Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Placebo SC Q2W Year 1: Standard of Care
Report: Acute myocardial infarction

Subject [redacted] was a 76-year-old white man participating in Study 20120138 who developed an acute myocardial infarction (reported term: non ST elevation myocardial infarction). The subject's medical history included dyslipidemia, angina, hypertension, ischemic heart disease, stent placement, and hyperlipidemia. Concomitant medication included acetylsalicylic acid, glyceryl trinitrate, a combination of candesartan and hydrochlorothiazide, and metoprolol. Previous and ongoing treatment for hyperlipidemia included rosuvastatin.

The subject received placebo in the parent study from 10 May same year* to 19 July same year*. He was enrolled into Study 20120138 on 16 August [redacted] and assigned to standard of care treatment. On 27 December same year*, the subject experienced chest tightness and developed a non ST segment elevation myocardial infarction. The subject was hospitalized for the event on the same day. The subject's blood troponin T was 0.308 µg/L. The subject's laboratory investigations on the same day revealed hematological tests within normal range. Creatinine was slightly elevated at 130 µmol/L (a baseline creatine value was not available; the value on 08 November same year* was 111 µmol/L). Coronary angiogram performed on 27 December same year* revealed a patent left main stent, left anterior descending coronary artery (LAD) proximal 100%, dominant posterior descending artery (PDA) distal subtotal occlusion, a patent right coronary artery (RCA), a previously occluded saphenous vein graft (SVG), and a patent left interior mammary artery bypass graft of the left anterior descending coronary artery (LIMA LAD). Treatments reported after the onset of the event included lercanidipine and ticagrelor. The event of acute myocardial infarction was reported as resolved on 29 December 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 receiving standard of care.

The investigator reported that there was not a reasonable possibility that the event of Non ST segment elevation myocardial infarction 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 20110115, Evolocumab SC 140 mg Q2W Year 1: Evolocumab SC 420 mg QM + Standard of Care
Report: Gout

Subject [redacted] was a 76-year-old white man participating in Study 20120138 who developed gout (reported term: inflammation of gout tophus). The subject's medical history included hyperuricemia, osteoporosis, osteoarthritis, spinal column stenosis, and spinal osteoarthritis. Concomitant medication included colecalciferol, alendronate, zestoretic, calcium carbonate, nandrolone decanoate, paracetamol, and ibuprofen. Previous treatment for hyperlipidemia included atorvastatin.

The subject received evolocumab in the parent study from 03 July same year* to 11 September same year*. He received the first dose of evolocumab in Study 20120138 on 09 October [redacted]. Approximately 6 months later, on 18 March one year after*, the subject developed a gouty tophus on his toe. Approximately 3 weeks later, on 10 April one year after*, the subject was hospitalized for evaluation. The outcome of the event gouty tophus on toe was reported as resolved on 14 April one year after* and the subject was discharged from the hospital on the same day. Open-label investigational study drug was continued.

The subject was continuing home dosing of evolocumab as of the data cutoff date of [redacted], and the last documented in-clinic dose prior to the event was on 19 March one year after*.

The investigator reported that hyperuricemia with some asymptomatic gout tophus was the predisposing risk factor for the event. The investigator reported that there was not a reasonable possibility that the event of gout 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 20110115, Evolocumab SC QM 420 mg Year 1: Standard of Care
Report: Bacterial arthritis

Subject [redacted] was a 64-year-old white woman participating in Study 20120138 who developed bacterial arthritis (reported term: septic arthritis).

The subject's medical history included dyslipidemia, gonarthrosis, and right knee arthroscopy. Concomitant medication included tramadol, ramipril, and barnidipine. Previous and ongoing treatment for hyperlipidemia included simvastatin.

The subject received evolocumab in the parent study from 22 May same year* to 16 July same year*. She was enrolled into Study 20120138 on 18 September [redacted] and assigned to standard of care treatment. The subject underwent right knee arthroscopy on 21 January one year after*. On 03 February one year after*, the subject developed bacterial arthritis of the right knee. She was treated with a combination of amoxicillin and clavulanic acid from 03 February one year after* to 06 February one year after*. On 06 February one year after*, the subject was hospitalized. During hospitalization, arthroscopic evaluation of the knees was performed. The outcome of the event of bacterial arthritis was reported as resolved on 04 March 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 16 July same year* (during Study 20110115). Standard of care treatment in Study 20120138 was continued and the subject continued in the study.

The investigator reported that there was not a reasonable possibility that the event of septic arthrosis was related to study procedures.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Placebo SC QM Year 1: Evolocumab SC QM 420 mg + Standard of care
Report: Basal cell carcinoma

Subject [redacted] was a 71-year-old white woman participating in Study 20120138 who was diagnosed with basal cell carcinoma (reported term: left lower lid basal cell carcinoma). The subject's medical history included hyperlipidemia. Concomitant medications included lorazepam, and terazosin. Previous treatment for hyperlipidemia included atorvastatin and ongoing treatment for hypercholesterolemia included rosuvastatin.

The subject received placebo in the parent study from 08 April same year* to 03 June same year*. She received the first dose of evolocumab in Study 20120138 on 02 July [redacted].

During the screening phase of the study, the subject developed left lower eye lid basal cell carcinoma. The investigator reported that a growth was present since January thirteen years ago*. On 26 July same year*, a tumor biopsy was performed, and the subject underwent a left lower eye lid carcinoma excision. On 28 August same year* pathology report confirmed the diagnosis of basal cell carcinoma. The event of basal cell carcinoma was reported as resolved on 08 August same year*.

The date of the subject's last dose of evolocumab prior to the event was on 02 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 documented prior to that date was 17 December same year*. The subject continued in the study.

The investigator reported that there was not a reasonable possibility that the event of basal cell carcinoma was related to evolocumab or 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 20110115, Placebo SC Q2W + Placebo PO QD Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Hemoptysis

Subject [redacted] was a 77-year-old white man participating in Study 20120138 who experienced hemoptysis. The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, atrial fibrillation, aortic valve replacement (mechanical), permanent VVIR pacemaker insertion, hypertension, prostatectomy 10 years ago for prostate cancer (no evidence of recurrence), and chronic microcytic anemia with a recent colonoscopy that was normal. Concomitant medications included warfarin and acetylsalicylic acid. Previous and ongoing treatment for hyperlipidemia included atorvastatin.

The subject received placebo in the parent study from 24 April same year* to 19 July same year*. He received the first dose of evolocumab in Study 20120138 on 02 August [redacted]. The subject had intermittent dry cough since approximately October and weight loss of approximately 10 pounds since November with a decrease in appetite and energy level. The subject's international normalized ratio (INR) was between 2 to 3 a week before the event. On 02 February one year after*, the subject presented to the emergency room with a sudden onset of rigors, which started 2 hours prior to presentation and was followed by an acute onset of hemoptysis (about 50 mL of frank blood without clots or mucus). The subject was hospitalized on the same day.

On the same day, a physical examination showed that all systems were normal except for 2+ pitting edema with small cervical lymph nodes, fever of 38.2°C, and blood pressure of 165/78 mmHg. Laboratory investigations revealed INR of 3.1, hemoglobin stable at 12.5 g/dL and white blood cell (WBC) count of 8.6 × 10^9 cells/L (normal). Chest radiograph showed lower parenchymal opacity at the right lung base with mild increase in the right basal lung opacity. Computed tomography (CT) scan of the chest showed areas of ground glass and air space opacity in the lower lobes that were non-specific and might represent areas of infection, alveolar pulmonary edema, or pulmonary hemorrhage. No pulmonary mass was identified and the subject had mild lymphadenopathy. The most probable diagnosis was reported to be hemoptysis secondary to bronchitis/bronchiolitis; pulmonary embolism was considered to be unlikely as the subject had a Well's Criteria score of 1 and normal D dimer. Warfarin and

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acetylsalicylic acid were held during hospitalization, and the patient received ceftriaxone, azithromycin, and furosemide. A respiratory culture and a nasopharyngeal swab were found to be negative. At the time of discharge, the subject's condition improved with decreased hemoptysis and he had only a small amount of blood and whitish sputum. The subject was advised to continue warfarin at a decreased dose and to continue other medications including amlodipine, metoprolol, ramipril, cefuroxime, and atorvastatin. Acetylsalicylic acid was discontinued due to an increased risk of bleeding. The subject was discharged from the hospital on 05 February one year after* and the event was ongoing at the time of the data cutoff.

The subject's last dose of evolocumab prior to the event was on 17 January one year after*. Evolocumab was continued and the subject continued in the study. As of the data cutoff date of [redacted] the subject was reportedly continuing home dosing; no clinic dose more recent than 17 January one year after* was documented.

The investigator reported that there was not a reasonable possibility that the event of hemoptysis 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 20110115, Evolocumab SC Q2W 140 mg Year 1: Standard of Care
Report: Transient ischemic attack

Subject [redacted] was a 47-year-old white man participating in Study 20120138 who experienced a transient ischemic attack. The subject's medical history included dyslipidemia, hypertension, hyperlipidemia, sleep apnea, and type 2 diabetes mellitus. Concomitant medication included metformin, diclofenac, acetylsalicylic acid, perindopril, indapamide, and diltiazem. Previous and ongoing treatment for hyperlipidemia included rosuvastatin.

The subject received evolocumab in the parent study from 05 June same year* to 15 August same year*. On 11 September [redacted] he enrolled in Study 20120138 and was assigned standard of care treatment. Approximately 2 months later, on 08 November same year*, the subject presented with slurred speech, right side weakness and dizziness. Subsequently, at the emergency room he was diagnosed with a transient ischemic attack. A computerized tomography scan of the head revealed no acute intracranial abnormality. There was no history of previous similar events. The outcome of the event of transient ischemic attack was reported as resolved on 08 November same year*.

The subject's last dose of evolocumab prior to the event and last dose of evolocumab as of the data cutoff date of [redacted] was on 15 August same year* (during Study 20110115). The subject continued in the study.

The investigator reported that there was not a reasonable possibility that the event transient ischemic attack was related to any study procedures.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Parent study and regimen: Study 20110115; Evolocumab SC QM 420 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Vaginal prolapse

Subject [redacted] was a 64-year-old white woman participating in Study 20120138 who developed a vaginal prolapse (reported term: prolapse vaginal). The subject's medical history included primary hyperlipidemia/mixed dyslipidemia, coronary artery disease, hypertension, ulcer, and dyspepsia. Concomitant medications included glyceryl trinitrate, acebutolol, omeprazole, drotaverine, aminophylline, methylprednisolone, beclametasone, roxithromycin, acetylsalicylic acid, simvastatin, molsidomine, codeine and nitrendipine. Previous treatment for primary hyperlipidemia/mixed dyslipidemia included ezetimibe/simvastatin; and ongoing treatment included rosuvastatin.

The subject received evolocumab in the parent study (Study 20110115) from 29 May same year* to 24 July same year*, and received the first dose of evolocumab in Study 20120138 on 22 August [redacted].

On 14 July same year*, while participating in the parent study, the subject developed a vaginal prolapse after coughing.

On 02 September same year*, coagulation panel and culture urine microbiology examination showed no pathological findings. The subject was hospitalized on 19 September same year*. Medication included diazepam, nitrazepam, metronidazole, morphine, thiethylperazine, sulfamethoxazole and trimethoprim, diclofenac, and bemiparin.

On 20 September same year*, the subject's laboratory tests included hemoglobin 131 g/L, red blood cell count 4.2 x 10^{12}/L, and platelet count 160 x 10^{9}/L. On the same day, the subject underwent uncomplicated hysterectomy and colpoplasty for vaginal prolapse.

The event of vaginal prolapse was reported as resolving and the subject was discharged from the hospital on 25 September same year*. On 04 December same year*, the subject's control examination showed good results. The event of vaginal prolapse was reported as resolved on the same day.

The date of the subject's last dose of evolocumab prior to the event of vaginal prolapse was on 13 June same year*, while on the parent study. Her last dose before the surgical procedures on 20 September same year* was on 22 August same year*. Evolocumab was continued. As of the data cutoff

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date of [redacted], the subject was continuing at-home dosing with the last in-clinic dose documented on 21 November same year*.

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

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Placebo SC Q2W Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Meniscus injury

Subject [redacted] was a 62-year-old white man participating in Study 20120138 who experienced a meniscus injury. The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, borrelia infection (twice), repeated arthroscopy for meniscal lesions, ligament strain of the knee, and chondropathy of the left knee joint. Previous and ongoing treatment for hyperlipidemia included rosuvastatin.

The subject received placebo in the parent study from 22 May same year* to 05 August same year*. He received the first dose of evolocumab in Study 20120138 on 02 September [redacted]. Approximately 2 months later, on 27 October same year*, the subject fell down in the mountains and twisted his right knee. The following day, on 28 October same year*, physical examination revealed edema of the right knee. Ballottement was slightly positive, flexion was limited, and the popliteal fossa was tender. A radiograph of the right knee revealed a sprain. The subject was recommended crutches, a brace, and ice compresses. During the follow-up visit on 30 October same year*, the subject was diagnosed with hemarthrosis of the right knee and a knee arthroscopy was scheduled. Nadroparin calcium was started. On 04 November same year*, the subject underwent an uncomplicated elective arthroscopy of the right knee, with a partial lateral and medial meniscectomy. The subject was discharged from the hospital on 05 November same year*. The event of meniscus injury was reported as resolved on 13 November same year*. Evolocumab was continued and the subject continued in the study.

The subject's last dose of evolocumab prior to the event was on 30 September 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 November same year*.

The investigator reported that there was not a reasonable possibility that the event of meniscus injury 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 20110115, Evolocumab SC QM 420 mg Year 1: Evolocumab SC Evolocumab SC Q2W 140 mg + Standard of Care
Report: Thermal burn

Subject [redacted] was a 63-year-old white woman participating in Study 20120138 who experienced a thermal burn. The subject's medical history included dyslipidemia, hypertension, chronic ischemic heart disease since two years ago*, paroxysmal atrial fibrillation, and coronary angiography in one year ago* and in same year*.

Concomitant medication included acetylsalicylic acid, amlodipine, lansoprazole, perindopril, trimetazidine, bisoprolol, glyceryl trinitrate, and a combination of hesperidin and diosmin. Previous and ongoing treatment for hyperlipidemia included rosuvastatin.

The subject received evolocumab in the parent study from 28 June same year* to 22August same year*. She received the first dose of evolocumab in Study 20120138 on 19 September [redacted]. Approximately 4 months later, on 23 January one year after*, the subject was at work when an explosion occurred due to a gas leak. The subject was transported to the hospital in good condition. The subject had burns of grade IIa and grade IIb on the face, the ventral part of neck, and the dorsal parts of the hands, which involved 6% of her total body surface area. She had swelling of the face but no evidence of inhalation trauma. The subject's hair and eyelashes were scorched. She was given an intramuscular dose of tetanus vaccine.

On the same day, the subject's ophthalmic examination showed that her conjunctivas were slightly irritated and her corneas were intact. The subject's ear, nose, and throat examination was normal. Redness, itching, and mild swelling of the eyelids was observed after ophthalo-azulene administration. Treatment reported after the onset of the event included perindopril, bisoprolol, atenolol, trimetazidine, acetylsalicylic acid, omeprazole, nadroparin, tramadol, ibuprofen, diclofenac potassium, escin, promethazine, ambroxol, sodium gualenate hydrate, framycetin, carbomer, cetrimide, sulfamethoxazole/trimethoprim, and protease.

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On 29 January one year after*, the subject was discharged from the hospital. Upon discharge, she was advised to continue treatment with acetylsalicylic acid and sulfamethoxazole/trimethoprim, and to lubricate the burned areas several times a day.

The subject's last dose of evolocumab prior to the event was on 09 January one year after*. As of the data cutoff date of [redacted], the subject continued home dosing and remained in the study.

The investigator reported that there was not a reasonable possibility that the event of thermal burn 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 20110115, Evolocumab SC QM 420 mg Year 1: Standard of Care
Report: Prostate cancer

Subject [redacted] was a 72-year-old white man participating in Study 20120138 who was diagnosed with prostate cancer. The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, prostatitis (diagnosed on 16 July same year*), transurethral prostatectomy (2 procedures in twelve years ago*), low grade dysplastic colon polyp, polypectomy, right sided colectomy, plastic surgery for right sided hydrocele, and surgery for right sided inguinal hernia. His concomitant medications included norfloxacin. Previous treatment for hyperlipidemia included atorvastatin; ongoing treatment for hyperlipidemia included rosuvastatin.

The subject received evolocumab in the parent study from 25 July same year* to 19 September same year*. He started Study 20120138 on 17 October [redacted].

On an unspecified date, the subject had a prostate-specific antigen (PSA) level of 8 ng/mL. On 11 November same year*, the subject had a positive histology finding of carcinoma with a Gleason score of 3+3. The subject was hospitalized on 27 November same year* and underwent radical retropubic prostatectomy on 28 November same year*, during which the carcinoma was verified. The subject's postoperative course was uncomplicatedand he was discharged on 04 December same year*.

The histology report revealed C61 acinar adenocarcinoma of the prostate cT2bNOMO and a Gleason score of 4+3; there was both-sided infiltration of approximately 5% of the tissue on the right side and 15% on the left side. Perineural spreading was noted. Extraprostatic extension and vascular invasion was not seen, the resection borders of prostate and sperm ducts were negative, and the structure of the sperm ducts and the prostatic urethra were regular.

The subject's last dose of evolocumab prior to the event was on 19 September same year* (during the parent study). Standard of care treatment was continued in Study 20120138 and the subject continued in the study.

*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 prostate cancer was related to any study activity.

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: Meniscus injury

Subject [redacted] was a 51-year-old white woman participating in Study 20120138 who experienced a meniscus injury (reported term: rupture of the medial meniscus of the right knee). The subject's medical history included mixed dyslipidemia, primary hyperlipidemia, bilateral knee pain, ilio-sacral pain, osteoarthritis of right knee, and hypertension. Concomitant medications included ibuprofen and telmisartan. Previous and ongoing treatment included atorvastatin (starting five years ago*).

The subject received placebo and ezetimibe in the parent study from 05 June same year* to 28 August same year*, and received the first dose of evolocumab in Study [redacted] on 28 August [redacted].

Approximately 1 month later, on 01 October same year*, the subject was admitted to the hospital with a diagnosis of rupture of the medial meniscus of the right knee. Treatment included rehabilitation and local injections with non-steroidal anti-inflammatory drugs without improvement.

On 02 October same year*, right sided arthroscopy with partial medial meniscectomy was performed. Surgical diagnosis was rupture of the medial meniscus in the right knee, posterior horn chondromalacia of the medial femoral condyle and medial tibial plate of grade III. The procedure also showed mild synovitis and normal patella, femoropatellar joint, and cartilages. Treatment medication after the onset of the event included hyaluronate sodium.

The event of meniscus injury was reported as resolved on 04 October 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 25 September same year*. As of the data cut-off date of [redacted], the subject's last documented in-clinic dose of evolocumab was on 20 November same year* and the subject was continuing at-home dosing.

The investigator reported that there was not a reasonable possibility that the event of meniscus injury 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 20110115, Placebo SC Q2W Year 1: Standard of care
Report: Cholelithiasis

Subject [redacted] was a 60-year-old white woman participating in Study 20120138 who had cholelithiasis. The subject's medical history included dyslipidemia, hypertension, varicose vein surgery, obesity, hepatic steatosis, and drug allergy (quinine). Concomitant medications included amlodipine, perindopril arginine/indapamide, bromazepam, and lansoprazole. No prior treatment for dyslipidemia was reported; ongoing treatment included rovastatin.

The subject participated in the parent study (Study 20110115) from 06 June same year* to 17 September same year* and received the last dose of placebo in the parent study on 15 August same year*. The subject was randomized to standard of care (SOC) in Study 20120138 on 17 September [redacted].

On an unknown date in May same year*, the subject was diagnosed with cholelithiasis. The subject had symptoms of dyspepsia after having a fatty meal. On 20 January one year after*, the subject was admitted to the hospital for planned surgery due to symptomatic cholelithiasis. On an unknown date, the subject underwent uneventful laparoscopic cholecystectomy. The outcome of the event cholecystectomy due to cholelothiasis was reported as resolved on 23 January one year after* and the subject was discharged from the hospital on the same day in good condition.

The subject was continuing in the study on the standard of care arm as of the data cutoff date of [redacted].

The investigator reported that there was not a reasonable possibility that the event cholecystectomy due to cholelithiasis was related to investigational product 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 20110115, Evolocumab SC Q2W 140 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Hypertension

Subject [redacted] was a 46-year-old white man participating in Study 20120138 who developed arterial hypertension. The subject's medical history included hyperlipidemia and dyslipidemia, overweight, varicose veins on both legs, and tobacco use. Concomitant medication included omeprazole. Previous treatment for hyperlipidemia included rosuvastatin.

The subject received evolocumab in the parent study from 09 July same year* to 19 September same year*. He received the first dose of evolocumab in Study 20120138 on 15 October [redacted]. Approximately 4 months later, on 17 February one year after*, the subject developed arterial hypertension. On 18 February one year after*, he experienced a stomach ache of sudden onset. He awoke at midnight and began to vomit, and he experienced abdominal spasms, cold sweat, and dizziness but had normal bowel movements with no diarrhea. He took a thiethylperazine maleate suppository at home with no response. When the event persisted, he was admitted to the hospital for dyspepsia (abdominal pain, nausea, and vomiting).

During physical examination, the subject's blood pressure was 140/75 mmHg, and his saturated oxygen was measured as 99%. Swelling was present in his lower limbs, and a peripheral pulse was detectable in both limbs. Thorough evaluation with ECG, chest and cervical spine radiographs, and abdominal ultrasound did not disclose any significant abnormalities related to the symptoms. Sequential laboratory tests also did not reveal significant acute abnormalities.

Uncontrolled hypertension with accompanying manifestations (headache, dizziness) was present along with esophageal reflux disease during hospitalization.

On 24 February one year after*, the subject was discharged in stable condition. The event of arterial hypertension was ongoing.

The subject was continuing home dosing as of the data cutoff of [redacted] and the last in-clinic dose was documented on 08 January one year after*.

*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 arterial hypertension was related to evolocumab or device. Risk factors include overweight and tobacco use.

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Evolocumab SC Q2W 140 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Alcoholism

Subject [redacted] was a 58-year-old white man participating in Study 20120138 who developed alcohol dependence. The subject's medical history included dyslipidemia, bipolar disorder, anxiety, depression, insomnia, and tobacco use. He had a family history of depression and suicide. He had abstained from alcohol from January to July same year*, and reported withdrawal symptoms. He then started to drink again most days in a week. The subject did not report drug abuse or over-the-counter drug abuse but did admit rare use of bromazepam. Concomitant medications were venlafaxine, quetiapine, pregabalin, bromazepam, and zolpidem. Previous treatment for hyperlipidemia included atorvastatin and simvastatin.

The subject received evolocumab in the parent study from 13 June same year* to 26 August same year*. He received the first dose of evolocumab in Study 20120138 on 19 September [redacted].

Approximately 2 months later, on 23 November same year*, the subject was admitted to a psychiatric hospital for alcohol dependence. He had been intoxicated every day for the last 2 weeks. At the time of hospitalization, an alcohol test showed the subject's alcohol value to be 1.4%.

Laboratory data included the following values: total bilirubin 27.4 µmol/L, glucose 10.8 mmol/L, total protein 65.2 g/L, alanine aminotransferase (ALT) 0.63 µKat/L (37.8U/L), aspartate aminotransferase (AST) 1.16 µKat/L (69.6U/L), and gamma-glutamyl transferase 1.68 µKat/L (100.8U/L). Previous hepatic function tests of 5 June same year* showed total bilirubin 5 µmol/L ALT 23 U/l, and AST 18 U/L; glucose was 4.9 mmol/L. On the same day, urine analysis revealed the presence of ketones, blood, and protein along with yeast in the urine. Treatment included detoxification and therapy with diazepam to prevent withdrawal symptoms. The subject's condition stabilized, and his liver function was stable. The expected time of hospitalization was 3 months. Evolocumab was discontinued.

On 09 December same year*, a neurological examination revealed a suspected cognitive disorder, cerebellar syndrome, and polyneuropathy on lower limbs thought to be of toxic and metabolic origin.

*新薬承認情報提供時に置き換え

Treatment medication included betahistine, bromhexine, omeprazole, cyanocobalamin, pyridoxine, thiamine, paracetamol, naphazoline, calcium, cyanocobalamin, nicotinamide, riboflavin, *Silybum marianum*, magnesium sulfate, caffeine, paracetamol, propyphenazone, and diclofenac.

The outcome of the alcohol dependence event was reported as resolved on 21 February one year after*, and the subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event was on 14 November same year*; evolocumab treatment was discontinued after the event of alcohol dependence.

The investigator reported that there was not a reasonable possibility that the event of alcohol dependence 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 20110115, Placebo SC Q2W + Placebo PO QD Year 1: Evolocumab SC Q2W 140 mg + SOC
Report: Femoroacetabular impingement

Subject [redacted] was a 66-year-old white woman participating in Study 20120138 who developed femoroacetabular impingement (reported term: right coxalgia on the basis femoroacetabular impingement syndrome). The subject's medical history included osteoarthritis, rib fracture, wrist fracture, forearm fracture, meniscus injury and meniscus operation, sciatica, obesity, osteoporosis, and back pain. Concomitant medication included cholecalciferol and calcium, risedronic acid, and nimesulide. Previous treatment for hyperlipidemia included atorvastatin.

The subject received placebo in the parent study from 17 June same year* to 09 September same year*. She received the first dose of evolocumab in Study 20120138 on 21 October [redacted]. Approximately 4 months later, on 03 March one year after*, the subject developed femoroacetabular impingement syndrome and was hospitalized on the same day due to weakness of the right hip and right groin pain. Magnetic resonace imaging (MRI) of the lumbar spine and electromyography ruled out discopathy, vasculopathy, and foramina. The subject underwent ultrasound examination of the right hip which showed femoroacetabular impingement syndrome. Based on the radiograph and computed tomography (CT), osteoarthritis of the hip joint was present. Treatment reported after the onset of event included nonsteroidal antiinflammatory drugs, muscle relaxants, corticosteroids, systemic therapy, local therapy, and physiotherapy of the right hip. The outcome was reported as resolved on 15 March one year after*. On the same day, the subject's weakness of the right hip and groin pain was mild and the subject was discharged from the hospital in good condition. The subject continued in the study with no interruption in evolocumab dosing.

The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose was documented on 13 January same year*.

The investigator reported that there was not a reasonable possibility that the event of femoroacetabular impingement 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: Study 20110115, Evolocumab SC QM 420 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Sudden death

Subject [redacted] was a 69-year-old white woman participating in Study 20120138 who died suddenly (reported term: sudden death [symptoms, diagnosis, and cause are unknown]). The subject's medical history included metabolic syndrome, primary hyperlipidemia, mixed dyslipidemia, elevated C reactive protein (5.26mg/L), peptic ulcer, hypertension, arthralgia and depression. The subject had no history of cardiac events. Concomitant medications included pantoprazole, amlodipine, citalopram, hydrochlorothiazide, valsartan, captopril, and dihydrocodeine. Previous treatment for hyperlipidemia and mixed dyslipidemia included rosuvastatin and ezetimibe; ongoing treatment included rosuvastatin.

The subject received evolocumab in the parent study (Study 20110115) from 28 May same year* to 16 August same year* and received the first dose of evolocumab in Study 20120138 on 16 August [redacted].

Approximately 6 weeks later, on 03 October same year*, the subject died suddenly. Diagnostic tests were not performed at the time of the event. Information regarding the clinical sequence of events leading to death was unknown. Investigational product had not been discontinued at the time of the subject's death. The visiting physician considered acute myocardial infarction as the possible cause of death. However, the final cause of death was not determined. An autopsy was not performed.

The subject's last dose of evolocumab prior to the event was on 16 August same year*. According to the investigator, it was unknown if the subject received investigational product in September same year*. No further in-clinic doses were documented.

The investigator reported that there was a reasonable possibility that the event of sudden death was related to evolocumab.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Evolocumab SC Q2W 140 mg Year 1: Evolocumab SC QM 140 mg + SOC
Report: Acute pancreatitis

Subject [redacted] was a 59-year-old white man participating in Study 20120138 who developed acute pancreatitis. The subject's medical history included primary dyslipidemia, hypertension, smoking, occasional alcohol use, laparoscopic surgeries for inguinal hernia, and cortical cysts in both kidneys. Triglycerides at selection were at 2.32 mmol/L and fasting glucose at 7.4mmol/L. Concomitant medication included: amlodipine, metoprolol and hydrochlorothiazide/losartan. Previous and ongoing treatment for hyperlipidemia included atorvastatin.

The subject received evolocumab in the parent study from 20 June same year* to 29 August same year*. He received the first dose of evolocumab in Study 20120138 on 26 September [redacted]. Approximately 3 months later, on 29 December same year*, the subject experienced acute pancreatitis and was hospitalized. Abdominal examination was normal. Abdominal ultrasonography showed normal findings of the liver, pancreas, and bile ducts; a cortical cyst was seen in the right kidney. On 02 January one year after*, abdominal computed tomography (CT) scan showed the following: pancreatitis located in the pancreatic head; edema along the right prerenal fascia; small cortical cysts in both kidneys; left-sided inguinal hernia with part of the bladder; suspect focus in the left hepatic lobe; character of saturation corresponded with hemangioma. CT scan on 03 January one year after* did not show relevant differences.

Relevant laboratory tests included the following: alanine aminotransferase (ALT) 0.38 to 0.61 µkat/L, serum amylase 0.9 to 3.5 µkat/L, aspartate aminotransferase (AST) 0.50 to 0.74 µkat/L, alkaline phosphatase 0.97 to 1.44 µkat/L, total bilirubin 5.2 to 8.9 µmol/L, C-reactive protein 33.3 to 343.2 mg/L, hematocrit 0.36 to 0.37, platelet count 264 to 347 K/µL, and white blood cell (WBC) count 7.5 to 10.2 K/µL.

Treatment after the onset of event included the following: analgesic and spasmolytic, fluid infusion, ciprofloxacin, metronidazole, diclofenac, electrolytes, ramipril, fenofibrate, omeprazole, cefotaxime, metronidazole, and cefuroxime. The subject's oral intake was limited to bitter tea. Nystatin and clofibrate were introduced due to triglycerides up to 6.12 mmol/L with good

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response. On 07 January one year after*, the event of acute pancreatitis was reported as resolved and the subject was discharged from the hospital.

The subject's last dose of investigational study drug prior to the event was on 26 September same year*. Study drug was discontinued on 15 January one year after*. As of the data cutoff date of [redacted], the last in-clinic dose was documented on 19 December one year after*.

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

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Placebo SC Q2W Year 1: Standard of Care
Report: Atrial flutter

Subject [redacted] was a 63-year-old white woman participating in Study 20120138 who developed atrial flutter. The subject's medical history included chronic pulmonary obstructive disease, primary hyperlipidemia, mixed dyslipidemia, hypertension, artificial heart valve due to insufficiency, and aortic aneurysm (non-ruptured). Concomitant medications included carvedilol, ramipril, bendroflumethiazide with potassium chloride, warfarin, fluticasone propionate/salmeterol xinafoate, , and amlodipine. Previous and ongoing treatment for hyperlipidemia included simvastatin.

The subject received placebo in the parent study (Study 20110115) from 22 May same year* to 31 July same year*. The subject was randomized to the standard of care arm in Study 20120138 on 04 September [redacted]. Approximately 11 days later, on 15 September same year*, the subject experienced atrial flutter. On 16 January one year after*, the subject was hospitalized and underwent successful radioablation. The atrial flutter was reported as resolved on 17 January one year after*. On 18 January one year after*, the subject was discharged from the hospital.

As of the data cutoff date of [redacted], the subject continued in the study. Simvastatin was discontinued on 17 February one year after* and atorvastatin started on 24 February one year after*.

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

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Placebo SC Q2W + Ezetimibe 10 mg PO QD Year 1: Standard of Care
Report: Intestinal diverticulum (multiple events)

Subject [redacted] was a 69-year-old white woman participating in Study 20120138 who experienced intestinal diverticulum (2 events). The subject's medical history included primary hyperlipidemia, headaches, osteoarthritis of the knees, appendicitis, appendectomy, varicose veins and sore throat. Concomitant medications included estradiol, magnecyl-kodein, ibuprofen, bromhexin, and paracetamol. Previous treatment for primary hyperlipidemia included simvastatin; ongoing treatment included atorvastatin.

The subject received placebo and ezetimibe in the parent study (Study 20110115) from 24 May same year* to 15 August same year*. The subject was randomized to the standard of care arm in Study 20120138 on 06 September [redacted]. On 17 January one year after*, she developed abdominal discomfort. Approximately 3 weeks later, on 05 February one year after*, she was hospitalized for abdominal discomfort. The subject underwent gastroscopy, which showed a moderate hiatal hernia. The subject's chest radiograph and abdominal ultrasound were normal. Treatment for abdominal discomfort included esomeprozole. On the next day, the event of abdominal discomfort resolved, and the subject was discharged from the hospital on 06 February one year after*.

Approximately 11 days later, on 17 February one year after*, the subject was again hospitalized for abdominal discomfort. On the same day, computerized tomography (CT) of the abdomen with contrast showed the presence of liver cysts. Treatment for abdominal discomfort included pantoprazole. The event of abdominal discomfort was resolved, and the subject was discharged 2 days later, on 19 February one year after*. Follow-up abdominal ultrasound on 26 February one year after* was normal.

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

The investigator reported the findings of moderate hiatal hernia and liver cysts did not explain the abdominal discomfort. The investigator also reported that there was not a reasonable possibility that the events of abdominal discomfort were related to study conduct.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Evolocumab SC QM 420 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Polymyalgia rheumatica

Subject [redacted] was a 71-year-old white man participating in Study 20120138 who developed polymyalgia rheumatica. The subject's medical history included cough, impotence, chronic non-infectious diarrhea, excised basal cell carcinoma of the face, and arthralgia. Concomitant medications included vi-siblin (psyllium husk), sildenafil, and ibuprofen. No previous or ongoing treatment for hyperlipidemia was reported.

The subject received evolocumab in the parent study from 01 July same year* to 26 August same year*. He received the first dose of evolocumab in Study 20120138 on 01 November [redacted]. Approximately 3.5 months after the first dose, on 15 March one year after*, the subject developed polymyalgia rheumatica (nonserious). Study drug had been previously withdrawn in response to the event of lung infection (start date 04 December same year*) on 27 December same year*. No treatment was reported, and no actions were taken with standard of care treatment due to the event of polymyalgia rheumatica. On 28 March one year after*, the subject experienced another event of polymyalgia rheumatica. The subject was hospitalized on that same date. Treatment included tramadol and paracetamol. The event was ongoing at the time of last report.

As of the data cutoff date of [redacted], the subject was continuing in the study and the last in-clinic dose of evolocumab was documented on 27 December same year*.

The investigator reported that the event of polymyalgia rheumatica was not 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 20110115, Evolocumab SC QM 420 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Osteoarthritis

Subject [redacted] was a 68-year-old white woman participating in Study 20120138 who developed osteoarthritis (reported term: worsening of arthrosis in left knee). The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, hypertension, atrial fibrillation, peripheral edema, and osteoarthritis. Concomitant medications included calcium, vitamin D, paracetamol, clopidogrel, atovaquone/proguanil, enalapril, hydrochlorothiazide, metronidazole, roxithromycin, and tramadol. Previous and ongoing treatment for hyperlipidemia included simvastatin.

The subject received evolocumab in the parent study from 18 July same year* to 12 September same year*. She received the first dose of evolocumab in Study 20120138 on 09 December [redacted]. On that date, she presented with worsening of arthritis in the left knee. She was hospitalized for left knee arthroplasty on 16 January one year after*. Treatment medications reported after the onset of the event included pantoprazole, oxycodone, dicloxacillin, tranexamic acid, metoclopramide, chlorzoxazone, cefuroxime, tinzaparin, and bisacodyl. The subject developed nausea and pain related to the surgery. No actions were taken with study medications due to the event of osteoarthritis. The outcome of the event of osteoarthritis was reported as resolved on 16 January one year after*, and the subject was discharged from the hospital on 22 January one year after*.

The subject's last dose of evolocumab prior to the event was 06 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 03 March one year after*.

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

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Evolocumab SC 420 mg QM + Placebo PO Year 1: Standard of Care
Report: Prostate cancer, Adenocarcinoma

Subject [redacted] was a 65-year-old white man participating in Study 20120138 who was diagnosed with prostate cancer/adenocarcinoma. The subject's medical history included hyperlipidemia and hypertension. Concomitant medication included enalapril. Previous and ongoing treatment for hyperlipidemia included simvastatin.

The subject received evolocumab and placebo in the parent study from 24 July same year* to 16 October same year*. The subject was enrolled in Study 20120138 on 29 October [redacted] and was assigned to the standard of care arm. Approximately 6 months later, on 23 March one year after*, the subject was diagnosed with prostate cancer (adenocarcinoma) through CT scan and PSA test (21 mg/L). The subject was hospitalized on April one year after* and staging did not show lymph node spreading or metastasis. No action was taken with the standard of care treatment. Treatment reported included triptorelin and neoadjuvant radiotherapy. The subject was discharged on 16 April one year after*. The event was reported as ongoing at the time of last available report.

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

The investigator reported that the event of prostate cancer was not related to study conduct.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Placebo SC Q2W Year 1: Standard of Care
Report: Radius fracture

Subject [redacted] was a 67-year-old white woman participating in Study 20120138 who experienced a fracture of the left radius (reported term: intra-articular comminuted fracture of distal radius left wrist). The subject's medical history included dyslipidemia, hypertension, hyperlipidemia, hiatal hernia, right shoulder pain, and herpes zoster. Concomitant medications included amlodipine, enalapril, metoprolol, bendroflumethiazide-potassium chloride, pantoprazole, calcium and colecalciferol supplements, paracetamol, and acyclovir. Previous and ongoing treatment for hyperlipidemia included simvastatin.

The subject received placebo in the parent study from 09 August same year* to 18 October same year*. She was randomized to the standard of care arm in Study 20120138 on 11 December [redacted]. Approximately 1 week later, on 18 December same year*, the subject fell at home (home accident, not syncopal event) and suffered a fracture to the left wrist. After evaluation in the emergency department that day, the subject was treated with analgesics and discharged with surgical intervention planned. Two days later, on 20 December same year*, the subject was hospitalized and underwent surgical osteosynthesis (internal fixation) of the left wrist. Treatments also included tramadol, paracetamol, and morphine. No action was taken with the standard of care medication due to the event. The event was reported as resolved and the subject was discharged from the hospital on 21 December 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 radius fracture was related to study conduct. The investigator also reported that the fall that caused the radius fracture was considered to be nonserious.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Placebo SC Q2W + Placebo PO QD Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Coronary artery disease

Subject [redacted] was a 50-year-old white man participating in Study 20120138 who developed coronary artery disease (reported term: worsening of coronaropathy disease). The subject's medical history included dyslipidemia, familial hypercholesterolemia, severe coronary artery disease with past myocardial infarction in thirteen years ago*, obesity, type II diabetes mellitus, and tabagism. The subject's family history included myocardial infarction to father at the age of 42 (died) and 2 brothers at the age of 29 and 40 years (died), and cancer to mother at the age of 40 years (died). Concomitant medications included acetylsalicylate and bisoprolol. Previous and ongoing treatment for hyperlipidemia included atorvastatin and ezetimibe.

The subject received placebo in the parent study from 31 July same year* to 08 October same year*. He received the first dose of evolocumab in Study 20120138 on 5 November [redacted]. Approximately 5 months later, on 30 March one year after*, the subject underwent a stress test, myocardial scintigraphy and coronarography, and was found to have worsening of coronary artery disease. Subsequently, the subject was hospitalized and scheduled for surgical intervention. Acetylsalicylate and bisoprolol were discontinued. On the next day, 31 March one year after*, the subject underwent recommended coronary bypass grafting surgery.

Following cardiac surgery, cardiac troponin blood levels were found to be elevated at 10.8 ng/mL. Levels improved over subsequent blood draws over the next 3 days (3.44 ng/mL on 01 April one year after*, 2.45 ng/mL on 02 April one year after*, and 1.39 ng/mL on 03 April one year after*). The investigator stressed that the subject did not experience a myocardial infarction; the elevated troponin levels were due to the cardiac surgery. No action was taken with the study drug or standard of care medications due to the event. The subject was discharged from hospital and the event was reported as resolved on 10 April one year after*.

The subject's last dose of evolocumab prior to the event was on 24 March 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 28 January one year after*.

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

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Evolocumab SC Q2W 140 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Jaw fracture

Subject [redacted] was a 69-year-old white man participating in Study 20120138 who experienced a jaw fracture (reported term: fracture of collum mandibulae right). The subject's medical history included dyslipidemia, hypertension, hypothyroidism, prostatic hypertrophy, and coronary heart disease. Concomitant medications included bisoprolol, ramipril, potassium iodide, tamsulosin, isosorbide mononitrate, and clindamycin. Previous treatment for dyslipidemia included pravastatin; ongoing treatment was none.

The subject received evolocumab in the parent study from 01 July same year* to 09 September same year*. He received the first dose of evolocumab in Study 20120138 on 08 October [redacted]. Approximately 5 months later, on 10 March one year after*, the subject stumbled and fell on a stage and suffered a fracture to the right side of the jaw. On 11 March one year after*, the subject was hospitalized for the event of jaw fracture and underwent an uncomplicated surgery the same day. Treatment also included prophylactic use of clindamycin. The event of jaw fracture resolved on 14 March 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 08 October 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 03 January one year after*.

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

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Placebo SC QM + Ezetimibe PO QD 10 mg Year 1: Standard of Care
Report: Pain

Subject [redacted] was a 51-year-old white man participating in Study 20120138 who experienced worsening of chronic pain (reported term: worsening of chronic pain disorder). The subject's medical history included dyslipidemia, chronic pain due to osteoarthritis, and gastroesophageal reflux. Concomitant medications included pantoprazole, methocarbamol, tramadol, and enoxaparin. Previous treatment for dyslipidemia was not reported; ongoing treatment included atorvastatin.

The subject received placebo in the parent study from 16 July same year* to 10 September same year*. He was randomized to the standard of care arm in Study 20120138 on 08 October [redacted]. Approximately 1 month later, in November same year*, the subject experienced worsening of chronic pain. He was admitted to the hospital for planned rehabilitative therapy on 18 November same year*. Additional treatments for the event of pain included ibuprofen. No action was taken with the standard of care medication due to the event. The event of pain resolved on 06 December 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 of pain was related to any study activity.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Placebo SC QM + Ezetimibe PO QD 10 mg Year 1: Standard of Care
Report: Sciatica

Subject [redacted] was a 56-year-old white man participating in Study 20120138 who experienced sciatica (reported term: ischialgia). The subject's medical history included primary hyperlipidemia and mixed hyperlipidemia, hypertension, insomnia and alopecia. Concomitant medications included mirtazapine, enalapril and finasteride. Previous and ongoing treatment for hyperlipidemia and dyslipidemia was not provided.

The subject received placebo in the parent study from 05 July same year* to 13 September same year*. He was randomized to the standard of care arm in Study 20120138 on 26 September [redacted]. Approximately 4 weeks later, on 23 October same year*, the subject developed acute pain in the ischial area of his hip and was hospitalized on 26 October same year*. Treatments for the event included an unspecified local injection, manual therapy, heat and tramadol. There were no relevant findings on laboratory and other diagnostic testing. No action was taken with the standard of care medication due to the event. The event of sciatica resolved on 23 October same year*, and the subject was discharged from the hospital on 26 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 sciatica was related to study conduct.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Evolocumab SC Q2W 140 mg + Placebo PO QD Year 1: Standard of Care
Report: Fibromyalgia

Subject [redacted] was a 48-year-old white woman participating in Study 20120138 who experienced fibromyalgia (reported term: worsening fibromyalgia). The subject's medical history included dyslipidemia, osteoporosis, coronary heart disease, hypertension, hypothyroidism, menopause, osteopenia, fibromyalgia and restless leg syndrome. Concomitant medications included acetylsalicylic acid, progesterone, vitamin D, levodopa-benserazide, carvedilol, levothyroxine, losartan, estradiol, and venlafaxine. Previous treatment for dyslipidemia was not reported; ongoing treatment included simvastatin.

The subject received evolocumab in the parent study from 03 July same year* to 09 September same year*. She was randomized to the standard of care arm in Study 20120138 on 14 October [redacted]. Approximately 5 months later, on 17 March one year after*, the subject experienced worsening of fibromyalgia. On the same day, the events of osteopenia and restless leg syndrome were also reported. She was hospitalized on 17 March one year after* for worsening of fibromyalgia, to evaluate and optimize its treatment. No action was taken with the standard of care medication due to the event. The subject was discharged from the hospital on 02 April one year after*, and the event of fibromyalgia resolved on that same date. Treatment medications included: venlafaxine, benserazide, levodopa, progesterone, and vitamin D.

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 fibromyalgia was related to study conduct.

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Subject No: [redacted]
Treatment: Parent study and regimen: Study 20110115, Placebo SC QM + Placebo PO QD Year 1: Standard of Care
Report: Lumbar vertebral fracture

Subject [redacted] was a 68-year-old white woman participating in Study 20120138 who experienced a lumbar vertebral fracture (reported term: fracture lumbar interbody 3 traumatic). The subject's medical history included dyslipidemia, chronic gastritis, and chronic obstructive pulmonary disease. Concomitant medications included omeprazole, budesonide, and formoterol. Previous and current treatment for primary hyperlipidemia or mixed dyslipidemia included atorvastatin.

The subject received placebo in the parent study from 15 May same year* to 12 August same year*, and was randomized to standard of care in Study 20120138 on 03 September [redacted].

Approximately 2 weeks later, on 17 September same year*, after working, the subject developed back pain (dorsalgia). Some days later, she went to her practitioner and was started on diclofenac 75 mg 3 times daily. The pain did not improve, so she presented to the hospital on 30 September same year*. On that day, the subject was hospitalized and was diagnosed with lumbar vertebral fracture. On 01 October same year*, she underwent kyphoplasty of the lumbar interbody 3. On 03 October same year*, diclofenac was decreased to 75 mg one-half tablet twice daily. The subject was discharged from the hospital on the same day. The event of lumbar vertebral fracture was reported as resolved on 03 October same year*.

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

The investigator reported that there was no reasonable possibility that the event of lumbar vertebral fracture was related to study conduct.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Evolocumab SC QM 420 mg +Placebo PO QD Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Sciatica

Subject [redacted] was a 68-year-old white woman participating in Study 20120138 who developed sciatica. She has a medical history of lumbar back (spinal) pain since thirteen years ago*, cervicobrachial syndrome, gastroesophageal reflux disease, and hypothyroidism. She was a very active runner. Concomitant medication included amlodipine, candesartan, hydrochlorothiazide, metoprolol, acetylsalicylic acid, promethazine, metamizole, and pantoprazole. Previous and ongoing treatment for hyperlipidemia included atorvastatin.

The subject received evolocumab in the parent study from 01 August same year* to 24 October same year*. She received the first dose of evolocumab in Study 20120138 on 07 November [redacted]. Approximately 12 weeks after the first dose, on 10 February one year after*, the subject experienced lumboischialgia on the right. One month later on 10 March one year after*, the subject was hospitalized for further diagnostic and therapeutic measures. The subject was diagnosed with osteochondrosis and disk degeneration at L1-S1, scoliosis at the thoracolumbar junction, and multi segmental protrusion arthrosis of the zygapophyseal joints. Treatment included unspecified analgesic medication, physical measures, and unspecified local injections. The outcome of the event lumboischialgia was reported as resolved on 11 March one year after* and the subject was discharged from the hospital on the same day No action was taken with evolocumab or standard of care treatment. No additional treatment was reported.

The subject's last dose of evolocumab prior to the event was on 30 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 30 January one year after*.

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

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Placebo SC Q2W + Ezetimibe PO QC 10 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Angina pectoris, Syncope

Subject [redacted] was a 52-year-old white woman participating in Study 20120138 who developed angina pectoris and syncope. The subject's medical history included hyperlipidemia, hypertension, gastroesophageal reflux disease, carotid sinus syndrome, intermittent second degree atrioventricular (AV) block, and coronary heart disease. Concomitant medications included trimetazidine, amlodipine, carvedilol, losartan, clopidogrel, clonazepam, hydrochlorothiazide, glyceryl trinitrate, indapamide, vinpocetine, meloxicam, and esomeprazole. Previous treatment for hyperlipidemia was not reported; ongoing treatment included ezetimibe.

The subject received placebo and ezetimibe in the parent study from 27 June same year* to 19 September same year*. She received the first dose of evolocumab in Study 20120138 on 03 October [redacted]. Approximately 2.5 months after the first dose, on 17 December same year*, the subject developed angina pectoris and syncope and was hospitalized on 18 December same year*. Coronary angiography showed left main disease on an unspecified date. Evolocumab was temporarily withheld due to the events. The subject underwent aorto-coronary bypass graft (CABG) surgery on 16 January one year after*. Additional treatment included heparin. On 27 January one year after*, the events of angina pectoris and syncope were reported as resolved, and the subject was discharged from the hospital on the same day. The subject was in cardiac rehabilitation from 27 January one year after* until 18 February one year after*. Investigational product was restarted on 27 February one year after*.

The subject's last dose of evolocumab prior to the event was on 26 November same year*. As of the data cutoff date of [redacted], the subject was continuing home dosing and the last in-clinic dose of evolocumab was documented on 27 February one year after*.

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

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Evolocumab SC Q2W 140 mg Year 1: Standard of Care
Report: Atrial fibrillation

Subject [redacted] was a 70-year-old white woman participating in Study 20120138 who developed atrial fibrillation. The subject's medical history included dyslipidemia, hypertension, Type 2 diabetes mellitus, hysterectomy, hyperlipidemia, atherosclerosis of carotid artery, and atrial fibrillation since seven years ago*. Concomitant medications included metformin, acetylsalicylic acid, glimepiride, amlodipine, ramipril, metoprolol, spironolactone, and captopril. Previous treatment for dyslipidemia was not reported; ongoing treatment included atorvastatin.

The subject received evolocumab in the parent study from 27 June same year* to 19 September same year*. She was enrolled in Study 20120138 on 03 October [redacted] and was assigned to the standard of care treatment. Approximately 2 months later, on 02 December same year*, the subject complained of palpitations. The subject was hospitalized and followed with Holter monitoring, which showed 3 ventricular extrasystoles (VES) and 129 supraventricular extrasystoles (SVES) with heart rate of 59 beats per minute and no atrial fibrillation. Chest radiograph showed enlargement of the heart but normal appearing lungs. The subject's ambulatory blood pressure monitoring was elevated at 179/74 (mean arterial pressure 109 mmHg) and her pulse rate 62 beats per minute. Spirometry testing was normal. No action was taken with the standard of care treatment due to the event. Treatment medications after the onset of event included indapamide, propafenone and rilmenidine. The event of atrial fibrillation was reported as resolved on 02 December same year* and the subject was discharged from the hospital on 19 December 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 atrial fibrillation was related to study conduct.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Evolocumab SC QM 420 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Uterine hemorrhage

Subject [redacted] was a 46-year-old white woman participating in Study 20120138 who experienced a uterine hemorrhage (reported term: excessive bleeding from the uterus). The subject's medical history included dyslipidemia, hypertension, uterine leiomyoma, hypercholesterolemia, and irregular menstruation. Concomitant medications included perindopril. Previous and ongoing treatment for hyperlipidemia included simvastatin.

The subject received evolocumab in the parent study from 24 July same year* to 20 September same year*. She received the first dose of evolocumab in Study 20120138 on 17 October [redacted]. Between 17 December same year* and 17 January one year after* the subject had menorrhagia. On 17 January one year after*, the subject was hospitalized because of the bleeding and underwent uterine curettage on the same day. No additional treatments were reported, and no action was taken with the study medications. The event of uterine hemorrhage resolved on 18 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 12 December same year*. As of the data cutoff date of [redacted], the subject had ended the study on 20 February one year after* due to withdrawal of consent. No further details were provided.

The investigator reported that there was not a reasonable possibility that the event of uterine hemorrhage was related to evolocumab or device. The investigator also confirmed that a predisposing risk factor for the event included leiomyoma.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Evolocumab SC QM 420 mg Year 1: Evolocumab SC QM 420 mg + Standard of Care
Report: Angina pectoris

Subject [redacted] was a 71-year-old white man participating in Study 20120138 who experienced angina pectoris. Medical history reported included dyslipidemia, mitral and tricuspid valve incompetence, osteoarthritis, cervicobrachial syndrome, coronary artery disease with previous myocardial infarction and angina pectoris, atrial fibrillation and cerebrovascular disorder. Concomitant medications included amiodarone, losartan, glyceryl trinitrate, piracetam, amlodipine, rilmenidine, pantoprazole, and warfarin. Previous treatment for dyslipidemia was not reported; ongoing treatment included atorvastatin.

The subject received evolocumab in the parent study from 05 July same year* to 30 August same year*. He received the first dose of evolocumab in Study 20120138 on 26 September [redacted]. Approximately 6 months later, on 30 March one year after*, the subject developed angina pectoris. The subject was hospitalized on the same date. Troponin I values on 30 and 31 March were normal. ECG did not disclose acute ischemic changes. The subject's blood pressure was between 170/90 and 210/90 mmHg.On 01 April he underwent coronarography, which did not show any stenosis amendable to intervention. Treatments included glyceryl trinitrate and trimetazidine. No additional treatments were reported, and no action was taken with the study medications. The subject's blood pressure was normalized. The event of angina pectoris resolved on 03 April one year after*, and he was discharged on 07 April one year after*

The subject's last dose of evolocumab prior to the event was on 14 March one year after*. The subject was continuing home dosing as of the data cutoff date of [redacted].

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

*新薬承認情報提供時に置き換え