Subject No: [redacted]
Treatment: Parent study and regimen: Study 20110109, Placebo SC QM Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Invasive papillary breast carcinoma

Subject [redacted] was a 62-year-old white woman participating in Study 20120138 who developed invasive papillary breast carcinoma (reported term: micropapilar invasive breast carcinoma right side). The subject's medical history included appendectomy, eyelid ptosis, dyslipidemia, mixed hyperlipidemia, and hypertension. The subject`s father had lung cancer. Concomitant medications included betaxolol, trimecaine and a combination of amiloride and hydrochlorothiazide. Previous and ongoing treatment for hyperlipidemia included rosuvastatin.

The subject received placebo in the parent study (Study 20110109) from 31 May one year ago* to 30 May same year*. She received the first dose of evolocumab in Study 20120138 on 18 September [redacted].

On 23 September same year*, ultrasound revealed a 13-mm irregular hyperechogenic formation behind the areola of the right breast with normal lymph nodes. On 30 September same year*, a mammogram suggested invasive breast cancer. Needle biopsy revealed samples of mammary gland, cancer consisting of small papillary structures, with proliferative activity, positive for estrogen and progesterone receptors, and with positive membrane expression of c-erbB-2. The results suggested micropapillary invasive cancer of the mammary gland. No suspected metastases were found. Biopsy of sentinel lymph nodes showed invasive micro-papillary breast cancer grade 3. On 09 October same year*, a partial mastectomy was performed and the sentinel node biopsy was repeated, which revealed invasive ductal carcinoma with tubular admixture (20% max) and deposit of suspect micro-papillary cancer lymphoangio invasion.
The event was reported as resolved on 09 October same year*. Evolocumab was discontinued due to the event.

The subject's last dose of evolocumab prior to the event was on 18 September same year*, which was also her last and only dose in the study. As of the data cutoff date of [redacted], the subject was continuing in the study.

The investigator reported that there was a reasonable possibility that the event of invasive papillary breast carcinoma was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110109, Evolocumab SC QM 420 mg Year 1: Standard of Care
Report: Radiation gastroenteritis

Subject [redacted] was a 62-year-old white woman participating in Study 20120138 who developed radiation gastroenteritis (reported term: postradiation colitis). The subject's medical history included hyperlipidemia, goiter, thyroidectomy, uterine cancer (since November one year ago*), type 2 diabetes mellitus, hypertension, asthma, depression, cervical conization (twice), and resection of benign tumors in the breast. Concomitant medications included hydrochlorothiazide, losartan, isradipine, metformin, levothyroxine, loperamide, sertraline, and trazodone. Previous and ongoing treatment for hyperlipidemia included atorvastatin.

The subject received evolocumab in the parent study from 15 June one year ago* to 14 May same year*. She enrolled in Study 20120138 on 05 November [redacted] and was randomized to the standard of care arm.

Approximately 1.5 months after the Week 0 visit, on 19 November same year*, the subject was hospitalized due to abdominal pain and suspected postradiation enterocolitis. The subject had received unspecified chemotherapy, radiation, and brachytherapy until February same year* as treatment for uterine cancer. Physical examination revealed tenderness in the right and left lower abdomen. Peristaltis was present, and the liver and spleen were not enlarged. Abdominal ultrasonography showed diffuse hepatic steatosis. The liver was mildly enlarged, and the gallbladder had a normal configuration but a small amount of sludge could not be excluded. The subject had pancreatic lipomatosis but otherwise normal findings in the intra-abdominal organs, including the flow of the hepatic portal vein.

Laboratory tests from 20 November same year* did not disclose any relevant abnormality besides a slightly elevated C-reactive protein at 0.9 mg/L.

On 21 November same year*, a colonoscopy showed incomplete examination, with multiple angiodysplasia corresponding to radiation colitis and adhesions in the lower pelvis. On 22 November same year*, a barium enema was normal. Passage of contrast through the gastrointestinal tract was unobstructed. During the hospitalization the subject received

*新薬承認情報提供時に置き換え

iomeprol, metformin, losartan, atorvastatin, levothyroxine, sertraline, and trazodone. The subject was discharged from the hospital on 23 November same year*. On 27 November same year*, the subject had a consultation with gastroenterologist and was diagnosed with gastroenteritis and colitis due to radiation; the subject was treated with mesalazine. The event of radiation gastroenteritis was ongoing as of data cutoff date of [redacted].

The subject's last dose of evolocumab prior to the event was on 14 May same year* (during the parent study; also the last documented in-clinic dose). As of the data cutoff date of [redacted], standard of care treatment was continued and the subject continued in the study.

The investigator reported that there was not a reasonable possibility that the event of radiation gastroenteritis was related to study conduct.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110109, Evolocumab SC QM 420 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Intraductal proliferative breast lesion

Subject [redacted] was a 68-year-old white woman participating in Study 20120138 who developed an intraductal proliferative breast lesion (reported term: ductal carcinoma in situ left breast). The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, intervertebral disc protrusion, and depression. Concomitant medication included bendroflumethiazide with potassium, venlafaxine, furosemide, and fish oil/tocopherol. Previous and ongoing treatment for hyperlipidemia included simvastatin.

The subject received evolocumab in the parent study from 07 May one year ago* to 08 April same year*. She received the first dose of evolocumab in Study 20120138 on 23 September [redacted].

Approximately 4 months after the first dose of evolocumab in Study 20120138, on 15 January one year after*, the subject was diagnosed with an intraductal proliferative breast lesion. Mammography results showed a left breast ductal carcinoma in situ. On 07 February one year after*, the subject underwent an outpatient lumpectomy. Prophylactic radiation treatment was planned.

On 07 February one year after*, the event intraductal proliferative breast lesion was reported as resolved.

The subject's last dose of evolocumab prior to the event was on 16 December same year*. The subject was continuing home dosing as of the data cutoff date of [redacted] and the last in-clinic dose was documented on 16 December same year*. Evolocumab was continued and the subject continued in the study.

The investigator reported that there was not a reasonable possibility that the event of intraductal proliferative breast lesion was related to evolocumab or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110109, Placebo SC QM Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Allergy to arthropod sting

Subject [redacted] was a 73-year-old white man participating in Study 20120138 who developed allergy to an arthropod sting. The subject's medical history included primary hyperlipidemia and mixed dyslipidemia. Previous treatment for hyperlipidemia was atorvastatin. No other concomitant medications were reported.

The subject received evolocumab in the parent study from 22 May one year ago* to 22 April same year*. He received the first dose of evolocumab in Study 20120138 on 23 August [redacted]. On 07 November same year* the subject was hospitalized for anaphylactic reaction to a bee sting and was treated with epinephrine, prednisolone, cetirizine, and hydrocortisone. He was observed for 24 hours. No signs of arrhythmia were detected by telemetry, and laboratory test results were not reported. The subject had not previously experienced the event and was referred to allergy testing and provided with an epi-pen for safety reasons. The subject was released from the hospital the following day, and the event was reported as resolved. No co-suspect medicated was identified by the investigator.

The subject's last dose of evolocumab prior to the event was on 18 October same year*. Evolocumab was continued, and the subject continued in the study. As of the data cutoff date of [redacted], the subject's last in-clinic dose of evolocumab was on 15 November same year* but home dosing was continued.

The investigator reported that there was not a reasonable possibility that the event of allergy to arthropod sting was related to evolocumab or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110109, Evolocumab SC QM 420 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Rectocele

Subject [redacted] was a 47-year-old white woman participating in Study 20120138 who developed rectocele. The subjects medical history included hypercholesterolemia, uterine fibroid, ectopic pregnancy, benign ovarian cyst, osteoporosis, rectocele, obesity, gastric bypass surgery, hypertension, allergy to arthropod bite, and hysterectomy. Concomitant medication included paracetamol, ibuprofen, azithromycin, potassium, enalapril, raloxifene, amlodipine, and cetirizine. Previous and ongoing treatment for hypercholesterolemia included atorvastatin and simvastatin.

The subject received evolocumab in the parent study from 23 May one year ago* to 30 April same year*. She received the first dose of evolocumab in Study 20120138 on 29 August [redacted]. On 15 April same year* the subject was diagnosed with rectocele. On 04 December same year*, the subject was hospitalized and underwent rectocele surgery due to worsening symptoms. Surgery was uneventful. Treatment medications after the onset of rectocele included estradiol, tinzaparin, and naproxen. The event was reported as resolved on 05 December same year* and the subject was discharged from the hospital.

Evolocumab was continued, and the subject continued in the study. As of the data cutoff date of [redacted], the subject's last in-clinic dose of evolocumab was documented on 18 November same year*, but home dosing continued.

The investigator reported that there was not a reasonable possibility that the event of rectocele (surgery) was related to evolocumab or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110109, Placebo SC QM Year 1: Evolocumab SC 140 mg Q2W + Standard of care
Report: Angina pectoris

Subject [redacted] was a 57-year-old white woman participating in Study 20120138 who had angina pectoris. The subject's medical history included dyslipidemia, ischemic heart disease, coronary artery bypass, percutaneous coronary intervention, and hypertension. Concomitant medications included clopidogrel, acetylsalicylic acid, ramipril, bisoprolol, and nitrate patch. Previous treatment for dyslipidemia included atorvastatin and ezetimibe. Ongoing treatment included atorvastatin.

The subject received placebo in the parent study from 25 July one year ago* to 26 June same year*. She received the first dose of evolocumab in Study 20120138 on 21 October [redacted].

Approximately 3 month after the first dose, on 22 January one year after*, the subject developed worsened hypertension. Subsequently, on 23 January one year after*, the subject was hospitalized. On 30 January one year after*, the subject's Holter monitor did not show ST depression or malignant arrhythmias. On 02 February one year after*, the subject's ambulatory blood pressure monitor showed normal blood pressure. On 06 February one year after*, the subject's echocardiography did not show any wall motion disorder. On 10 February one year after*, the subject's treadmill stress test was negative.

The investigator reported that the cause of the hypertension was angina pectoris, and computed tomography ruled out the possibility of further intervention. The event term was updated from hypertensive reaction to angina pectoris. The subject's treatment medications after the onset of the event included carvedilol, ivabradine, valsartan, trimetazidine, spironolactone, and levothyroxine. The outcome of the event was reported as resolved on 12 February one year after* and the subject was discharged from the hospital on the same day. Evolocumab was continued and the subject continued the study.

The subject's last dose of evolocumab prior to the event was on 14 January one year after*. The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose was documented on 15 January one year after*.

The investigator reported that there was not a reasonable possibility that the event of angina pectoris was related to evolocumab or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110109, Evolocumab SC QM 420 mg Year 1: Evolocumab SC 140 mg Q2W + Standard of care
Report: Vertigo, Laboratory test abnormal, Urinary tract infection

Subject [redacted] was a 58-year-old white woman participating in Study 20120138 who had vertigo, laboratory abnormalities, and urinary tract infection. The subject's medical history included primary hyperlipidemia and mixed dyslipidemia, obesity, hypertension, current smoking. Concomitant medications included alprazolam, piroxicam, nimesulide, selegiline, amantadine, atorvastatin, tramadol, valsartan/hydrochlorothiazide, indacaterol, tiotropium bromide, levothyroxine, vinpocetine, and clopidogrel. Previous treatment for hyperlipidemia included atorvastatin.

The subject received evolocumab in the parent study from 23 May one year ago* to 24 April same year*. She received the first dose of evolocumab in Study 20120138 on 11 December [redacted].

Approximately 2.5 months after the first dose, on 27 March one year after*, the subject had vertigo and was hospitalized on the same day. On 28 March one year after*, laboratory tests showed aspartate aminotransferase (AST) of 63 U/L (normal <44 UI/L), alanine aminotransferase (ALT) of 75 U/L (normal< 50UI/L), alkaline phosphatase (ALP) of 135 U/L normal< 105 UI/L),and gamma-glutamyltransferase of 93 U/L (normal < 70 UI/L), c-reactive protein (CRP) of 11.62 mg/l, and neutrophils of 8.71 g/L. The investigator confirmed that the subject did not have predisposing risk factors for liver disease such as alcohol consumption, history of diabetes, or gastric bypass surgery. Previous AST was 46 UI/L and ALT was 43 UI/L.

On 29 March one year after*, laboratory tests showed neutrophils of 14.20 g/L and CRP of 25.28 mg/L. On the same day, the subject was diagnosed with a urinary tract infection. Laboratory testing also demonstrated subclinical hypothyroidism. Treatments reported after the onset of the event included amoxicillin with clavulanic acid, valsartan and hydrochlorothiazide, nebivolol, piracetam, trimetazidine, and famotidine.

The outcome of the event of vertigo was reported as resolved on 04 April one year after* and the subject was discharged from the hospital on the same day. Evolocumab was continued and the subject continued the study. The outcome of the events of non-alcoholic steatohepatitis and urinary tract infections were ongoing.

*新薬承認情報提供時に置き換え

The subject's last dose of evolocumab prior to the events was not known. The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose was documented on 05 March one year after*.

The investigator reported that there was not a reasonable possibility that the events of vertigo, laboratory abnormalities, and urinary tract infection were related to evolocumab, or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110109, Evolocumab SC QM 420 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Angina pectoris

Subject [redacted] was a 69-year-old white woman participating in Study 20120138 who developed angina pectoris.

The subject's medical history included hyperlipidemia, hypertension, atherosclerosis, myocardial infarction, cerebrovascular disease, type 2 diabetes and gastroesophageal reflux .

Concomitant medication included cardevilol, clopidogrel, valsartan, pantoprazole, glyceryl trinitrate, nifedipine, amlodipine, and piracetam.

Previous and ongoing treatment for hyperlipidemia included atorvastatin and ezetimibe.

The subject received evolocumab in the parent study from 26 January one year ago* to 28 January same year*. She received the first dose of evolocumab in Study 20120138 on 08 October [redacted].

Approximately 2 months after the first dose of evolocumab, the subject developed angina pectoris, and was hospitalized on 27 November same year*. A chest radiograph performed on the day of admission revealed no clinically significant findings. Treatments for the event included administration of single doses of inhaled glyceryl trinitrate, oral clopidogrel, and intravenous heparin and fentanyl. On 27 November same year*, blood creatine phosphokinase was 94 IU/L, blood lactate dehydrogenase was 6.03 μkat/L, and troponin T was 0.02 μg/L. On 28 November same year*, blood creatine phosphokinase was 73 IU/L, blood lactate dehydrogenase was 388 IU/L, and troponin T was 0.018 ng/mL.

The last dose of study medication prior to the event was on 05 November same year*. The event angina pectoris was reported as resolved on 27 November same year* and the subject was discharged from the hospital on 28 November same year*. The subject continued in the study and received the next dose of study drug on 03 December same year*. The investigator reported that there was no reasonable possibility that the event angina pectoris was related to investigational product or to the device.

Evolocumab was continued and the subject continued in the study. As of the data cutoff date of [redacted] the subject was continuing home dosing, and the last in-clinic dose was documented on 06 January one year after*.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110109, Evolocumab SC QM 420 mg Year 1: Standard of care
Report: Malignant lung neoplasm

Subject [redacted] was a 66-year-old woman of mixed race participating in Study 20120138 who developed a malignant lung neoplasm (reported term: left lung cancer). The subject's medical history included hyperlipidemia, hypercholesterolemia, mixed dyslipidemia, osteoarthritis, ischemic heart disease, hypertension, chronic obstructive pulmonary disease, and heavy smoking. Concomitant medications included: amlodipine, atenolol, isosorbide mononitrate, isosorbide dinitrate, paracetamol, acetylsalicylic acid, carbamazepine, atorvastatin, ezetimibe, tramadol, and losartan. Previous and ongoing treatment for hyperlipidemia included atorvastatin.

The subject received evolocumab in the parent study from 03 August one year ago* to 04 July same year*. The subject was randomized to the standard of care treatment arm in Study 20120138 on 21 November [redacted].

Approximately 3 weeks later on 15 December same year*, the subject was found to have pleural effusion and diagnosed with metastatic lung cancer. Three days later on 18 December same year* she was admitted to the hospital with dyspnea, progressive malaise, weight loss, pleuritic chest pain, and shortness of breath. A chest radiograph revealed a left lung pleural effusion and a computed tomography scan identified lymph, lung, and cerebral metastases. An extensive left mass-nodal complex was associated with primary bronchus carcinoma with complete encasement of the right upper lobe pulmonary artery, left pulmonary artery and branches, trachea, carina, and esophagus by the mass complex. A left brachiocephalic vein thrombus, extensive mediastinal lymphadenopathy, and hilar lymphadenopathy with sclerotic lesions were noted. The liver demonstrated multiple solid, rounded, and hypodense lesions suggestive of metastatic lesions. A left adrenal complex cystic lesion, a bilateral cervical lymphadenopathy, and an enlarged left supraclavicular lymph node were noted. The subject underwent 2 fine needle aspiration biopsies of the lung that confirmed small cell carcinoma of lung (OAT cell type) and squamous cell carcinoma with necrosis.

The subject was discharged to home 9 days after entering the hospital (27 December same year*). On 02 February one year after* the subject died due to metastatic lung cancer.

The subject's last dose of evolocumab was in the parent study (04 July same year*). As of the data cutoff date of [redacted], the subject continued in the study in the standard of care.

The investigator reported that there was not a reasonable possibility that the malignant lung neoplasm was related to the study conduct.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110109, Evolocumab SC QM 420 mg Year 1: Evolocumab SC 420 mg QM + Standard of care
Report: Cholelithiasis

Subject [redacted] was a 41-year-old mixed race woman participating in Study 20120138 who had cholelithiasis (reported term: worsening of gallstones). The subject's medical history included obesity, dyslipidemia, familial hypercholesterolemia (Type IIa hyperlipidemia), osteoarthritis, asthma, anxiety, gallstones and severe backache. Concomitant medications included combination of caffeine, codeine, meprobamate, combination of paracetamol and tramadol, omeprazole, sertranine, salbutamol, and alprazolam. Previous treatment for dyslipidemia included atorvastatin and ezetimibe.

The subject participated in the parent study (Study 20110109) from 03 August two years ago* to 01 August one year ago* and received the last dose of evolocumab in the parent study on 04 July one year ago*. The subject received the first dose of evolocumab in Study 20120138 on 29 January [redacted].

Before administration of the first dose of investigational product, on 26 January same year*, the subject experienced a severe backache and was treated with diclofenac injection and oral analgesics. Laboratory tests showed increased alanine aminotransferase (ALT) 428 U/L and aspartate aminotransferase (AST) 236 U/L which were possibly due to gallstones (baseline ALT was 16 and AST 15 U/L). This was confirmed by ultrasound of the abdomen conducted on 31 January same year*. As per the investigator, the etiological or predisposing risk factor associated with the event worsening of gallstones included gender (woman) and high body mass index. The investigator confirmed that the subject did not receive any previous treatment for gallstones.

On 13 February same year*, the subject was hospitalized and underwent elective laparoscopic cholecystectomy. Treatment medications included ibuprofen, and paracetamol. The outcome of the event worsening of gallstones was reported as resolved on 14 February same year* and the subject was discharged from the hospital on the same day.

*新薬承認情報提供時に置き換え

The subject's last dose of evolocumab prior to the events was on 29 January same year*. The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose was documented on 26 March same year*.

The investigator reported that there was not a reasonable possibility that the event worsening of gallstones was related to the investigational product or to the device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110109, Placebo SC QM Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Osteoarthritis

Subject [redacted] was a 69-year-old white man participating in Study 20120138 who developed osteoarthritis (reported term: severe left knee osteoarthritis). The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, osteoarthritis of the knees, benign prostatic hyperplasia, erectile dysfunction, medial epicondylitis of left elbow, hypertension, hyperglycemia, shortness of breath, right bundle branch block, cholecystectomy, inguinal hernia repair, left knee arthroscopy, appendectomy, tonsillectomy, colonoscopy, cardiac catheterization, and vasectomy. Concomitant medication included multivitamins, acetylsalicylic acid, benzonatate, diclofenac, histamine, and nystatin. Previous treatment for hyperlipidemia included atorvastatin.

The subject received placebo in the parent study from 18 April one year ago* to 20 March same year*. He received the first dose of evolocumab in Study 20120138 on 05 August [redacted]. Approximately 3 months after the first dose, on 13 November same year*, the subject developed severe left knee osteoarthritis and was admitted to the hospital on the same day. The subject underwent total left knee replacement with induction of general anesthesia; cefazolin was administered as a pre-operative antibiotic and rivaroxaban was given for deep vein thrombosis prophylaxis. The subject tolerated the procedure well without complications and was transferred from the operating room to the recovery room in good condition.

Additional treatment included a combination of oxycodone and paracetamol, magnesium, combination of docusate and senna alexandria, and physical therapy. The outcome of the event was reported as resolving, and the subject was discharged from the hospital on 15 November same year*. The subject's last dose of the investigational product prior to the event was on 08 November same year*. As of the data cutoff date, [redacted], home dosing of evolocumab was reported as continuing; no dose more recent than November same year* was documented.

The investigator reported that there was not a reasonable possibility that the event severe left knee osteoarthritis was related to the investigational product or the device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110109, Evolocumab SC QM 420 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Urinary incontinence

Subject [redacted] was a 60-year-old white woman participating in Study 20120138 who developed urinary incontinence. The subject's medical history included hyperlipidemia. Concomitant medication included cetirizine. Previous and ongoing treatment for hyperlipidemia included atorvastatin.

The subject received evolocumab in the parent study from 26 January one year ago* to 27 December one year ago*. She received the first dose of evolocumab in Study 20120138 on 20 May [redacted]. Atorvastatin was stopped on 30 June same year*. Approximately 1.5 months after the first dose, on 02 July same year*, the subject was hospitalized for increasing problems with urinary incontinence. Examination showed uterine and bladder prolapses with a questionable polyp. The subject had a positive cough standing stress test with her prolapse reduced and with a full bladder. She had an atypical cystocele and her cervix was quite deviated to the left side and scarred. Supracervical hysterectomy, anterior sacrocolpopexy, monarc transobturator midurethral sling, and cystoscopy with suprapubic tube placement were performed. Additional treatment included cefazolin. On 04 July same year*, the event was reported as resolved and the subject was discharged from the hospital. The subject's last dose of evolocumab prior to the event was on 12 June same year*. As of the data cutoff date of [redacted], the subject's last dose of evolocumab was on 27 March one year after*. Evolocumab was continued and the subject continued in the study.

The investigator reported that there was not a reasonable possibility that the event of urinary incontinence was related to evolocumab or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110109, Placebo SC QM Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Contrast media allergy

Subject [redacted] was a 55-year-old white woman participating in Study 20120138, who developed a contrast media allergy (reported term: allergic reaction to intravenous dye injection). The subject's medical history included hyperlipidemia, mixed dyslipidemia, seasonal allergies, osteoporosis, chronic low back pain, and food allergy. Concomitant medications included vitamin D, and denosumab. Previous and ongoing treatment for hyperlipidemia and mixed dyslipidemia included atorvastatin.

The subject received placebo in the parent study from 08 February one year ago* to 23 January same year*. She received the first dose of evolocumab in Study 20120138 on 24 May [redacted]. Approximately 3 weeks later, on 13 June same year*, the subject underwent an elective magnetic resonance imaging study in order to rule out disc disease, and intravenous (IV) dye injection was administered. The subject started "feeling strange" within minutes after administration of the dye injection. The subject experienced chest pressure and loss of vision and was transferred to emergency services. The investigator reported that the subject had eaten shellfish/shrimp prior to the onset of the event, which made her "chest tight". Treatment included IV diphenhydramine and further unspecified medications. The subject had no previous episodes similar to the event, and no previous reactions. The event of contrast media allergy was reported as resolved on 14 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 was on 06 June same year*. Evolocumab was continued. The subject was continuing home dosing as of the data cutoff date of [redacted] and the last in-clinic dose was documented on 07 November same year*.

The investigator reported that there was not a reasonable possibility that the event of contrast media allergy was related to evolocumab or the device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110109, Evolocumab SC QM 420 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Carotid artery disease

Subject [redacted] was a 68-year-old white woman participating in Study 20120138 who developed carotid artery disease. The subject's medical history included hyperlipidemia and overweight. Concomitant medications included metoprolol, acetylsalicylic acid, antacids, and calcium. Previous and ongoing treatment for hyperlipidemia included atorvastatin.

The subject received evolocumab in the parent study from 02 July one year ago* to 03 June same year*. She received the first dose of evolocumab in Study 20120138 on 08 July [redacted]. On the same day, during the initial evaluation and physical examination, it was noted that the subject had a left carotid bruit, confirmed as a left carotid stenosis by computed tomography angiography. The subject was hospitalized on 29 January one year after*, underwent a left carotid endarterectomy, and was hospitalized for about 24 hours. The event of carotid artery atherosclerosis was resolved on 30 January 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 on 21 January one year after*. As of the data cutoff date of [redacted], home dosing was reported to be continuing; no clinic doses were documented after the 21 January one year after* date.

The investigator reported that there was not a reasonable possibility that the event of carotid artery atherosclerosis was related to evolocumab or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110109, Evolocumab SC QM 420 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Asthma and Non-cardiac chest pain

Subject [redacted] was a 63-year-old white woman participating in Study 20120138 who developed non-cardiac chest pain and asthma (reported term: asthma exacerbation). The subject's medical history included hyperlipidemia, mixed dyslipidemia, asthma, gastroesophageal reflux disease, hypothyroidism, pneumonia, chronic obstructive pulmonary disease, depression, and anxiety disorder. Concomitant medications included levothyroxine, citalopram, calcium, potassium, multivitamins, docusate, cimicifuga racemosa extract, valeriana officinalis root, omeprazole, melatonin, hydrocodone, and naproxen. Previous treatment for hyperlipidemia (through 25 July same year*) included atorvastatin.

The subject received evolocumab in the parent study from 10 April one year ago* to 13 February same year*. She received the first dose of evolocumab in Study 20120138 on 29 April [redacted]. Approximately 7 months later, on 02 December same year*, the subject presented to the emergency room with symptoms of cough, chest pain, intermittent shortness of breath for 10 days, and was hospitalized for asthma exacerbation. The investigator confirmed that the asthma exacerbation was due to missing asthma medication (a combination of fluticasone and salmeterol) for a month. During hospitalization, the subject was diagnosed with pneumonia. Treatment after the onset of the events included salbutamol. The subject was restarted on a combination of fluticasone and salmeterol. The serious adverse events of chest pain and asthma exacerbation were reported as resolved on 04 December same year*, and the subject was discharged from the hospital on 07 December same year*.

The subject's last dose of evolocumab prior to the event was not available. Evolocumab was continued and the subject continued in the study. As of the data cutoff date of [redacted], home dosing was continuing and the last documented clinic dose was on 29 March one year after*.

The investigator reported that there was not a reasonable possibility that the events of asthma exacerbation and chest pain were related to evolocumab or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments Parent study and regimen: Study 20110109, Evolocumab SC QM 420 mg Year 1: Standard of Care
Report: Spinal hematoma

Subject [redacted] was a 59-year-old white man participating in the Study 20120138 and developed a spinal hematoma (reported term: cervical spine hematoma). The subject's medical history included dyslipidemia, recurrent cervical pain (since September one year ago* following a motor vehicle accident), osteoporosis, allergies, headaches, hemorrhoidectomy, gastroesophageal reflux disease, erectile dysfunction, insomnia, rhinoplasty, left meniscus repair, and osteoarthritis. Concomitant medications included lansoprazole, melatonin, montelukast, sildenafil, and trazodone. Previous and ongoing treatment for hypercholesterolemia or hyperlipidemia included fish oil.

The subject received evolocumab in the parent study (Study 20110109) from 24 April one year ago* to 23 April same year*. He was randomized to the standard of care arm in Study 20120138 on 20 May [redacted].

On 20 August same year*, the subject had an epidural injection for pain management without complications. Approximately 5 months after randomization, on 21 October same year*, the subject had a second epidural injection and within 2 hours had severe pain and loss of feeling and control of extremities. On the same day, the subject presented to the emergency room by ambulance. Magnetic resonance imaging was performed and confirmed a hematoma had formed as the result of blood vessel damaged during the epidural injection. The subject was observed in the neurology intensive care unit and then in the neurology unit. The hematoma resolved on its own without surgery. Additional treatment information was not provided.

The event of spinal hematoma was reported as resolved on 23 October same year* and the subject was discharged from the hospital on the same day.

As of the data cutoff date of [redacted], the subject was continuing in the study.

The investigator reported that there was not a reasonable possibility that the event cervical hematoma was related to study activity. Epidural injection was reported as co-suspect.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110109, Evolocumab SC 420 mg QM Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Spinal deformity

Subject [redacted] was a 63-year-old white man participating in Study 20120138 who was diagnosed with a spinal deformity (reported term: flat back syndrome status post L4-S1 fusion). The subject's medical history included arthritis, back surgery (thirty-eight years ago* and thirty-six years ago*) with long term acquired degenerative spondylolisthesis, lumbar spinal stenosis (starting in three years ago*), and lower back pain. Concomitant medication included naproxen, acetylsalicylic acid, oxycodone, and oxycocet. Previous treatment for hyperlipidemia included atorvastatin.

The subject received evolocumab in the parent study from 22 March one year ago* to 21 February same year*. He received the first dose of evolocumab in Study 20120138 on 11 June [redacted]. Approximately 9 months later, on 31 March one year after*, the subject underwent a lumbar laminectomy. The subject's pre and post-operative diagnosis included spinal stenosis of L3-L4, and flat back syndrome status post L4-S1 fusion. Treatment provided on 31 March one year after* included paracetamol, amlodipine, bisacodyl, cefazolin, ceftriaxone, diphenhydramine, enalapril, metoprolol, morphine, ondansetron, and coloxyl with senna. The outcome of the event was reported as resolving. On 04 April one year after* the subject was discharged to a rehabilitation facility.

The subject's last dose of evolocumab prior to the event was not known. The subject was continuing home dosing as of the data cutoff date of [redacted] and the last in-clinic dose was documented on 11 December same year*.

The investigator reported that there was not a reasonable possibility that the event of flat back syndrome status post L4-S1 fusion was related to evolocumab or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Parent study and regimen: 20110109, Evolocumab SC QM 420 mg Year 1: Standard of Care
Report: Breast cancer

Subject [redacted] was a 53-year-old white woman participating in Study 20120138 who was diagnosed with breast cancer. The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, hypertension, obesity, dyspepsia, benign breast neoplasm, benign tumor excision, hysterectomy, intestinal operation, allergy to codeine phosphate, cholecystectomy, and tobacco use. She had a history of breast cancer (ductal carcinoma in situ [DCIS]) diagnosed in eleven years ago*, followed by radiation therapy, left breast lumpectomy, and tamoxifen.

Concomitant medications included dexlansoprazole, torasemide, alprazolam, and combination of amlodipine and olmesartan. Previous and ongoing treatment for primary hyperlipidemia or mixed dyslipidemia included atorvastatin and ezetimibe.

The subject received evolocumab in the parent study (Study 20110109) from 08 August one year ago* to 11 July same year*, and was randomized to standard of care in Study 20120138 on 08 August [redacted].

During her participation in Study 20120138 the subject was diagnosed with a recurrence of breast cancer in the radiated breast. On 08 August same year*, a mammogram and an ultrasound revealed a 6 x 8 x 5 mm hypoechoic nodule at the 3 o'clock position 3 cm from the nipple. On 14 August same year*, an ultrasound-guided core biopsy was performed. Breast pathology report revealed moderately differentiated invasive ductal carcinoma. Ductal carcinoma in situ was also present, intermediate to high nuclear grade. The invasive carcinoma demonstrated negative staining for estrogen receptor (< 1% nuclear staining) and progesterone receptor (0% nuclear staining), while demonstrated a positive score for HER-2/neu with 3+ staining.

Further investigation with magnetic resonance imaging on 23 August same year* and with focal ultrasound on 30 August same year* revealed a suspect lymph node within the left axilla; metastatic infiltration could not be excluded. On 16 September same year*, the subject was hospitalized for left breast mastectomy and reconstruction. The event of breast cancer and the hospitalization remained ongoing at the time of this report.

*新薬承認情報提供時に置き換え

As of the data cutoff date of [redacted], the subject was continuing in Study 20120138 and was receiving standard of care.

The investigator reported that there was not a reasonable possibility that the event of breast cancer was related to any study activity/procedure.

Subject No: [redacted]
Treatment: Parent study and regimen: Study 20110114, Evolocumab SC QM 420 mg + Placebo PO QD Year 1: Standard of care only
Report: Breast cancer

Subject [redacted] was a 42-year-old Asian woman participating in Study 20120138 who was diagnosed with breast cancer (reported term: carcinoma right breast). The subject's medical history included hyperlipidemia, mixed dyslipidemia, congenital ventricular septal defect, systolic heart murmur, migraine headache, and gastroesophageal reflux disease. She did not have a history of cancer or a family history of breast cancer, radiation exposure, obesity, precocious puberty, delayed menopause, allergies, or consumption of alcohol or tobacco. Concomitant medications included ibuprofen, etonogestrel, and a combination of aluminum hydroxide, magnesium hydroxide and simethicone. No previous treatment for primary hyperlipidemia or mixed dyslipidemia was reported.

The subject received evolocumab and placebo in the parent study from 06 February same year* to 02 May same year*. She was randomized to standard of care in Study 20120138 on 27 June [redacted].

On the day of randomization, the subject complained of a 2-week history of right breast pain. No breast mass was palpated. On 17 July same year*, bilateral breast mammogram and ultrasound showed images consistent with a neoplastic lesion at 12 o'clock 3 cm from the nipple and an additional complex cyst in the right breast. A biopsy performed on 23 July same year* showed invasive carcinoma right breast grade 2, invasive ductal carcinoma, strongly estrogen receptor (ER) and progesterone receptor (PR) positive.

On 30 July same year*, a lymphoscintigraphy identified a right axillary lymph node and a right internal mammary sentinel lymph node. The subject underwent right breast lumpectomy and sentinel lymph node biopsy. Histology results showed tumor cells identified in 1 sentinel node and no evidence of malignancy in other 5 sentinel lymph nodes; right breast lesion showed multiple foci of grade 2 invasive ductal carcinoma (ranging from 28 mm to 2.2 mm) associated with multifocal intermediate to high-grade ductal carcinoma in situ (DCIS). Foci were suggestive of

*新薬承認情報提供時に置き換え

lymphovascular invasion (LVI); carcinoma was present at the inferior and superficial margin and very close to the medial margin, ER and PR positive and Her-2 negative.

On 12 August same year*, the subject underwent an elective re-excision of the right breast. Histological results of the right breast tissue sample showed a 7-mm residual invasive ductal carcinoma. The investigator reported that the subject did not need any further surgery; radiotherapy and hormone therapy were planned. On 05 September same year*, etonogestrel implant was removed, and 6 days later, on 11 September same year*, the subject started chemotherapy (3-weekly cycles) with fluorouracil, epirubicin, and cyclophosphamide, and also received adjunct prophylactic treatment with aprepitant, dexamethasone, pegfilgrastim, palonosetron, and metoclopramide. The investigator stated that radiotherapy would be considered after the completion of chemotherapy. Tamoxifen was started on 07 March one year after*.

The investigator reported that etiological or predisposing risk factors associated with the event of breast cancer included the use of etonogestrel implant.

As of the data cutoff date of [redacted], the event remained unresolved, and the subject was continuing in the study.

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

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110114, Placebo SC Q2W + Ezetimibe PO QD 10 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Myocardial infarction

Subject [redacted] was a 48-year-old white woman participating in Study 20120138 who experienced a fatal myocardial infarction. The subject's medical history included dyslipidemia with very high Lp(a) (219 nmol/L on 20 September same year* and 195 nmol/L on 11 December same year*), hypertension, depression, and smoking. The subject did not have any cardiac history or familiar history of premature coronary disease. Concomitant medication included hydrochlorothiazide, losartan, salbutamol, venlafaxine hydrochloride, and aripiprazole. Previous treatment for hyperlipidemia included ezetimibe.

The subject received placebo and ezetimibe in the parent study from 06 March same year* to 28 May same year*. She received the first dose of evolocumab in Study 20120138 on 17 June [redacted]. Approximately 6 months later, on 27 December same year*, the subject experienced a myocardial infarction with the outcome reported as fatal.

The subject's last dose of evolocumab prior to the event (and only dose) was on 17 June same year*.

The investigator reported that there was not a reasonable possibility that the fatal event of myocardial infarction may have been caused by investigational drug or device. According to the investigator, the etiological or predisposing factors associated with the event of myocardial infarction were cigarette smoking and hypertension.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110114, Placebo SC Q2W + Ezetimibe PO QD 10 mg Year 1: Standard of Care
Report: Dyspnea

Subject [redacted] was a 60-year-old white man participating in Study 20120138 who developed dyspnea (reported term: acute dyspnea).

The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, bronchitis, pneumonia, hypertension, ischemic heart disease, impaired fasting blood glucose, and smoking. The subject's family history revealed an early myocardial infarction in the subject's father.

Concomitant medications included olmesartan.

Previous and ongoing treatment for hyperlipidemia included atorvastatin and ezetimibe.

The subject received placebo and ezetimibe in the parent Study 20110114 from 27 March same year* to 20 June same year*. The subject was randomized into the standard of care arm of Study 20120138 on 30 September [redacted]

Approximately 28 weeks after randomization, on 20 January one year after*, the subject was hospitalized for acute dyspnea following a 1- to 2-day history of shortness of breath associated with intermittent chest tightness. On the same day, a cardiac workup, including an exercise stress test (Bruce protocol) and troponin measurement, was completed and all results were negative. The physician was of the opinion that the shortness of breath was unlikely due to cardiac involvement. Treatment medications reported after the onset of the event included rabeprazole, atorvastatin, a combination of fluticasone and salmeterol, and acetylsalicylic acid. The outcome of the event dyspnea was reported as resolving, and the subject was discharged from the hospital the following day. The investigator reported that there was not a reasonable possibility that the event dyspnea was related to study conduct.

As of the data cutoff date of [redacted], the subject continued in the study in the standard of care arm and the last visit was on 27 March one year after*.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110114, Placebo SC Q2W + Ezetimibe PO QD 10 mg Year 1: Evolocumab SC QM 420 mg + Standard of care
Report: Adenocarcinoma of colon

Subject [redacted] was a 78-year-old white woman participating in Study 20120138 who was diagnosed with adenocarcinoma of the colon (reported term: colon cancer, adenocarcinoma). The subject's medical history included hyperlipidemia, previous tobacco use and chronic obstructive pulmonary disease. Concomitant medication included budesonide, clopidogrel, calcium, ergocalciferol, ibuprofen, pantoprazole, paracetamol, tramadol, and furosemide. Previous and ongoing treatment for hyperlipidemia included ezetimibe.

The subject received placebo and ezetimibe in the parent study from 25 April same year* to 01 July same year*. The first dose of evolocumab in Study 20120138 was on 23 September [redacted]. Approximately 3 months after the first dose of investigational drug, on 16 December same year*, laboratory results revealed hemoglobin of 86 g/L, hematocrit of 28%, red blood cell (RBC) count of 3.5 x 10^6/mm^3, and red cell distribution width of 20.4%.

Colonoscopy and biopsy on 31 January one year after* revealed malignant tumor of the cecum. The subject was diagnosed with colon adenocarcinoma. Six days later, on 06 February one year after*, a computer tomography scan of the thorax and abdomen revealed a tumor of the cecum and no metastasis. A laparotomy and hemicolectomy were conducted 12 days later, on 18 February one year after*. The outcome of the event was reported as resolved on that date and the subject was discharged from the hospital on 21 February one year after*.

The investigator considered smoking a predisposing risk factor associated with the event. The date of the last dose of evolocumab before the diagnosis of colon adenocarcinoma was not known, and the last dose on study was reported to be administered on 07 January one year after* in clinic and home dosing was continued. As of the data cutoff date of [redacted] subject continued in the study.

The investigator reported that there was not a reasonable possibility that the event of colon adenocarcinoma was related to investigational drug or to the device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110114, Placebo SC Q2W + Ezetimibe PO QD 10 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Craniocerebral injury; Laceration; Radius fracture

Subject [redacted] was a 57-year-old white man participating in Study 20120138 who experienced a craniocerebral injury (reported term: traumatic brain injury), laceration (reported term: facial lacerations and left middle finger laceration), and radius fracture (reported term: open right extra-articular distal radius fracture). The subject's medical history included hyperlipidemia, mixed dyslipidemia, tonsillectomy, adenoidectomy, and smoking. Concomitant medications were not reported. Previous treatment for hyperlipidemia and mixed dyslipidemia was not provided.

The subject received placebo and ezetimibe in the parent study from 08 March same year* to 31 May same year*. He received the first dose of evolocumab in Study 20120138 on 31 May [redacted]. Approximately 2 months later, on 02 August same year*, the subject was pushed out of a car that was moving at a speed of approximately 30 mph. The subject landed on his face and bilateral upper extremities. He was brought to the hospital by the emergency medical services.

His physical examination revealed significantly deformed right wrist with a dorsal wound at the distal radius and ulna, at the level of the extensor wrist crease, measuring approximately 2.5 cm, primarily over the ulnar aspects. Head CT showed no evidence of acute intracranial abnormality, soft tissue laceration, and hematoma of the right frontal scalp without evidence of acute bony abnormality, sinus mucosal disease of the maxillary and ethmoid sinuses which could be seen in the setting of chronic sinusitis, and degenerative changes of the left C2 to C3 vertebrae facet joint.

Radiograph of the right elbow showed no fracture, normal alignment, and no soft tissue abnormality. There was an obliquely complex open distal radius fracture, with volar displacement and foreshortening. There was also a non-displaced obliquely oriented fracture of the distal ulna. Bone fragments within a widened distal radioulnar joint were seen. The ulnar styloid was also fractured, located in the soft tissues palmar to the distal radius. There was gas in the soft tissues, indicating that the fracture was open. On the same day (02 August same year*), the subject had an open reduction surgery for internal fixation of the right extra articular distal radius fracture, and irrigation and debridement of skin and subcutaneous tissue of open wound

*新薬承認情報提供時に置き換え

on the right wrist. Also, the subject had irrigation and debridement of multiple complex lacerations of the forehead that were stellate in nature (approximately 30 cm total length) and complex layered closure of all lacerations.

The final diagnosis was open radial and ulnar fracture; facial laceration; and multiple other simple lacerations.

Additional treatment included oxycodone, fentanyl, morphine, ondansetron, hydromorphone, metoclopramide, tetanus, cefazolin, ophthalmic ointment (containing dexamethasone, neomycin, polymyxin B), senna alexandrina, multivitamins (ascorbic acid, calcium, ergocalciferol, nicotinamide, pyridoxine, retinol, riboflavin, and thiamine), docusate, antibiotic ointment, zolpidem, lidocaine with epinephrine, enoxaparin, and paracetamol. The subject was discharged from the hospital on 06 August same year*.

The events of craniocerebral injury, laceration, and radius fracture were reported as resolved on 18 October same year*. The subject's last dose of evolocumab prior to the event was on 31 May same year* which was also his last dose in the study. Evolocumab was discontinued based on the subject's request.

As of the data cutoff date of [redacted] the subject continued in the study.

The investigator reported that there was not a reasonable possibility that the events of craniocerebral injury, laceration, and radius fracture were related to evolocumab or the device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110114, Placebo SC QM + Ezetimibe 10 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Ataxia

Subject [redacted] was a 36-year-old white man participating in Study 20120138 who developed ataxia (reported term: drug induced ataxia). The subject's medical history included dyslipidemia, dizziness, anxiety, bipolar disorder, carotid or vertebral artery disease, congestive heart failure, depression, hypercholesterolemia, hypertension, myocardial infarction, permanent pacemaker, post-traumatic stress disorder, psychosis, stroke/cerebral infarction, and type 2 diabetes mellitus. Concomitant medications included beclometasone, salbutamol, risperidone, trazodone, aripiprazole, paroxetine, zolpidem, doxepin, and ziprasidone. Previous treatment for hyperlipidemia included ezetimibe.

The subject received placebo and ezetimibe in the parent study from 28 February same year* to 25 April same year*. He received the first dose of evolocumab in Study 20120138 on 21 May [redacted].

Approximately 8 months later, on 24 January one year after*, the subject developed ataxia and was hospitalized on the same day. No supporting laboratory data or treatment information was reported. The outcome of the event ataxia was reported as resolved on 25 January one year after* and the subject was discharged in stable condition on the same day.

The subject received the last dose of the open label investigational study drug prior to the event on 03 December same year*. The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose was documented on 25 March one year after*.

The investigator reported that there was not a reasonable possibility that the event ataxia was related to open label investigational study drug or to the device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110114, Evolocumab SC QM 420 mg + placebo PO QD Year 1: Standard of Care
Report: Bronchitis

Subject [redacted] was a 47-year-old white woman participating in Study 20120138 who developed bronchitis (reported term: acute bronchitis). The subject's medical history included depression, migraine, insomnia, dyslipidemia and childhood asthma. Concomitant medication included oxaprozin, estrogens conjugated, metoprolol, cyclobenzaprine, milnacipran, morphine, topiramate, oxycodone, and bupropion. No previous treatment for hyperlipidemia was reported.

The subject received evolocumab in the parent study from 07 March same year* to 02 May same year*. She received standard of care in Study 20120138 starting on 30 May [redacted].

Approximately 6 months later, on 14 November same year*, the subject presented to the emergency room with complaints of shortness of breath and was hospitalized on the same day for acute bronchitis. The subject was treated with unspecified intravenous and oral antibiotics. The outcome of the event acute bronchitis was reported as resolved on 17 November same year* and the subject was discharged from the hospital on the same day in a stable state.

As of [redacted], the subject was continuing in the study.

The investigator reported that there was not a reasonable possibility that the event bronchitis was related to study participation.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110114, Placebo SC Q2W + Ezetimibe 10 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Alanine aminotransferase increased, Aspartate aminotransferase increased

Subject [redacted] was a 44-year-old white woman participating in Study 20120138 who developed increased alanine aminotransferase and aspartate aminotransferase. The subject's medical history included dyslipidemia, hypertension, irritable bowel syndrome, migraine, seasonal allergies, sinus congestion and upper respiratory congestion. Concomitant medication included norethisterone, zestoretic, paracetamol, fluticasone, and amoxicillin. Previous and ongoing treatment for hyperlipidemia included atorvastatin and ezetimibe.

The subject received placebo and ezetimibe in the parent study from 19 March same year* to 29 May same year*. She received the first dose of evolocumab in Study 20120138 on 10 July [redacted].

A month earlier, on 12 June same year*, laboratory tests revealed alanine aminotransferase (ALT) 34 U/L, aspartate aminotransferase (AST) 26 U/L, alkaline phosphatase 64 /L, and direct bilirubin 0.2 mg/dL. Approximately 5.5 months later, on 23 December same year* at the week 24 study visit, the subject complained of upper respiratory congestion and sinus congestion. Laboratory tests on the same day revealed ALT 474 U/L, AST 150 U/L, alkaline phosphatase 354 U/L, and direct bilirubin 0.4 mg/dL. The subject had not experienced any previous episodes of AST or ALT elevation and there were no etiological or predisposing risk factors associated with the event. Laboratory tests for liver function were repeated 4 days later, on 27 December same year*, and revealed ALT 131 U/L, AST 41 U/L, alkaline phosphatase 179 U/L, and direct bilirubin 0.3 mg/dL. Two weeks after the initial elevated levels, on 07 January one year after*, laboratory tests were repeated and revealed liver function tests within normal ranges: ALT 33 U/L, AST 22 U/L, alkaline phosphatase 82 U/L, and direct bilirubin 0.3 mg/dL. The outcome of the event increased AST was reported as resolved on 27 December same year*. The outcome of the event increased ALT was reported as resolved on 07 January one year after*.

The subject's last dose of investigational product prior to the event was reported to be on 11 December same year*. The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose was documented on 23 December same year*.

*新薬承認情報提供時に置き換え

The investigator reported that the elevated liver function tests were not related to study participation; however, they were possibly related to upper respiratory infection. The investigator considered paracetamol as a co-suspect medication.

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110114; Evolocumab SC QM 420 mg + Placebo PO QD Year 1: Evolocumab SC QM 420 mg + Standard of care
Report: Road traffic accident

Subject [redacted] was a 55-year-old white man participating in Study 20120138 who had a road traffic accident (reported term: motor vehicle accident [MVA]). The subject's medical history included primary hyperlipidemia/mixed dyslipidema. Concomitant medications included ibuprofen, meloxicam, and tramadol. No previous treatment for primary hyperlipidemia and mixed dyslipidemia was provided.

The subject received evolocumab and placebo in the parent study from 14 March same year* to 04 June same year*. The subject received the first dose of evolocumab in Study 20120138 on 04 June [redacted]. Approximately 2 months later, on 21 August same year*, the subject had a road traffic accident and was hospitalized on that day. Two days later, on 23 August same year*, the subject was discharged.

The date of the subject's last dose of evolocumab before the events was not available. The subject was continuing home dosing as of the data cutoff date of [redacted] and the last in-clinic dose was documented on 19 November same year*. The investigator reported that there was not a reasonable possibility that the event of road traffic accident was related to evolocumab or to the device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent Study and regimen: Study 20110114, Placebo SC Q2W + Placebo PO QD Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Suicidal ideation

Subject [redacted] was a 61-year-old white woman participating in Study 20120138 who developed suicidal ideation. The subject's medical history included primary hyperlipidemia and depression. Concomitant medications included oxybutynin, phenazopyridine, finasteride, prednisone, morniflumate, multivitamins combination, levothyroxine, zolpidem, fluticasone, duloxetine, vitamin B, loratadine, omeprazole, macrogol, cetirizine, and an unknown ophthalmic solution. The subject did not receive any previous treatment for primary hyperlipidemia.

The subject received placebo in the parent study from 28 March same year* to 31 May same year*. The subject received the first dose of evolocumab in Study 20120138 on 27 June [redacted].

Approximately 2 months later, on 26 August same year*, the subject was experiencing suicidal ideation and was admitted to a mental health facility. The investigator reported that the subject's son died in June one year ago*, which was given as the reason for her depression and suicidal thoughts. Treatment included duloxetine. On 30 August same year*, the subject was discharged from the facility but continued her outpatient therapy. The event was reported as resolved after on 30 November same year*.

The subject's last dose of evolocumab prior to the event was on 22 August same year*. Evolocumab was continued. The subject was continuing home dosing as of the data cutoff date of [redacted] and the last in-clinic dose was documented on 12 December same year*.

The investigator reported that there was not a reasonable possibility that the event of suicidal ideation was related to evolocumab or the device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent Study and regimen: Study 20110114, Placebo SC Q2W + Ezetimibe PO QD 10 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of care
Report: Perforated appendicitis

Subject [redacted] was a 62-year-old white woman participating in Study 20120138 who developed a perforated appendicitis (reported term: appendix rupture). The subject's medical history included dyslipidemia. Concomitant medications included acetylsalicylic acid. No previous treatment was reported for dyslipidemia.

The subject received placebo and ezetimibe in the parent study from 18 March same year* to 13 June same year*. She received the first dose of evolocumab in Study 20120138 on 26 June [redacted].

Approximately 2.5 months later, on 02 September same year*, the subject was hospitalized due to lower abdominal pain. The subject was diagnosed with perforated appendicitis, and surgery was performed. Treatment included ciprofloxacin, metronidazole, dimenhydrinate, hydromorphone, morphine, lorazepam, ibuprofen, and heparin. The event of perforated appendicitis was reported as resolved on 04 September same year*, and the subject was discharged from the hospital on that date.

The subject received the last dose of evolocumab prior to the event on 22 August same year*. Evolocumab was continued. The subject was continuing home dosing as of the data cutoff date of [redacted] and the last in-clinic dose was documented on 11 December same year*.

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

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Parent study and regimen: Study 20110114, Placebo SC QM + Ezetimibe PO QD 10 mg Year 1: Standard of Care
Report: Non-cardiac chest pain

Subject [redacted] was a 58-year-old white woman participating in Study 20120138 who developed non-cardiac chest pain (reported term: chest pain, non cardiac, unknown etiology). The subject's medical history included dyslipidemia, hyperlipidemia, generalized anxiety disorder, panic attacks, tobacco and alcohol use, breast enlargement with implant, removal of breast capsule, ectopic pregnancy, hypothyroidism, gastroesophageal reflux disease, depressive disorder, peripheral neuropathy, degenerative disc disease, mitral valve prolapse and allergies to naproxen, oxycodone, and acetaminophen. Family history included coronary artery disease, hypertension, breast cancer, and diabetes. Concomitant medications included levothyroxine, venlafaxine, omeprazole, tocopherol, fluticasone, multivitamins, and rabeprazole. Previous treatment for hyperlipidemia was not provided; ongoing treatment included simvastatin.

The subject received placebo and ezetimibe in the parent study (Study 20110114) from 14 March same year* to 14 June same year*, and was randomized to standard of care in Study 20120138 on 31 July [redacted].

In February same year*, the subject underwent cardiac computerized angiography and had a coronary calcium score of 297, which placed her at the 97th percentile for age and sex.

On 02 October same year*, the subject experienced rapid onset of substernal chest pain (mild diaphoresis only, no typical radiation, no relation to effort). Acetylsalicylic acid and glyceryl trinitrate provided only partial relief. She was brought to the emergency room and then hospitalized for further evaluation. Physical examination confirmed mitral prolapse, and disclosed no other abnormality. Electrocardiogram showed normal sinus rhythm with no ST segment changes indicative of acute ischemia.

Vital signs included blood pressure of 120/65 mmHg, pulse 64 bpm and oxygen saturation of 95%. Cardiac examination was normal except for a mitral valve click.

*新薬承認情報提供時に置き換え

Laboratory data including cardiac enzymes were normal. Chest radiograph showed no radiographic evidence of active cardiopulmonary disease. Magnetic resonance imaging of the cervical spine without contrast showed degenerative changes.

On 03 October same year*, the subject complained of tightness of the chest and angiography was performed. Additional treatment included morphine and ondansetron. The subject was discharged from the hospital on the 03 October same year*. On 04 October same year*, cardiac catheterization did not disclose any clinically significant treatable coronary stenosis. The event non-cardiac chest pain was reported as resolved on 03 October same year*.

As of the data cutoff date of [redacted], the subject was continuing in the study.

The investigator reported that there was not a reasonable possibility that the event of non-cardiac chest pain was related to any study activity.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments Parent study and regimen: 20110114, Evolocumab SC QM 420 mg + Placebo PO QD Year 1: Evolocumab SC QM 420 mg + Standard of care
Report: Malignant melanoma

Subject [redacted] was a 63-year-old white woman participating in Study 20120138 who was diagnosed with malignant melanoma (reported term: malignant melanoma right lower leg). The subject's medical history included hyperlipidemia, dyslipidemia, appendectomy, carpal tunnel surgery, hysterectomy, right breast in situ breast cancer, and right thumb surgery. Concomitant medications included ascorbic acid, biotin, calcium, ergocalciferol, vitamin B complex, and combination of hydrocodone and paracetamol. The subject had no reported previous treatment for primary hyperlipidemia.

The subject received evolocumab and placebo in the parent study from 06 March same year* to 29 May same year*. She received the first dose of evolocumab in Study 20120138 on 18 June [redacted]. Approximately 10 days later, on 28 June same year*, the subject underwent right leg lesion biopsy, which showed malignant melanoma of grade 2. The subject did not have any previous episode of malignant melanoma or history of skin cancer. The lesion was removed. The subject received cephalexin and sulfamethoxazole/trimethoprim. The outcome of the event of malignant melanoma was reported as unknown.

The date of the subject's last dose of evolocumab prior to the event of malignant melanoma was on 18 June same year*. Evolocumab was continued. The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose documented prior to that date was on 03 December same year*.

The investigator reported that there was not a reasonable possibility that the event of malignant melanoma was related to the evolocumab or the device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Parent study and regimen: Study 20110115; Placebo SC QM + Ezetimibe PO QD 10 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Pericarditis

Subject [redacted] was a 62-year-old white man participating in Study 20120138 who developed pericarditis. The subject's medical history included primary hyperlipidemia/mixed dyslipidemia, ischemic heart disease, hypertension, hypercholesterolemia, and pericarditis (three years ago*). Concomitant medications included acetylsalicylic acid, candesartan, and metoprolol. Previous and ongoing treatment for primary hyperlipidemia/mixed dyslipidemia included rosuvastatin.

The subject received placebo and ezetimibe in the parent study (Study 20110115) from 26 March same year* to 18 June same year* and received the first dose of evolocumab in Study 20120138 on 23 July [redacted]. Approximately 2 months later, on 12 September same year*, the subject developed pericarditis and was hospitalized. Upon admission, laboratory tests included creatine kinase of 171 U/L, 124 U/L and 127 U/L, urate of 0.49 mmol/L, C-reactive protein of 1.7 mg/L, eosinophil percentage of 3%, lymphocyte percentage of 32%, monocyte percentage of 7%, neutrophil percentage of 58%, and troponin T of 9, 10, and 11 ng/L. Additional laboratory results were within normal range. An echocardiogram showed no abnormal findings.

Repeat ECGs were consistent with pericarditis diagnosis, disclosing normal heart rates, PR, QRS and QT (or QTc) intervals, and variable morphology abnormalities, such as lateral Q waves, anterior (V1-V4) RT-ST depression, and ST elevation (of variable magnitudes) in II, III aVF and anterior (V1-V4) leads

Treatment included colchicine, pantoprazole, morphine, oxycodone, paracetamol, and ibuprofen. The next day, on 13 September same year*, an additional ECG showed heart rate of 61 beats per minute (bpm), QRS 92ms, QT 408ms, QTc 412ms. An ECG performed on 14 September same year* showed heart rate 104 bpm, RR 578 ms, P 108 ms, PR 134 ms, QRS 90 ms, QT 336 ms, QTc 442 ms.

The event of pericarditis was reported to have resolved on 17 September same year* and the subject was discharged from the hospital on that date.

*新薬承認情報提供時に置き換え

The subject had previously experienced an episode of pericarditis in three years ago*. At that time, the subject had experienced chest pain that was worse on inspiration. He was observed in the hospital where an ECG showed widespread ST elevation. The subject was treated with ibuprofen during hospitalization. The subject was reviewed following hospitalization, on 09 November three years ago*, his pain was noted to have resolved and an ECG showed only minimal changes. His blood pressure was 120/80 mmHg, chest was clear and heart sounds were normal. An echocardiogram showed good left ventricular function and no evidence of any pericardial effusion.

The subject's last dose of evolocumab prior to the event was on 27 July same year*. Evolocumab was continued. The subject was continuing home dosing as of the data cutoff date of [redacted] and the last in-clinic dose was documented on 07 January one year after*.

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

*新薬承認情報提供時に置き換え