included hypercholesterolemia, benign prostatic hyperplasia, umbilical hernia, and obesity (weight of 101.5 kg and height of 176 cm). He had a family history of premature coronary heart disease. Concomitant medications included tamsulosin hydrochloride and vitamin E. Previous treatment for hypercholesterolemia included atorvastatin.

The subject received the first dose of atorvastatin on 10 May same year* and of evolocumab on 15 June [redacted]. Twelve days later, on 27 June same year*, the subject died. Resuscitation was performed; however, the report was not available. On 29 June same year*, an autopsy was performed that reported the cause of death as myocardial infarction complicated with cardiac tamponade. The forensic diagnosis report noted direct cause of death as heart tamponade, with complications causing death including generalized atherosclerosis of Grade 1-3, predominantly on coronary arteries, and acute myocardial infarction of left ventricular posterior wall, and thrombosis of the right coronary artery. Hemorrhages in the muscle of the left ventricular posterior wall and interventricular septum, and blood in the pericardium (380 grams) were also reported. Further autopsy findings included fracture of sternum and ribs after resuscitation.

The subject received only one dose of evolocumab on 15 June same year*. Last dose of atorvastatin was on 22 June same year*. The investigator reported obesity as a risk factor associated with the event. The investigator reported that there was not a reasonable possibility that the event of myocardial infarction was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 80 mg, ezetimibe 10 mg)
Report: Gastritis

Subject [redacted] was a 47-year-old white man participating in Study 20110109 who developed gastritis (reported term: gastritis due to antiagregative treatment). The subject's medical history included hypercholesterolemia, myocardial infarction, mild left ventricular dysfunction, coronary artery bypass graft surgery, tonsillectomy, seasonal allergy, allergy to animal, house dust allergy, and knee operation. Concomitant medications included acetylsalicylic acid, clopidogrel, metoprolol, perindopril, vitamin E, and glyceryl trinitrate. Previous treatments for hypercholesterolemia included rosuvastatin and ezetimibe.

The subject received the first dose of atorvastatin and ezetimibe on 23 March same year* and of evolocumab on 27 April [redacted]. On 27 July same year*, the subject was hospitalized due to worsening breathing status. One day later, on 28 July same year*, the subject's hemoglobin level was 107 g/L, and he was diagnosed with anemia which was also reported to be the cause of worsening breathing status. On 09 August same year*, a gastroscopy was performed that showed gastritis. The investigator reported that the anemia was a consequence of gastritis. Treatment for the event included combination of ferrous sulfate and serine, lansoprazole, and lidocaine. The subject also received pethidine hydrochloride, macrogol, and benzodiazepine derivatives. On 30 July same year*, the subject was discharged from the hospital. The event of gastritis resolved on 15 October same year*, and the event of anemia resolved on 03 January one year after*.

The subject's last dose of evolocumab prior to the event of gastritis was on 20 July same year*. Atorvastatin, ezetimibe, and evolocumab were continued, and the subject received the last dose of evolocumab on 27 March one year after*. The investigator reported that there was not a reasonable possibility that the event of gastritis was related to evolocumab. The investigator reported that co-suspect medication included acetylsalicylic acid. The subject completed the study on 26 April one year after*.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 10mg)
Report: Cardiac failure

Subject [redacted] was a 60-year-old white man participating in Study 20110109 who developed cardiac failure. The subject's medical history included dyslipidemia, hypertension, current cigarette use, asthma, chronic bronchitis, penicillin allergy, eczema, seasonal allergy, pollen allergy, dyspepsia, reflux esophagitis, hemangioma of the liver, hepatic cyst, vertigo, osteoporosis, intervertebral disc compression, back pain, peripheral edema, and varicose ulceration in lower extremities.

Concomitant medications included colecalciferol, betamethasone, combination of alendronate and colecalciferol, levocetirizine, aminophylline, betahistine, combination of fenoterol and ipratropium, omeprazole, dexamethasone, verapamil, zolpidem, oxycodone, combination of calcium, colecalciferol, copper, magnesium, manganese and zinc, furosemide, vitamin E, and combination of paracetamol and tramadol. The subject's previous treatment for the hypercholesterolemia included atorvastatin and ciprofibrate.

The subject received the first dose of atorvastatin on 19 April same year* and of evolocumab on 29 May [redacted]. On 07 June same year*, the subject developed sideropenic anemia. On the same day, ultrasound investigation revealed diffuse hepatopathy. Approximately one month later, on 04 July same year*, the subject developed edema of left lower extremity. Approximately 4 months and 1 week after receiving first dose of evolocumab, on 06 October same year*, the subject died due to cardiac failure. On 08 October same year*, an autopsy was performed. The cause of death according to the autopsy was heart failure caused by chronic heart insufficiency. Underlying diseases included grade 3 central atherosclerosis, advanced coronary atherosclerosis with multiple stenosis (> 75%) and exacerbation of chronic atrophic bronchitis (acute purulent bronchitis). Complications reported included disperse myofibrosis corresponding to clinical diagnosis of chronic ischemic heart disease, vascular nephrosclerosis, chronic heart insufficiency (cyanotic induration of organs) and evidence of acute circulatory failure (pulmonary edema, brain edema and acute venostasis in organs). Additional findings included fracture of 2nd to 4th and 6th to 10th left-sided ribs in the medioclavicular line with vital reaction, flat hematoma on the left side of the chest, subtotal tooth defect and status post prostatectomy. Natural death was secondary autopsy diagnosis. The investigator reported that ischemic heart disease was predisposition for the fatal event.

*新薬承認情報提供時に置き換え

The subject's last dose of evolocumab prior to the event was on 21 August same year*. The investigator reported that there was not a reasonable possibility that the fatal event cardiac failure was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 80 mg)
Report: Uterine cancer

Subject [redacted] was a 60-year-old white woman participating in Study 20110109 who developed carcinoma uterine cervix (reported term: carcinoma colli uteri). The subject's medical history included hyperlipidemia, type 2 diabetes mellitus, hypertension, menopause, goiter and thyroidectomy. The subject had negative history of other malignancy, sexually transmitted diseases, smoking, family history of cervical cancer or any other cancer. Reportedly, the subject had no history of 3 or more full term pregnancies, or oral contraceptive use. Concomitant medications included metformin, omeprazole, combination of losartan and hydrochlorothiazide, isradipine, and levothyroxine. Previous treatment for the hypercholesterolemia included rosuvastatin.

The subject received the first dose of atorvastatin on 02 May same year* and of evolocumab on 15 June [redacted]. Approximately 5 months later (01 November same year*), the subject developed irregular and abnormal gynecological bleeding. Subsequently, on 04 December same year*, the subject was hospitalized for hysteroscopy and treatment. Speculum examination revealed clean vagina, smooth cervix, and minimum spotting from the cervix. Uterus was positioned in retroversion-flexion, appeared small, solid and had no tender with non-differentiated adnexa. On the next day, 05 December same year*, ultrasound examination revealed the presence of tumor of irregular shape in uterine cervix (size - 16 [CC] x 22 [AP] x 18/LL/mm) with the suspect infiltration of anterior and right sided parametrium. Tumor was bigger than half of the uterine cervix, major perfusion in the tumor was not shown, flows were not measurable and suspect infiltration on the right side was noted. Lymphadenopathy was not differentiated, and renal calyces and pelvic system were not dilated on both kidneys. Biopsy from the uterine cervix showed grade 1spinocellular cancer. Laboratory investigation showed squamous cell carcinomas antigen of 18.70 µg/L. On 07 December same year*, cystoscopy revealed no focal changes in bladder mucosa; and normal findings on the trigone and proximal urethra. Radiogram of heart and lungs showed poor drawing and increased transparency on both the sides. Focuses, infiltration and congestion in lower circulation were not shown and suspect shadow of nipple on the right basal-lateral side was observed. Histology revealed grade 1 squamous cell carcinoma with no angio invasion. The subject was diagnosed with cancer of the uterus, which caused disability. The investigator reported that there were no etiological risk factors associated with the event. The investigator confirmed that the abnormal gynecological

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bleeding was considered a symptom for uterine cancer. On 04 January one year after*, computerized tomography/positron emission tomography-FGD of trunk (with contrast) concluded that focuses of significantly increased glucose consumption that could be suspect for neoplasm had not been shown.

The subject received radiotherapy to lower pelvis (total dose 55 Gray, radiation X, energy 6 MV and 18 MV) from 10 January one year after* to25 February one year after*. Concomitantly, the subject was treated with intravenous cisplatin, on a weekly basis (5 cycles) from 15 January one year after*. On 05 February one year after*, brachytherapy (4 applications planned) was started.

On 28 February one year after*, the subject was discharged to outpatient care in adequate condition and without signs of pulmonary and circulatory insufficiency. The event of carcinoma uterine cervix was reported as ongoing and resolving. The subject's last dose of evolocumab prior to the event was on 30 November same year*. Atorvastatin and evolocumab were continued and the subject received the last dose of evolocumab on 14 May one year after*. The investigator reported that there was not a reasonable possibility that the event carcinoma uterine cervix was related to evolocumab. The subject completed the study on 14 June one year after*.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 80 mg)
Report: Biliary tract disorder

Subject [redacted] was a 63-year-old white man participating in the Study 20110109 who had a biliary tract disorder (reported term: biliary attack). The subject's medical history included hypercholesterolemia, Dupuytren's contracture, foot operation, gastrointestinal ulcer disease, hepatitis A, current cigarette use, chronic bronchitis, and bronchopneumonia. Concomitant medication included vitamin E.

The subject received the first dose of atorvastatin on 11 April same year* and of evolocumab on 25 May[redacted]. Baseline laboratory tests performed on 24 May same year* showed ALT of 30 U/L, AST of 22 U/L, and a bilirubin level of 8.55 µmol /L. Approximately 6 months after the first dose of evolocumab, on 09 November same year*, the subject had an alanine aminotransferase (ALT) level of 57 U/L, aspartate aminotransferase (AST) level of 37 U/L, and bilirubin level of 6.84 µmol /L. Approximately 9 months after the first dose of evolocumab, on 01 February one year after*, the subject had biliary colic associated with suspected gallstones and was hospitalized on the same day. He presented with one day history of abdominal pain in the right subcostal area and 1 episode of vomiting. The subject had no signs of acute abdomen and the digital rectal examination was normal. He was reported as "slightly altered due to pain"; axillary temperature was 36.7°C, rectal temperature was 36.9°C, heart rate was 84 beats per minute, oxygen saturation was 98%, and blood pressure was 155/85 mm Hg. The subject had temporary improvement after treatment with diclofenac potassium and intravenous hyoscine butylbromide. The subject also received metamizole. On 04 February one year after*, the subject underwent laparoscopic cholecystectomy. His postoperative course was uneventful. The event of biliary colic resolved on 06 February one year after* and the subject was discharged from the hospital. Laboratory tests performed on 08 February one year after* showed ALT level of 117 U/L, AST level of 41 U/L, and bilirubin level of 8.55 µmol/L.

The subject's last dose of evolocumab prior to the event was on 04 January one year after*, after which evolocumab was withheld due to the event of biliary colic. Atorvastatin was continued. Evolocumab administration was reinitiated on 01 March one year after* and the last dose of evolocumab was given on 26 April one year after*. Laboratory tests at the end of study visit on 23 May one year after* showed ALT of 24 U/L, AST level of 16 U/L, and bilirubin level of 10.16 µmol /L.

*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 biliary colic was related to evolocumab.

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 10 mg)
Report: Osteoarthritis

Subject [redacted] was a 67-year-old white woman participating in the Study 20110109 who developed osteoarthritis (reported term: TEP coxae l. Dx for coxartorosis). The subject's medical history included hypercholesterolemia and hypertension. Concomitant medications included metoprolol and vitamin E.

The subject received the first dose of atorvastatin on 02 April same year* and of evolocumab on 09 May [redacted]. Approximately 1 year later, on 10 April one year after*, the subject underwent planned endoprosthesis surgery (right side total hip replacement) for osteoarthritis. Additional treatment included rivaroxaban, omeprazole, dypirone, piritramide, alprazolam, combination of caffeine, paracetamol, and propyphenazone, and iron preparations. Operation and postoperative condition were uncomplicated. On 17 April one year after*, the subject was discharged to rehabilitation. The event of osteoarthritis was reported as resolved on 26 April one year after* and the subject was discharged home.

The subject's last dose of evolocumab prior to the event was on 09 April one year after*, which was also her last dose in the study, per protocol. Atorvastatin was completed.

The investigator reported that there was no reasonable possibility that the event of osteoarthritis was related to evolocumab. The subject completed the study on 06 May one year after*.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 10 mg)
Report: Palpitations

Subject [redacted] was a 71-year-old white woman participating in Study 20110109 who developed palpitations. The subject's medical history included hypercholesterolemia and intermittent cystitis. Concomitant medications included included estradiol and vitamin E. The subject had no reported previous treatment for hypercholesterolemia.

The subject received the first dose of atorvastatin on 04 April same year* and of evolocumab on 10 May [redacted]. Approximately 1 month later, on 07 June same year*, she developed palpitations. On 12 June same year*, she had normal blood pressure with a pulse of 88 beats per minute. Electrocardiogram showed moderate ST depression which was not cardiac and may have been caused by hyperventilation due to stress and worry. The subject did not report chest pain or radiation. The subject was hospitalized and observed overnight. The investigator stated that acute myocardial infarction (AMI) was ruled out due to negative cardiac enzymes, normal blood samples, and "no events on electrocardiogram (ECG) monitor". No treatment information was provided. The subject's TSH was 1.91 during screening on 28 March same year*. The event was reported as resolved on 13 June same year* and the subject was discharged from the hospital on the same day with no abnormal findings and no AMI.

The subject's last dose of evolocumab prior to the event and in the study was on 04 June same year* (week 4). Evolocumab was discontinued at the subject's request on 02 July same year*. Atorvastatin was continued. The subject completed the study on 06 May one year after*.

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

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Placebo SC QM (plus diet; atorvastatin 80 mg; ezetimibe 10 mg)
Report: Atrial fibrillation, Sinus bradycardia

Subject [redacted] was a 68-year-old white woman participating in Study 20110109 who developed atrial fibrillation (reported term: worsening of atrial fibrillation) and sinus bradycardia (reported term: bradycardia unspecified). The subject's medical history included hypercholesterolemia, pulmonary thrombosis, thrombosis in right leg, thrombosis in left leg, leg cramps, chronic cystitis, sleep apnea, arthrosis of both hands and feet, allergy to penicillin, and hypothyroidism. Concomitant medications reported at screening included paracetamol, warfarin, levothyroxine, quinine, chlorzoxazone, and rosuvastatin.

The subject received the first dose of atorvastatin and ezetimibe on 07 May same year* and of placebo injection on 27 June [redacted]. Approximately 5 months after the first dose of placebo, on 10 December same year*, the subject developed atrial fibrillation, and another 2 weeks later, on 23 December same year*, was hospitalized due to atrial fibrillation. On hospitalization, the subject reported feeling unwell and had palpitations. Blood pressure was 193/107 mmHg, heart rate 115/minute, and respiratory rate 28/minute. On admission (23 December same year*), an electrocardiogram (ECG) showed atrial fibrillation with a frequency of 70 to 100; laboratory test results revealed white blood cell count (WBC) of 2.5 x 10^9/L, platelet count of 102 x 10^9/L, potassium of 3.3 mmol/L, and international normalized ratio (INR) of 2.0. Urinalysis and cardiac enzymes showed normal results. The subject had been taking levothyroxine since fifteen years ago*, which was reported as a predisposing risk factor associated with the event of atrial fibrillation. Treatment for the event of atrial fibrillation included metoprolol succinate, digoxin, and potassium chloride. The event of atrial fibrillation resolved on 24 December same year*, and the subject was discharged from the hospital on the same date. The subject's last dose of placebo, atorvastatin, and ezetimibe prior to the hospitalization for atrial fibrillation was on 10 December same year*. Placebo, atorvastatin, and ezetimibe were continued.

Two days later, on 26 December same year*, the subject was hospitalized with sinus bradycardia. An ECG (continuing) revealed atrial fibrillation with a lowest frequency of 39. Echocardiography showed normal ejection fraction and radiography of the thorax revealed normal results. Treatment with metoprolol succinate was stopped on 26 December same year*. The event of sinus bradycardia resolved on 28 December same year*, and the subject was discharged with follow-up as an outpatient in cardiological ambulatory care. The subject's last dose of placebo, atorvastatin,

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and ezetimibe prior to the hospitalization for sinus bradycardia was on 10 December same year*. Placebo, atorvastatin, and ezetimibe were continued. The investigator reported that there was not a reasonable possibility that the events of atrial fibrillation (first episode) and sinus bradycardia were related to placebo. Metoprolol succinate was reported as a co-suspect medication for the event of sinus bradycardia.

Approximately 2 weeks after discharge, on 09 January one year after*, the subject developed a second episode of atrial fibrillation and was hospitalized. On admission, the subject's vital signs showed blood pressure of 150/83 mmHg, heart rate of 84/minute, and respiratory rate of 19/minute. An ECG showed atrial fibrillation with a frequency of 95. Laboratory test results revealed troponin of < 0.03 ng/L. On the following day, on 10 January one year after*, troponin was < 0.03 ng/L, lactate dehydrogenase was 260 U/L, and INR was 1.7. The atrial fibrillation resolved without any intervention. At discharge, the subject had a blood pressure of 128/83 mmHg, heart rate of 64/minute, and respiratory rate of 17/minute. The second event of atrial fibrillation resolved on 10 January one year after*, and the subject was discharged on the same date. The subject's last dose of placebo, atorvastatin, and ezetimibe prior to the second episode of atrial fibrillation was on 09 January one year after*. Placebo, atorvastatin, and ezetimibe were continued. The investigator reported that there was not a reasonable possibility that the second event of atrial fibrillation was related to placebo.

Placebo was discontinued on 12 March one year after* due to pruritus and injection site hematoma; the last dose of placebo prior to discontinuation was on 08 February one year after*. Atorvastatin and ezetimibe were continued and the last doses were on 20 June one year after*. The subject completed the study on 20 June one year after*.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet; atorvastatin 10 mg)
Report: Breast prosthesis implantation; Device failure

Subject [redacted] was a 66-year-old white woman participating in Study 20110109 who had a breast prosthesis implantation and device failure (reported term: replacement of breast implants-due to ruptured implant right side). Her medical history included hypercholesterolemia, hypertension, thrombocytosis, spinal osteoarthritis, and breast implants. Concomitant medications reported at screening included bendroflumethiazide/potassium chloride, glucosamine, and acetylsalicylic acid/magnesium oxide. The subject was not receiving a statin before entering in the study.

The subject received the first dose of atorvastatin on 10 April same year* and evolocumab on 21 May [redacted]. On 15 January one year after*, the subject was hospitalized and underwent planned breast implant replacement due to a ruptured implant on the right side. She received cefuroxime as preoperative treatment. Treatment for the event included ibuprofen and paracetamol. The event was reported as resolved on 16 January one year after* and the subject was discharged from the hospital on the same day.

The last dose of evolocumab prior to the event was on 02 January one year after*. Evolocumab was continued and the subject received the last dose in the study on 22 April one year after*. The last dose of atorvastatin was on 21 May one year after*. The investigator reported that there was no reasonable possibility that the event of device breakage was related to evolocumab. The subject completed the study on 21 May one year after*.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 80 mg)
Report: Pulmonary embolism

Subject [redacted] was a 58-year-old white woman participating in Study 20110109 who developed pulmonary embolism (reported term: suspected pulmonary embolism). The subject's medical history included stroke, hypertension, panic disorder, vascular encephalopathy, Parkinson's disease, arthralgia, hypothyroidism, thyroidectomy, spinal segment fusion, bilateral intraocular lens implantation, hypercholesterolemia, mild left ventricular dysfunction, obesity, tonsillectomy, femur fracture, intramedullary rod insertion, spondylolisthesis, intervertebral disc protrusion, lumbar spinal stenosis, cardiac failure, cardiomyopathy, sleep apnea syndrome, and angiography. The subject was a current smoker.

Concomitant medications reported at screening included valsartan, hydrochlorothiazyde, levothyroxine, selegiline, amantadine, piracetam, alprazolam, nimesulide, piroxicam betadex, nebivolol, and venlafaxine. The subject was not receiving a statin before entering in the study.

The subject received the first dose of atorvastatin on 16 April same year* and evolocumab on 23 May [redacted]. On 13 December same year*, the subject was admitted to the emergency department due to chest pain after a fall, where pulmonary embolism was suspected. Physical examination revealed vesicular sounds in the lungs with bronchovesicular components, and prolonged expiratory phase. An electrocardiogram showed normal sinus rhythm; heart rate of 81 beats per minute, normal axis; PR of 166 ms; QRS of 96 ms; QTc of 430 ms; ST segments were isoelectric and no T wave changes. Chest radiograph showed signs of previous processes at the base of the right lung, mild cardiomegaly, and pulmonary congestion. Computerized tomography of the chest showed bilateral hydrothorax, which lateralized more to the right, and scarring characteristic of a previous pulmonary process. The examination showed no emboli in the pulmonary trunk, however, a right sided peripheral embolism could not be excluded; bilateral pleural effusion with right side predominance; and thoracic spondylosis. Laboratory tests showed D-dimer at 821 µg/L, white blood cell count of 13.71 g/L neutrophil percentage of 77.1%, lymphocyte percentage of 15%, monocyte percentage of 3.7%, red cell distribution width of 21.2%, platelet count of 338 10^9/L, international normalized ratio of 0.94, troponin at < 0.01 ng/mL, sodium of 136 mmol/L, potassium of 5.29 mmol/L ,lactate dehydrogenase of 763 U/L, and C-reactive protein of 22.66 mg/L.

*新薬承認情報提供時に置き換え

On 14 December same year*, duplex ultrasound of the lower extremities showed no evidence of deep vein thrombosis; some left-sided hydrothorax was seen. Laboratory tests showed fibrin D-dimer of 992 µg/l. On the same date, echocardiography showed the left ventricular cavity size and wall thickness within normal limits; overall left ventricular function was good and there was no significant wall motion abnormality. The left atrium was dilated, dimensions of the right atrium and ventricle were normal, and the mitral annulus was slightly calcified. Doppler test showed that left ventricular relaxation dysfunction was present with grade 2 mitral regurgitation, grade 2 tricuspid regurgitation, and grade 1 pulmonary regurgitation. The right ventricular systolic pressure was moderately elevated, there was no pericardial effusion and the inferior vena cava was of normal size. During hospitalization, the blood gas analysis showed pH of 7.43, pCO_2 of 34 mmHg, pO_2 of 57 mmHg, standard HCO_3 of 23.6 mmol/L, actual HCO_3 of 22.6 mmol/L, BE of -1.2 mmol/L, O_2 sat of 92% (FiO2 of 21%), sodium of 137 mmol/L, potassium of 3.3 mmol/L, calcium of 0.62 mmol/L, glucose of 5.4 mmol/L, hematocrit of 39%, and hemoglobin of 121 g/L. Treatment medication included enoxaparin, tramadol, diclofenac, ethylmorphine, furosemide, and potassium chloride. The subject was discharged from the hospital that day at her own request. The investigator reported that enoxaparin sodium was not tolerated by the subject and was stopped on 30 December same year*.

The event of pulmonary embolism was reported as resolved on 04 January one year after*. The subject's last dose of evolocumab prior to the event was on 05 December same year*. Both evolocumab and atorvastatin were continued; the subject received the last dose of evolocumab on 24 April one year after*. The investigator reported that there was no reasonable possibility that the event of pulmonary embolism was related to evolocumab, and there were no co-suspect medications. The subject completed the study on 22 May one year after*.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 80 mg, ezetimibe 10 mg)
Report: Back pain

Subject [redacted] was a 69-year-old white woman participating in Study 20110109 who developed back pain (reported term: lumbago). The subject's medical history included hypercholesterolemia, hypertension, type 2 diabetes, angina, myocardial infarction, coronary artery bypass graft, mixoma cordis, carotid artery stenosis, cholecystectomy, gastroesophageal reflux disease, biliary dilatation, arthroscopy, intervertebral disc protrusion, spinal operation, chronic renal failure, and low back pain.

Concomitant medications at the time of screening included carvedilol, clopidogrel, rosuvastatin, famotidine, valsartan, and piracetam.

The subject received the first dose of atorvastatin and ezetimibe on 08 May same year*, and of evolocumab on 19 June[redacted]. Approximately 6 months later, on 21 December same year*, the subject experienced worsening of lower back pain. Combined infusion therapy, electrotherapy, and mechanotherapy was performed. On 21 February one year after*, the subject was hospitalized. Treatment medications included diclofenac, alverine citrate, and diazepam. No relevant laboratory or diagnostic test results were reported. The event back pain was reported to have resolved on 06 March one year after* and the subject was discharged from the hospital.

The subject's last dose of evolocumab prior to the event was on 29 January one year after*. Atorvastatin, ezetimibe, and evolocumab were continued; the subject received the last dose of evolocumab on 21 May one year after*. The investigator reported that there was no reasonable possibility that the event back pain was related to evolocumab, and that there were no co-suspect medications. The subject completed the study on 18 June one year after*.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Placebo SC QM (plus diet, atorvastatin 80 mg, ezetimibe 10 mg)
Report: Peripheral sensory neuropathy

Subject [redacted] was a 53-year-old white man participating in Study 20110109 who developed peripheral sensory neuropathy (reported term: peripheral sensory neuropathy of the lower extremities). The subject's medical history included hyperlipidemia, hypertension, type 2 diabetes mellitus, myocardial infarction, percutaneous coronary intervention, and lumbago.

Concomitant medications at the time of screening included ramipril, nebivolol, clopidogrel, glimepiride, metformin, famotidine, and rosuvastatin. During the study, linagliptin was initiated.

The subject received the first dose of ezetimibe and atorvastatin on 05 April same year*, and the first dose of placebo on 16 May [redacted]. On 28 November same year* the subject developed lower back pain that radiated to the right lower extremities. A lumbar computerized tomography was performed which did not show radical compression. Approximately 8 months after the first dose, on 09 January one year after*, the subject developed peripheral sensory neuropathy of the lower extremities. On 19 February one year after* the subject was admitted to the hospital; symptoms included numbness in the right thigh while standing and lower back pain that radiated to the inguina. A thermo facetectomy was performed, the symptoms disappeared, and the event was reported as resolved on the same day. Additional treatment included topical administration of methylprednisolone acetate and midazolam. Two days later, on 21 February one year after*, the subject was discharged from the hospital.

The subject's last dose of placebo prior to the event was on 26 December same year*, and the last dose of atorvastatin and ezetimibe was on 09 January one year after*. Placebo, ezetimibe, and atorvastatin were continued and the subject received the last dose of placebo on 17 April one year after*. The last dose of atorvastatin and ezetimibe was on 15 May one year after*. The investigator reported that there was no reasonable possibility that the event of peripheral sensory neuropathy was related to placebo, and that there were no co-suspect medications. The subject completed the study on 15 May one year after*.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 80 mg, ezetimibe 10 mg)
Report: Metastatic ovarian cancer

Subject [redacted] was a 58-year-old white woman participating in Study 20110109 who developed metastatic ovarian cancer (reported term: gynecology carcinoma with metastasis). The subject's medical history included hypercholesterolemia, hyperlipidemia, hypertension, vertigo, left side subclavian artery stenosis, and obesity (baseline BMI = 34.89).

Concomitant medications at the time of screening included atorvastatin, bisoprolol, indapamide, piracetam, and betahistine.

The subject received the first dose of ezetimibe and atorvastatin on 05 April same year*, and the first dose of evolocumab on 16 May [redacted]. Since the middle of March one year after*, the subject had experienced nausea and vomiting and had a gastroenterology examination (results not provided). On 26 March one year after*, the subject had a gastroscopy which showed reflux esophagitis, hiatus hernia, and chronic gastritis. On 27 March one year after*, laboratory tests for tumor markers showed CA-125 of 759.1 U/mL and CA-15-3 of 40.2 U/mL. On 28 March one year after*, an abdominal ultrasound was performed which revealed a 71 x 82 x 99 mm "terimar" at ovarium L.d and 39 x 51 mm "terimar" behind the uterus. The investigator clarified that the ultrasound showed terime at ovarium L.d. Metastatic ovarian cancer was suspected and considered medically important. On 05 April one year after* a computerized tomography of the abdomen showed a 3 x 7 cm "termiar" at ovarium L.d and a 57 x 42 mm "terimar" at ovarium L.s. The 2 "terimars" were correlated to uterus ascites and peritoneal carcinoma.

On 09 April one year after*, the subject had an oncological examination where an ascites puncture for histology examination was planned. The histology report showed ovarian adenocarcinoma with immunohistology CA-125+. Treatment medications included carboplatin, nadroparin, and ondansetron. The event metastatic ovarian cancer was reported as ongoing and resolving.

The subject's last dose of evolocumab prior to the event was on 20 March one year after*, and the last dose of ezetimibe and atorvastatin was on 08 April one year after*. Evolocumab, ezetimibe, and atorvastatin were permanently discontinued due to the event. The investigator reported that there was no reasonable possibility that the event of metastatic ovarian cancer was related to evolocumab. The subject completed the study on 15 May one year after*.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet; atorvastatin 80 mg)
Report: Aspartate aminotransferase increased; Alanine aminotransferase increased

Subject [redacted] was a 57-year-old white woman participating in Study 20110109 who developed increased aspartate aminotransferase (AST) and increased alanine aminotransferase (ALT). The subject's medical history included hypercholesterolemia, hand fracture, tonsillectomy, female sterilization, miscarriage, hot flushes, menopause, headache, periodontal disease, and diarrhea. The subject was allergic to hay, dust, and mold. Concomitant medications while on study included ibuprofen, multivitamins, and *Lactobacillus acidophilus*. The subject was not receiving a statin before entering in the study.

The subject received the first dose of atorvastatin on 14 March same year* and the first dose of evolocumab on 18 April [redacted] On 07 March same year* and 11 April same year*, prior to the baseline, laboratory test values for AST, ALT, and alkaline phosphatase (AP) were below the laboratory upper limit of normal (ULN). Baseline laboratory tests on 18 April same year* obtained prior to the first dose of evolocumab revealed ALT of 50 U/L (ULN was 34 U/L), AST of 33 U/L (ULN 34 U/L), and AP of 145 U/L (ULN 123 U/L). Approximately 3 months after the first dose of evolocumab, on 10 July same year*, laboratory tests showed ALT of 695 U/L and AST of 539 U/L. Additional results included AP of 319 U/L, lactate dehydrogenase of 237 U/L (ULN 234 U/L), total bilirubin of 0.5 mg/dL, direct bilirubin of 0.3 mg/dL, and fasting glucose of 113 mg/dL. On this same date (10 July same year*), the investigator advised the subject to discontinue atorvastatin. Evolocumab was withheld.

Laboratory results of samples collected on 16 July same year* were negative for hepatitis B core, hepatitis C virus, and hepatitis A virus immunoglobulin M. Additional results included AP of 275 U/L, ALT of 631 U/L, AST of 414 U/L, lactate dehydrogenase of 237 U/L, prothrombin time of 10.4 sec, international normalized ratio (INR) of 0.9, total bilirubin 0.6 mg/dL, direct bilirubin 0.3 mg/dL, hemoglobin 12.2 g/dL, hematocrit of 38%, red blood cell (RBC) count 4.2 x 10^6/µL, and white blood cell (WBC) count 5.11 x 10^3/µL. On this date (16 July same year*), the subject stated that she had no symptoms, had no change in her concomitant medications, and denied pain or any other side effects due to medication or any additional alcohol consumption. On 18 July same year*, at her scheduled week 13 visit, the subject reported feeling well without any nausea, itching, anorexia or fever. The subject's blood pressure was 128/79 mmHg, pulse rate was 79 per minute; and physical examination was normal. Analysis of urine collected on 19 July same year* revealed specific gravity of 1.026, pH of 5.5, normal glucose, RBC count of 1/high

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power field (HPF), and WBC count of 1/HPF and the sample was negative for protein, bilirubin, and blood. The investigator noted that the event was "probable atorvastatin-hepatitis". No treatment was given for the events.

On 08 August same year*, the subject's liver function tests returned to baseline (AST 25 U/L, ALT 26 U/L, AP 100 U/L, total bilirubin of 0.3 mg/dL, direct bilirubin 0.1 mg/dL, and lactate dehydrogenase 161 U/L), and the end date for the events of increased AST and increased ALT was reported as 08 August same year*.

Laboratory results of a blood sample collected on 17 October same year* included total bilirubin 0.4 mg/dL, direct bilirubin 0.1 mg/dL, AP 86 U/L, AST 25 U/L, and ALT 14 U/L. Evolocumab was restarted on 17 October same year*. Laboratory test results obtained on 14 November same year* revealed AP of 70 U/L, ALT of 13 U/L, and AST of 18 U/L. On 12 December same year*, results were total AP of 68 U/L, ALT of 15 U/L, and AST of 21 U/L.

Laboratory tests performed on 16 January one year after* showed AP of 71 U/L, ALT of 15 U/L, and AST of 20 U/L. Repeated laboratory tests performed on 16 April one year after* showed AP of 72 U/L, ALT of 13 U/L, and AST of 20 U/L.

The subject's last dose of evolocumab prior to the elevated AST and ALT was on 10 July same year*. Evolocumab was withheld due to the events and was restarted on 17 October same year*. The subject's last dose of evolocumab was on 10 January one year after*. Last dose of atorvastatin was on 10 July same year*. The investigator reported that there was a reasonable possibility that the events of increased AST and increased ALT were related to evolocumab. Atorvastatin was reported as a co-suspect. The subject completed the study on 16 April one year after*.

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Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 80 mg, ezetimibe 10 mg)
Report: Non-cardiac chest pain

Subject [redacted] was a 66-year-old white man participating in Study 20110109 and had non-cardiac chest pain. The subject's medical history included hypercholesterolemia, hyperlipidemia, coronary artery disease, coronary artery bypass graft, intervertebral disc degeneration, spinal laminectomy, osteoarthritis, rotator cuff repair, gastroesophageal reflux disease, peptic ulcer, nephrolithiasis, insomnia, and seasonal allergy.

Concomitant medications at the time of screening included rosuvastatin, ezetimibe, esomeprazole, calcium carbonate/sodium fluorophosphates, tramadol, zolpidem, and multivitamins.

The subject received the first doses of evolocumab, atorvastatin, and ezetimibe on 11 June [redacted]. Approximately 6 weeks later, on 22 July same year* in the afternoon, he experienced chest pain. He took 2 doses of acetylsalicylic acid 81 mg and presented to the emergency room. On 22 July same year*, laboratory tests showed calcium 8.5 mg/dL, glucose 103 mg/dL, and monocytes 9.9%. A chest radiograph showed no gross acute abnormality and an electrocardiogram revealed sinus bradycardia, incomplete right bundle branch block, inferior infarct, age undetermined. Troponin values on 22 July same year* and 23 July same year* remained consistently below 0.02 ng/mL; levels of creatine phosphokinase (MB form) (CPK-MB) on those dates were within normal limits at 0.5 ng/mL or less. D-Dimer result was negative and myoglobin was within normal limits (46.0 ng/mL). On 23 July same year*, laboratory test results showed alanine aminotransferase 26 U/L, calcium 8.3 mg/dL, cholesterol 79 mg/dL, hemoglobin 12.4 g/dL, protein 6.0 g/dL, and monocytes 10.8%. According to the investigator, the subject had no myocardial infarction and chest pain was of unknown etiology. The event resolved on 23 July same year* and the subject was discharged from the hospital on the same date. Acetylsalicylic acid was initiated.

The subject's last dose of evolocumab prior to the event was on 10 July same year*. Atorvastatin, ezetimibe, and evolocumab were continued. The last dose of evolocumab was on 15 May one year after*; the last doses of atorvastatin and ezetimibe were on 13 June one year after*, and he

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

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet; atorvastatin 80 mg)
Report: Appendicitis

Subject [redacted] was a 41-year-old white woman participating in Study 20110109 who developed appendicitis. The subject's medical history included hypercholesterolemia, hypertriglyceridemia, hypertension, type 2 diabetes mellitus, cholecystectomy, hysterectomy, osteoarthritis, depression, anxiety, stress, obesity, pyelonephritis, nephrolithiasis, gastroesophageal reflux disease, and cesarean section.

Concomitant medications at the time of screening included lovastatin, glipizide, metformin, diclofenac, citalopram, trazodone, and lisinopril.

The subject received the first dose of atorvastatin on 23 February same year* and evolocumab on 29 March [redacted]. Approximately 4 months later, on 21 July same year*, the subject presented to the emergency room with severe abdominal pain. Ultrasound showed appendicitis. The subject was admitted to the hospital on 22 July same year* with a 1-day history of right low quadrant (RLQ) pain and fever. At 9:30 am, the subject became nauseated and had some non-bilious emesis; hours later, she first experienced some vague abdominal pain (periumbilical pain), progressing to localized pain in the RLQ, being constant. Pain was described as a constant dullness with accompanying intervals of severe crampy pain. Physical examination showed tenderness in the RLQ and fever of 102.1°F, and WBC was 11 x 10^9/L. Abdominal-pelvic CT showed multiple stones in the right kidney, multiple mildly enlarged lymph nodes within the right lower quadrant and mild stranding of the pericecal fat possibly related to panniculitis of the mesentery; the appendix was normal in appearance. The subject underwent appendectomy without complications. Procedure findings showed the subject had a very mildly inflamed appendix with no other obvious intra-abdominal pathology, and also had a large amount of scarring from previous surgeries. Treatment also included famotidine, ondansetron, unspecified IV antibiotics, docusate, acetaminophen/oxycodone, and heparin. Post-operative diagnosis was early mild acute appendicitis. The event appendicitis was reported as resolved on 22 July same year*. On 23 July same year*, the subject was discharged from the hospital in stable condition.

The subject's last dose of evolocumab prior to the event was on 19 July same year*. Both evolocumab and atorvastatin were continued; the last dose of evolocumab was on 27 February one year after*. The subject's last dose of atorvastatin was on 27 March one year after*. The

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investigator reported that there was no reasonable possibility that the event appendicitis was related to evolocumab. The subject completed the study on 27 March one year after*.

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Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 80 mg, ezetimibe 10 mg)
Report: Unstable angina

Subject [redacted] was a 54-year-old white man participating in Study 20110109 who developed unstable angina. The subject's medical history included hypercholesterolemia, hyperlipidemia, gastroesophageal reflux disease, arthralgia, musculoskeletal pain, and Raynaud's phenomenon.

Concomitant medications at the time of screening included simvastatin, ezetimibe, rabeprazole, and acetylsalicylic acid.

The subject received the first dose of atorvastatin and ezetimibe on 11 April same year* and the first dose of evolocumab on 13 June [redacted]. Approximately 2 months later, on 01 August same year*, the subject developed slowly progressive stable angina pectoris. The subject had angina on exertion (typically, brought on by walking). Over the next 3 months, the frequency of angina increased with reduced anginal threshold and the subject experienced angina while working with power tools using only arms. On 02 November same year*, a treadmill stress electrocardiogram with high risk features was performed. The subject experienced pain within 2 to 3 minutes of exercise, with marked ST depression in leads II, III, and aVF, and downsloping ST segments. The subject was able to exercise for only 5 minutes and the ST segment did not normalize until after 7 minutes of recovery. The subject was hospitalized for expedited cardiac catheterization. The subject underwent a coronary angiography, left ventricular angiography, and percutaneous coronary intervention with coronary stent. The procedure revealed 90% stenosis of the mid right coronary artery which was treated with overlapping Promus Element drug-eluting stents; and 70% to 80% sequential stenosis in the proximal and mid left anterior descending artery, which were treated with a Promus Element drug-eluting stent. The right coronary artery stents were postdilated to 3.75 mm and the stent placed in the left anterior descending artery was postdilated to 2.75 mm. The subject tolerated the procedure well and was transferred to the cardiovascular intervention unit for observation. Treatment medications for the event included clopidogrel, metoprolol, prasugrel, and nitroglycerine. The event unstable angina was reported as resolved on 02 November same year* and the subject was discharged from the hospital on 03 November same year*.

The subject's last dose of evolocumab prior to the event was on 11 July same year*. Evolocumab was not interrupted and atorvastatin was withheld during the angiography; the subject received the

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last dose of evolocumab on 15 May one year after*, and atorvastatin on 12 June one year after*. The investigator reported that there was not a reasonable possibility that the event of unstable angina was related to evolocumab. The subject completed the study on 12 June one year after*.

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Subject No: [redacted]
Treatment: Placebo SC QM (plus diet, atorvastatin 10 mg)
Report: Asthma

Subject [redacted] was a 58-year-old white woman participating in the Study 20110109 who developed asthma (reported term: worsening of asthma). The subject's medical history included hypercholesterolemia, hypertension, former cigarette use, asthma, osteoarthritis, back pain, hot flushes, hysterectomy, and seasonal allergy. The subject also had a history of 1 or 2 hospitalizations yearly due to exacerbation of asthma.

Concomitant medications at the time of screening included simvastatin, lisinopril, hydrochlorothiazide, felodipine, and acetylsalicylic acid.

The subject received the first dose of atorvastatin on 03 April same year* and first dose of placebo on 08 May [redacted]. Approximately 7 months after the first dose of placebo, on 28 November same year*, the subject was hospitalized due to worsening of asthma. The subject had several attacks of asthma. She did not have any respiratory infection or fever before the event. The subject reported change of weather and environmental factors as contributing factors to worsening of asthma. Upon admission to the hospital, the subject's body temperature was 98.3 degrees Fahrenheit, pulse rate was 97 beats per minute, respiratory rate was 24 breaths per minute, blood pressure was 91/70 mm Hg, and oxygen saturation was 93% to 94%. On the day of hospitalization, cardiac enzymes were normal, chest radiograph showed no acute pulmonary or pleural disease, and electrocardiogram was normal. On 30 November same year*, glucose level was 166 mg/dL, and full blood count and liver enzymes were normal. Treatment for the worsening asthma included oxygen, corticosteroids (intravenous and oral), levofloxacin, salbutamol, combination of fluticasone propionate and salmeterol xinafoate, combination of hydrocodone bitartrate and paracetamol, pantoprazole sodium sesquihydrate, intravenous fluids, and nebulizer treatment. The event of asthma resolved on 04 December same year* and the subject was discharged from the hospital.

The subject's last dose of placebo prior to the event was on 20 November same year*. Both placebo and atorvastatin were continued; the subject received the last dose of placebo on 09 April one year after*. The investigator reported that there was no reasonable possibility that the event of asthma was related to placebo. The subject completed the study on 07 May one year after*.

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Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 80 mg, ezetimibe 10 mg)
Report: Breast cancer

Subject [redacted] was a 67-year-old white woman participating in the Study 20110109 who developed breast cancer. The subject's medical history included hypercholesterolemia, dyslipidemia, tonsillitis, cholelithiasis, foot fracture, menorrhagia, allergy to codeine, insomnia, osteoarthritis, and meniscus injury. The subject had undergone tonsillectomy, cholecystectomy, hysterectomy, and surgery (pin inserted in toe of left foot). The subject consumed alcohol and had a family history of coronary artery disease.

Concomitant medications at the time of screening included atorvastatin and a combination of glucosamine sulfate and chondroitin sulfate.

The subject received the first dose of ezetimibe and atorvastatin on 20 April same year* and first dose of evolocumab on 24 May [redacted]. Approximately 8 months after the first dose of evolocumab, on an unspecified day in January one year after*, the subject was diagnosed with breast cancer. No additional details were available at the time of this report. The event was reported as not resolved.

The subject's last dose of evolocumab prior to the event was on 07 December same year*, which was also her last dose in the study. Atorvastatin and ezetimibe were discontinued on 16 January one year after* per subject's request. The investigator reported that there was no reasonable possibility that the event of breast cancer was related to evolocumab. The subject refused further follow-up and was early terminated on 20 February one year after* due to full informed consent withdrawal.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet; atorvastatin 10 mg)
Report: Pneumonia; Pleurisy; Renal neoplasm

Subject [redacted] was a 73-year-old white woman who was participating in Study 20110109 and developed pneumonia and pleuritis. Medical history included hypercholesterolemia and a 4-month history of cough. Concomitant medications included paracetamol (Panodil), cefatrizine (Cetrizin), tramadol, (Mandolgin), amlodipin, quinine(Kinin), calcium, colecalciferol (Unikalk Forte), diclofenac (Voltaren), and piroxicam(Felden). Previous treatments for hypercholesterolemia included fish oil. The subject received her first dose of evolocumab on 03 May [redacted]. Approximately 7 months later on 20 Dec ember same year*, the subject was admitted to the hospital for dyspnea and was diagnosed with left sided pleuritis and pneumonia by chest radiograph. Treatment included unspecified IV antibiotics, oral phenoxymethylpenicillin potassium (Vepicombin), and furosemide. The subject underwent ultrasound guided emptying of fluid within the interpleural space on two occasions. On 27 December same year* the events were reported as resolved and the subject was discharged from the hospital. The subject's last dose of evolocumab prior to the event was on 13 December same year*. Evolocumab was continued. The investigator reported that there was not a reasonable possibility that pneumonia and pleuritis were related to evolocumab.

After discharge the subject had a computerized tomogram (CT) of the thorax and abdomen in February one year after* that revealed a left kidney tumor and right side apical lung infiltrate, and the subject underwent a left nephrectomy on 22 April one year after*. A follow-up CT of the chest was planned for 17 June one year after*.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet; atorvastatin 10 mg)
Report: Increased blood creatine phosphokinase

Subject [redacted] was a 55-year-old woman who was participating in Study 20110109 and developed creatine phosphokinase (CPK) increase. Medical history included hypercholesterolemia, hypertension and borderline hypothyroidism (based on laboratory values noted below). Concurrent medications included valsartan, rilmenidine, carvedilol, indapamide, rabeprazole, pancreatin, calcium dobesilate, clonazepam, venlafaxine, carbamazepine, allopurinol, alverine citrate/DL methionine, pinaverium bromide, and furosemide. The subject received the first dose of atorvastatin on 11 April same year* and the first dose of evolocumab on 16 May [redacted]. Approximately 5 months later, on 15 October same year*, the subject developed an increased CPK of 2138 U/L and was referred to the emergency department. Baseline CPK on 16 May same year* was 134. The subject reported 2 days of dizziness, atypical chest pain, ankle and facial edema but no muscular or skeletal complaints or signs. The subject had bumped against the wall due to dizziness but there were no visible signs of injury or significant tenderness. Serum creatinine was normal at 102 µmol/L on presentation to the emergency department. Diuretic therapy was intensified with furosemide. Atorvastatin was discontinued on 23 October one year after*, and evolocumab was temporarily withheld. Consultation with an immunologist and nephrologist was obtained and CPK and creatinine levels were monitored. Immune serology testing for myositis was negative. On 24 October same year*, CPK was 2549 U/L and creatinine was 143 micromol/L. CPK and creatinine peaked at 5344 U/L and 177 micromol/L, respectively, on 27 December same year* and thyroid stimulating hormone (TSH) was found to be elevated at 191.2 mU/L. TSH values during screening were 2.79 and 6.95 mU/L on 29 March same year*, and 9 May same year*. Subsequently, severe hypothyroidism was diagnosed and thyroxine replacement was started. Further treatment included indapamide (Apadex), valsartan (Valsacor), rilmenidine (Tenaxum), potassium, spironolactone, esomeprazole, and tolperisone. On 31 January one year after*, CPK and creatinine levels decreased to 170 U/L and 124 micromol/L, respectively and TSH decreased to 37.210 mU/L.

The subject's last dose of evolocumab prior to the event was 03 October same year* and the last dose of atorvastatin prior to the event was 14 October same year*; both were discontinued. The investigator reported that there was not a reasonable possibility that creatine phosphokinse

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increase was related to evolocumab and considered the event a consequence of the subject's severe hypothyroidism.

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet; atorvastatin 80 mg)
Report: Syncope

Subject [redacted] was a 60-year-old white man participating in Study 20110109 who developed syncope. The subject's medical history included hypercholesterolemia, hyperlipidemia, hypertension, palpitations atrial tachycardia, chest pain, syncope (13 September one year ago*), dizziness, cardiac murmur, restless legs syndrome, gastroesophageal reflux disease, upper abdominal pain, intervertebral disc protrusion, back pain, spinal osteoarthritis, lumbar radiculopathy, somatoform disorder, cervical radiculopathy, musculoskeletal pain, epicondylitis, exposure to communicable disease, headache, hypogonadism, erectile dysfunction, varicocele, wound, ankle fracture, cellulitis, benign prostatic hyperplasia, urinary tract obstruction, fatigue, depression, insomnia, ex-tobacco user, weight decreased, actinic keratosis, rosacea, urticaria, drug hypersensitivity (to iodine, sulfa and penicillin; intolerance to nonsteroidal anti-inflammatory drugs [NSAIDS]). The subject does not abuse alcohol or drugs.

Concomitant medications were clonazepam, diltiazem, gabapentin, hydrochlorothiazide, sertraline, tamsulosin, nabumetone, butalbital/acetaminophen/caffeine, hydrocodone, acetaminophen, loperamide, simeticone, testosterone, trazodone, testosterone cypionate, tadalafil, pramipexole, potassium chloride, hydrocodone/paracetamol, and hyoscyamine.

The subject received the first dose of atorvastatin on 23 March same year* and the first dose of evolocumab on 25 April [redacted]. Approximately 5 months later, on 13 September same year*, the subject crashed his car into a guardrail while driving. The subject did not know if he fell asleep or lost consciousness; he did not feel lightheaded or dizzy or have chest pain or shortness of breath. The subject reported that he had a similar accident the previous year, when he either fell asleep or lost consciousness.

The subject was taken to the emergency room, complaining of neck pain and right shoulder pain and was found to have sinus bradycardia. He was mildly hypertensive and had borderline bradycardia with a heart rate around 60 beats per minute (bpm). An electrocardiogram showed QTc at 448 msec with a possible U wave. The subject denied headaches, chest pain, shortness of breath, or abdominal pain. He had paresthesias in the right arm and stated that the pain was significantly worse with any type of movement of the shoulder.

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The subject was admitted to telemetry on the same day for syncope. Vital signs on admission showed a body temperature of 36.6°C, heart rate 58 bpm, respiratory rate 18/minute, blood pressure 166/84 mmHg, and oxygen saturation 98% on room air. Physical examination on admission revealed neck with both midline and bilateral paraspinal tenderness onpalpation of the cervical region. Heart rate was regular, lungs were clear to auscultation bilaterally, without wheezes, rales or rhonchi. Extremities examination was significant for the right shoulder, as the subject was guarding his arm and holding it in flexion. Neurological examination showed that cranial nerves 2 through 12 were intact; motor was symmetric throughout with the exception of some weakness in the right arm, secondary to guarding the right shoulder injury; sensation was also intact. Intermittent dizziness was noted. Computerized tomogram (CT) scan of the head showed no acute trauma; CT scan of the spine showed no evidence of acute cervical spine pathology, status post C4-C5 and C6-C7 fusion. Osteoarthritic changes were noted. Radiograph of the shoulder showed internal fixation pins within the proximal humerus in the area of the greater tuberosity; there was an area of spurring off the lateral margin of the acromion; and no evidence of bony fractures and no evidence suggesting an anterior capsule separation or dislocation. The subject was put under observation on telemetry for more than 24 hours without having any episodes of bradyarrhythmias, tachyarrhythmias, or significant pauses, having rare premature atrial contraction and premature ventricular contraction. The next day, 14 September same year*, the subject's vital signs showed a pulse rate of 65 bpm, respiratory rate 14/minute, blood pressure 121/65 mmHg, and oxygen saturation 93% on room air. Orthostatic vital signs were negative and an electroencephalogram was also negative. Treatment medications included vancomycin. The subject underwent placement of an implanted loop recorder without complications. Sensitive setting showed 0.035 mV, ventricular tachycardia detected 16 beats at 176 bpm; fast VT detected 30/40 beats at 231 bpm; bradycardia was detected at 30 bpm for four beats, asystole for 3 seconds. The event syncope was reported as resolved on 13 September same year*, and the subject was discharged from the hospital on the next day, 14 September same year*. On 19 September same year*, the subject underwent right shoulder surgery. The loop recorder was negative for events at last check on 20 September same year*.

The subject's last dose of evolocumab prior to the event was on 10 September same year*. Both atorvastatin and evolocumab were continued. The subject's last dose of evolocumab in the study was on 28 March one year after* and the last dose of atorvastatin in the study was on 25 April one year after*. The investigator reported that there was no reasonable possibility that the event of syncope was related to evolocumab. The subject completed the study on 25 April one year after*.

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Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 80 mg, ezetimibe 10 mg)
Report: Migraine with aura

Subject [redacted] was a 29-year-old white woman participating in Study 20110109 who developed migraine with aura (reported term: worsening of migraine with aura [differential diagnosis - transient ischemic attack]). The subject's medical history included hypercholesterolemia, hyperlipidemia, nicotine dependence, tobacco user (5 cigarettes per day), allergy to arthropod bite, migraine, and familial hyperlipidemia. The subject had a family history of migraine.

Previous treatment for hypercholesterolemia was rosuvastatin. The subject was not taking any concomitant medications prior to the event.

The subject received the first dose of atorvastatin and ezetimibe on 14 May same year* and first dose of evolocumab on 03 July [redacted]. Approximately 8 months after the first dose of evolocumab, on 13 March one year after*, the subject presented with loss of visual field of the right eye; right-sided hemianopsia; paresthesia and dysesthesia on the acral parts of the right hand marching to the cranial side up to the whole right upper limb, right half of face, whole tongue, and hard palate resulting in unintelligible speech. The subject was hospitalized on the same day. The symptoms gradually resolved and the subject reported bitemporal pulse headache (2/10 intensity) with nausea. The subject was conscious, oriented, collaborating, and with no speech disorders. Motility of eye globes was not impaired; eye globes moved up to utmost positions; nystagmus was not present; and pupils were equal. The neurological examination was normal. Laboratory tests performed on 13 March one year after* were unremarkable. On 14 March one year after*, the computerized tomography (CT) of brain, CT angiography of brain, electroencephalogram, and transcranial ultrasound were normal. The transcranial color-coded sonography examination of right-left shunt did not show the right-left shunt. On 15 March one year after*, the magnetic resonance imaging of brain without contrast agent was normal; however; hyperplastic adenoid vegetation in nasopharynx was seen. Cardiac and pulmonary functions were permanently controlled and sinus rhythm was permanently recorded. Migraine with aura and transient ischemic attack in the area supplied by the left medial cerebral artery was considered as diagnosis. The subject was treated with acetylsalicylic acid. The symptoms were relieved; cephalea, nausea, photo- and phonophobia improved. During hospitalization, there was no relapse and the subject was released in a stable condition on 15 March one year after* with

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recommendations for permanent anti-platelet treatment with acetylsalicylic acid and cessation of smoking. On 28 March one year after*, during the follow-up visit, Holter monitoring showed normal sinus rhythm during the episode of vertigo.

The subject's last dose of evolocumab, atorvastatin, and ezetimibe prior to the event was on 13 March one year after*. Evolocumab, atorvastatin, and ezetimibe were continued. The subject's last dose of evolocumab in the study was on 04 June one year after* and the last dose of atorvastatin and ezetimibe in the study was on 02 July one year after*.

The investigator reported that there was no reasonable possibility that the event of migraine with aura was related to evolocumab. The subject completed the study on 02 July one year after*.

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Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 10 mg)
Report: Angina pectoris, hypomagnesemia, palpitations, ventricular extrasystoles

Subject [redacted] was a 49-year-old white woman participating in Study 20110109 who developed angina pectoris (reported term: cardiac chest pain), hypomagnesemia, palpitations, and ventricular extrasystoles (reported term: premature ventricular contractions). The subject's medical history included hypercholesterolemia, hypertension, family history of premature coronary heart disease, asthma, seasonal allergy, environmental allergy, rash, acne, migraine, anxiety, foot fracture, female sterilisation, and cholecystectomy.

The subject had no previous treatment for hypercholesterolemia. Concomitant medications included fluorine/xylitol, hydroxyzine, calcium carbonate, and multivitamins.

The subject received the first dose of atorvastatin on 01 February same year*, and the first dose of evolocumab on 07 March [redacted]. Approximately 6 months later, on 29 September same year*, the subject developed palpitations, chest pain, premature ventricular contractions (PVCs), and hypomagnesemia. Two days later, on 01 October same year*, the subject went to the emergency room with a 3-day history of irregular heartbeat and palpitations that were associated with some mild chest pain in the midsternal area. The subject also had mild dizziness and nausea. Upon admission, the subject reported that she had consumed alcohol which made the palpitations worse. The subject was placed on continuous cardiac monitoring. An electrocardiogram (ECG) was performed (01 October same year*) and showed sinus rhythm with occasional PVCs that was otherwise normal and a heart rate of 72 beats per minute. Laboratory data included magnesium 1.7 mg/dL, white blood cell count 96 x 10^3/µL, hemoglobin 13.7 g/dL, hematocrit 40.3%, platelet count 236 x 10^3/µL, international normalized ratio 1, sodium 136 mmol/L, potassium 3.3 mmol/L, chloride 99 mmol/L, glucose 83 mg/dL, blood urea 13 mg/dL, creatinine 0.58 mg/dL, calcium 8.9 mg/dL, troponin T 0.01 ng/mL, alkaline phosphatase 53 U/L, aspartate aminotransferase 21 U/L, alanine aminotransferase 25 U/L, and total bilirubin 0.3 mg/dL. Magnesium was 2.1 mg/dL at study baseline on 07 March same year*. On 02 October same year*, an echocardiogram was performed that did not show evidence of intracardiac mass, thrombus, or pericardial effusion and showed normal left ventricular systolic function; an ejection fraction of 60-65%; trace aortic regurgitation, and mild mitral and tricuspid regurgitation. A radiograph showed mild pleural thickening of the right lung and no evidence of acute lung disease. On 03 October same year*, a stress test was performed and showed non-ischemic findings in the electrocardiographic portion of the nuclear stress test, PVCs at rest, and a normal blood pressure response. A single photon

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emission computerized tomography was performed and showed no evidence of reversible ischemia. Treatment for the events included metoprolol, pravastatin, acetylsalicylic acid, magnesium, betamethasone/clotrimazole, phenazopyridine, and valacyclovir. The events angina pectoris, palpitations, and ventricular extrasystoles were reported to have resolved on 03 October same year* and the subject was discharged from the hospital. On 19 October same year*, the subject's magnesium value was 2.1 mg/dL and the event of hypomagnesemia was reported as resolved.

The subject's last dose of evolocumab prior to the events was on 16 September same year*. Evolocumab was continued. The subject received the last dose of evolocumab and atorvastatin in the study on 11 February one year after*. Magnesium remained normal at 2.1 mg/dL at end of study visit performed on 15 April one year after*.

The investigator reported that there was no reasonable possibility that the events of angina pectoris, hypomagnesemia, palpitations, and ventricular extrasystoles were related to evolocumab.

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Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 80 mg)
Report: Ovarian cyst

Subject [redacted] was a 46-year-old black woman participating in Study 20110109 who developed an ovarian cyst (reported term: left ovarian cyst [benign]). The subject's medical history included hypercholesterolemia, migraine, arthralgia, back pain, knee operation, anxiety, depression, bipolar disorder, current cigarette user, uterine leiomyoma, and hysterectomy.

The subject did not receive any previous treatment for hypercholesterolemia. Concomitant medication included estradiol, ziprasidone, trazodone, hydrocodone, and ibuprofen.

The subject received the first dose of atorvastatin on 22 March same year*, and the first dose of evolocumab on 26 April [redacted]. Approximately 4 months later, on 05 September same year*, a vaginal ultrasound was performed as the subject had some discomfort in the left pelvic region; the ultrasound showed a benign left ovarian cyst. Approximately 1 month later, on 05 October same year*, the subject was hospitalized and she underwent removal of the left ovarian cyst. Treatment medication included acetaminophen with codeine. The event resolved on 05 October same year* and the subject was discharged from the hospital on 09 October same year*.

The subject's last dose of evolocumab prior to the event was on 14 September same year*. Evolocumab and atorvastatin were temporarily withheld and restarted. The subject received the last dose of evolocumab and atorvastatin in the study on 25 March one year after*.

The investigator reported that there was no reasonable possibility that the event of ovarian cyst was related to evolocumab or atorvastatin. Estradiol was reported as a co-suspect medication. The subject completed the study on 22 April one year after*.

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Subject No: [redacted]
Treatment: Placebo SC QM (plus diet)
Report: Increased hepatic enzyme

Subject [redacted] was a 47-year-old black (African American) man participating in Study 20110109 who developed increased hepatic enzyme (reported term: markedly elevated liver enzyme). The subject's medical history included hypercholesterolemia, abnormal liver function test, fatigue, decreased appetite, diarrhea, exposure to chemical pollution (asbestos exposure), current cigarette use, drug abuse (use of crack cocaine, marijuana, phencyclidine), and possible heterosexual intercourse with human immunodeficiency virus (HIV) positive female (last HIV test in five years ago* negative). The subject did not have a history of hypersensitivity-type reactions, recent alcohol abuse or intravenous drugs, recent hospitalizations or significant illnesses, blood transfusions, prescription medicines, herbal or dietary supplements, plants, or mushrooms.

The subject did not receive any previous treatment for hypercholesterolemia and was not receiving any concomitant medications at the time of the event.

At screening, on 19 March same year*, laboratory tests showed direct bilirubin of 0.2 mg/dL, alanine aminotransferase (ALT) of 20 U/L and aspartate aminotransferase (AST) of 30 U/L. The subject received the first dose of placebo on 01 May [redacted]. Approximately 5 months later, on 16 October same year*, laboratory tests showed increased hepatic enzyme with ALT of 198 U/L, AST of 496 U/L, alkaline phosphatase 110 U/L, and bilirubin of 0.5 mg/dL. The investigator contacted the subject who reported feeling fine, with good appetite, no acute illness, and no fever. The subject had not received any new prescription medications, was not taking over-the-counter medications (including Tylenol), herbal supplements, alcohol or illicit drugs. The subject reported that he had not traveled recently and denied history of HIV. The subject had no previous history of clinical hepatitis, jaundice, or gallbladder disease. However, the subject reported that in eleven years ago*, he was not allowed to donate plasma due to an abnormal liver test and no further information was provided. Three days later, on 19 October same year*, the subject was reported to be afebrile with anicteric sclera; heart and lungs examination was clear; abdominal examination did not reveal tenderness, ascites, or hepatosplenomegaly. On the same date, 19 October same year*, laboratory test showed improved liver enzyme levels with direct bilirubin of 0.2 mg/dL, ALT of 107 U/L, and AST of 86 U/L. Completed blood cell count and differential count performed on 16 October same year* and 19 October same year* showed normal white counts and no eosinophilia. On 25 October same year*, the subject underwent an ultrasound of abdomen which

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revealed minimal heterogeneity of hepatic echotexture with nonspecific appearance. The ultrasound report stated that though the findings were most commonly seen with low-grade steatosis, they were to be correlated for appropriate risk factors. On 25 October same year*, hepatitis B (HB) serologic test was negative for HB core (HBc) antibody (AB) Immunoglobulin M (IgM), HB surface antigen (HBsAg), and HBc total. Serologic test for hepatitis A virus (HAV) was negative for HAV IgM and positive for HAV total (detection 3 to 6 months post infection). The gamma glutamyltransferase level on the same date was 176 U/L. Additional laboratory tests on 25 October same year* showed anti-smooth muscle AB negative; IgG of 900 mg/dL; haptoglobin of 194 mg/dL; antinuclear antibody negative; creatine phosphokinase and lactate dehydrogenase were within normal limits. The subject had no prior history of acute HAV infection or vaccine, and no evidence of acute Hepatitis A or B as per the report. On the same day, 25 October same year*, laboratory test revealed normal liver enzyme levels with direct bilirubin of <0.1 mg/dL, ALT of 30 U/L, and AST of 22 U/L, and the event increased hepatic enzyme was considered resolved without treatment or intervention. On 13 November same year*, on a scheduled visit, the subject was clinically stable and feeling well. Laboratory testing performed on the same date (13 November same year*) for hepatitis C and HIV 1+2 antibodies were reported to be nonreactive.

The subject's last dose of placebo prior to the event was 16 October same year*. Placebo was continued and the subject received the last dose of placebo in the study on 02 April one year after*.

The investigator reported there was no reasonable possibility that the event increased liver enzyme was related to placebo. The subject completed the study on 01 May one year after*.

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