Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q4W 350 mg Year 1 treatment: Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Uterine prolapse, Cystocele

Subject [redacted] was a 53-year-old white woman participating in Study 20110110 who developed uterine prolapse and cystocele (reported term: vaginal cystocele). The subject's medical history included hypercholesterolemia, menopause at age 48, and she was a smoker. Concomitant medications included amiloride, hydrochlorothiazide, clobetasol, ketoconazole, magnesium, potassium, pyridoxine, simvastatin, and acetylsalicylic acid. Previous and current treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 26 September two years ago* to 20 December two years ago* and received the last dose of evolocumab in the parent study on 24 November two years ago*. The subject was randomized to the standard of care arm on 20 December two years ago* and received the first dose of evolocumab in Study 20110110 on 15 January [redacted].

On 31 October one year ago*, the subject was diagnosed with vaginal cystocele. On 16 January same year*, the subject was referred for prolapse. An ultrasound was normal, showed normal ovaries and a small uterus; bladder had a pre void volume of 450 and 80 cc post void. The subject reported that she felt her uterus was falling out and the pressure symptoms were significant; this was also interfering with intercourse. Examination showed grade 2 to grade 3 cystocele and prolapse of the uterus, grade 2. The subject did not have a rectocele and adnexal examination was unremarkable. A urinary catheter was left in overnight as well as a packing placed in the vagina. The investigator confirmed that the event started when the subject was on standard of care and that surgery was planned to be done during the open-label phase.

Approximately 3 months and 2 weeks after the first dose of evolocumab in Study 20110110, on 02 May same year*, the subject was hospitalized due to uterine prolapse and vaginal cystocele.

On the same day, 02 May same year*, rectal swab culture was performed and no methicillin-resistant *Staphylococcus aureus*, no vancomycin resistant Enterococcus species and no extended spectrum beta lactamase (BSBL) producing organisms were isolated. On the same date, the

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subject underwent a vaginal hysterectomy and anterior repair without complications. Additional treatment included oxycodone. Additional treatment reported after the onset of the event included morphine and bupivacaine with epinephrine. The events of uterine prolapse and cystocele were reported to have resolved on 02 May same year* and the subject was discharged from the hospital on 04 May same year*. On 11 June same year*, the vault of the vagina was well healed and there was no prolapse whatsoever. The pathology report showed a weakly proliferative endometrium and normal cervix.

The subject's last dose of evolocumab prior to hospitalization was on 30 April same year*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study, and received the last dose of evolocumab prior to the data cutoff date on [redacted]. The investigator reported that there was no reasonable possibility that the events of uterine prolapse and cystocele were related to evolocumab.

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Subject No: [redacted]
Treatment: Parent study: Evolocumab SC Q2W 140 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Breast cancer

Subject [redacted] was a 72-year-old white woman participating in study 20110110, who was diagnosed with breast cancer (reported term: left breast cancer). The subject's medical history included hypercholesterolemia. Concomitant medications included combination of hydrochlorothiazide and triamterene, cyclobenzaprine, valsartan, fluticasone, mupirocin ointment, potassium chloride, triamcinolone acetonide, prednisone and salbutamol. Previous and current treatment for hypercholesterolemia included rosuvastatin.

The subject was in the parent study from 03 November one year ago* to 07 February same year* and received the last dose of evolocumab in the parent study on 10 January same year*. The subject received the first dose of evolocumab on 07 February [redacted].

Approximately 1 year and 4 months later, on 25 June one year after*, the subject underwent a computed tomography scan of the thorax, which revealed presence of numerous mildly enlarged mediastinal lymph nodes. Hazy extensive ground glass opacities were present in the right middle lobe and lower lobes bilaterally, associated with bronchiectasis and bronchiolectasis. More mild patchy areas of ground glass were noted in the upper lobes. There was a mild component of subpleural nonseptal fine reticulation with a more mid to lower lung zone predominance. Minor component of subpleural microcystic honeycombing was found in lungs. There was a mildly lobulated 14-mm soft tissue nodular density in the lateral aspect of the left breast.

A month later, on 18 July one year after*, the subject underwent bilateral mammography and ultrasound of breast, which revealed a spiculated mass within the left upper outer quadrant, towards 3 o'clock position, corresponding with the mass seen on computed tomography scan. Ultrasound examination showed presence of an irregular hypoechoic mass along the 3 o'clock position, 7 cm from the nipple corresponding with the mammographic mass and measuring 2.1 x 1.4 cm. Several minimally complicated scattered cysts were documented. Normal-appearing lymph nodes were noted. The breast core biopsy showed invasive mammary

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carcinoma, no special type, estimated Scarff-Bloom-Richardson grade II/III (score 6-7/9). No definite in situ component was seen. Microcalcifications were focally present in invasive tumor.

As of 29 August one year after*, the subject's lung disease seemed to restrict her mobility. She was recommended to have an open lung biopsy for better diagnosis and management plan. On 12 September one year after*, the subject underwent ultrasound localization of left breast, and the lumpectomy revealed invasive mammary carcinoma; margins were negative for invasive mammary carcinoma. Breast tissue re-excision of the medial margin showed fibrocystic changes, although was negative for malignancy. The BI-RADS IV test proved malignancy.

On 18 September one year after*, the subject underwent a VATS (video-assisted thoracoscopic surgery) right lung biopsy for interstitial lung disease and left breast lumpectomy with sentinel node biopsy. On 19 September one year after*, the subject was referred for lymphoscintigraphy sentinel node study prior to lumpectomy and sentinel nose biopsy for left breast cancer. A sentinel node was identified in the left anterior axilla. Postoperative diagnosis revealed invasive mammary carcinoma and interstitial lung disease. The subject did well postoperatively and was discharged with medications including combination of amlodipine and hydrochlorothiazide, fluticasone, cyclobenzaprine, rosuvastatin, valsartan, ibuprofen, salbutamol, and combination of paracetamol and tramadol. The event was reported as not resolved. Additional medications for the treatment of breast cancer include anastrazole from 27 December one year after* to 27 February two years after* and denosumab started on 17 January two years after*.

The subject's last dose prior to the event was on 25 June one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study, and received the last dose of evolocumab prior to the data cutoff date on [redacted].

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

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Parent study: Evolocumab SC Q2W 105 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Nephrolithiasis

Subject [redacted] was a 70-year-old white man participating in Study 20110110 who developed nephrolithiasis (reported term: left kidney stone enlarged). The subject's medical history included hypercholesterolemia, nephrolithiasis, hypertension, hypoacusis (right ear), obesity, intervertebral disc degeneration, osteoarthritis, anxiety, depression, benign prostatic hyperplasia, osteopenia, insomnia, rhinitis, and drug hypersensitivity (to codeine). The subject had no prior history of kidney stone removal. Concomitant medications included alendronic acid, morniflumate, finasteride, calcium, hydrochlorothiazide, acetylsalicylic acid, sertraline hydrochloride, alprazolam, tamsulosin, rosuvastatin calcium, colecalciferol, esomeprazole magnesium, and naproxen. Previous and current treatment for hypercholesterolemia included rosuvastatin.

The subject was in the parent study from 13 September same year* to 20 December same year* and received the last dose of evolocumab in the parent study on 22 November same year*. The subject received the first dose of evolocumab in Study 20110110 on 20 December [redacted].

Approximately 10 months later, On 03 October one year after*, an abdominal ultrasound revealed fatty infiltration of the liver; left kidney: multiple large stones 2 cm x 1.6 cm in the renal pelvis, 1.4 cm, 7 mm, 1.1 cm stones in the lower calyx, moderate hydronephrosis was noted; right kidney was intact with a small lower pole cortical cyst 3.4 x 3.2 cm. The subject had no prior history of kidney stone removal. On 22 November one year after*, the subject was hospitalized and underwent surgery (left percutaneous nephrostolithotomy) for removal of the left kidney stone on the same date. Treatment medication for the event included escitalopram and oxycodone. The event of nephrolithiasis was reported as resolved on 22 November one year after* and the subject was discharged from the hospital on 24 November one year after*.

The subject's last dose of evolocumab prior to hospitalization was on 20 November one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject received the last dose of evolocumab on 11 March three years after*.

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The investigator reported that there was no reasonable possibility that the event of enlarged kidney stone was related to evolocumab.

Subject No: [redacted]
Treatment: Parent study: Evolocumab SC Q4W 280 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Hemorrhoidal hemorrhage

Subject [redacted] was a 68-year-old white woman participating in Study 20110110 who experienced a hemorrhoidal hemorrhage (reported term: rectal bleed due to hemorrhoids). Her medical history included hypercholesterolemia, hypertension, osteoporosis, varicose veins, overweight, osteoarthritis, fibrocystic breast disease, allergies to bee sting and pyridium (phenazopyridine), internal hemorrhoids, and rectal bleeding. Concomitant medications included combination of hydrochlorothiazide and irbesartan; combination of calcium carbonate and colecalciferol; zoledronic acid; rosuvastatin; and ketotifen. Previous treatment for hypercholesterolemia included rosuvastatin.

The subject was in the parent study from 22 November one year ago* to 14 February same year* and received the last dose of evolocumab in the parent study on 17 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 14 February [redacted]. On 08 April same year*, the subject was diagnosed with rectal bleeding due to hemorrhoids and was hospitalized on 09 April same year*. On 10 April same year*, colonoscopy and gastroscopy were non-contributory. The event was reported to have resolved on 10 April same year* and the subject was discharged on the same day.

The last dose of evolocumab prior to the event was on 20 March same year*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff date on [redacted]. The investigator reported that there was no reasonable possibility that the event of hemorrhoidal hemorrhage was related to evolocumab. The investigator considered hemorrhoids as an etiological or pre-disposing risk factor associated with the event.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q4W 420 mg Year 1 treatment: Evolocumab SC 420 mg Q4W + Standard of care Years 2-5 treatment: Evolocumab SC 420 mg QM + Standard of care
Report: Metastatic lymphoma, Anal cancer stage 0

Subject [redacted] was a 63-year-old white woman participating in Study 20110110 who developed anal cancer stage 0. The subject's medical history included hypercholesterolemia, tonsillectomy, appendectomy, oophorectomy, cesarean section (twice), laparoscopy, hysterectomy, cardiac ablation, and a family history of lymphoma, breast cancer, and uterine cancer. Concomitant medications included estradiol, acebutolol, Vitamin B12, esomeprazole, potassium, ergocalciferol, calcium, and naproxen. Previous and ongoing treatment for hypercholesterolemia included atorvastatin.

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

On 27 January two years after*, the subject developed a lump in a left groin lymph node. The inguinal mass was firm in texture and freely mobile. On an unknown date, testing for Lyme disease was negative and papanicolaou (PAP) smear was normal. The lump continued to enlarge and became painful and a biopsy was conducted on 27 January two years after* that revealed metastatic squamous cell carcinoma with necrosis involving lymph node, and was reported as metastatic lymphoma. On 07 February two years after* the subject had a colonoscopy with biopsies of anal canal lesion that revealed multiple small fragments of metastatic squamous epithelium cell similar in appearance to the lymph node biopsy. Biopsy revealed a non-invasive component of the malignancy. Computed tomography of thorax, abdomen and pelvis from 20 February two years after* did not evidence metastatic disease. As of the last report no treatment had been given, with treatment to be determined following surgery. The events were ongoing.

The subject's last dose of evolocumab prior to the event was on 16 January two years after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study, and received the last dose of evolocumab prior to the data cutoff date on [redacted].

The investigator reported that there was no reasonable possibility that the event anal cancer stage 0 was related to evolocumab.

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Considering the results of the anal biopsy, the Sponsor considers the diagnosis of metastatic lymphoma inappropriate. Furthermore, the Sponsor finds a diagnosis of metastatic disease to be inconsistent with the report of Stage 0 cancer. Discussions are ongoing between the Sponsor and the investigational site to clarify the information from this interim datacut.

Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q2W 70 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Spontaneous abortion, Ectopic pregnancy

Subject [redacted] was a 32-year-old pregnant Asian woman participating in Study 20110110 who had a spontaneous abortion (reported term: miscarriage) and an ectopic pregnancy (reported term: termination of ectopic pregnancy). The subject's medical history included hypercholesterolemia, dyslipidemia, plantar fasciitis, right anterior cruciate ligament tear, 2 previous term pregnancies in ten years ago* and four years ago* with normal vaginal delivery of male infants and high blood pressure during her pregnancies. Concomitant medications included ibuprofen, prednisone, and paracetamol. Previous and ongoing treatment for hypercholesterolemia included rosuvastatin.

The subject was in the parent study from 04 October one year ago* to 06 January same year* and received the last dose of evolocumab in the parent study on 13 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 06 January [redacted].

Approximately a year later, on 14 November same year*, the subject was confirmed to be pregnant by a positive urine analysis. Human chorionic gonadotropin (hCG) was 36 IU/L. The date of the last menstrual period prior to conception was on 03 October same year*. Evolocumab was discontinued. On 18 November same year*, the subject notified the investigator that she had had a miscarriage. A follow-up visit on 24 November same year* did not disclose any complication. On 24 November same year*, blood hCG was less than 5 IU/L.

On 04 January one year after*, the subject took a pregnancy test that was found to be positive: beta-hCG of 1,842 IU/L. On 09 January one year after*, the subject presented to the emergency room due to sudden onset of left lower quadrant pain which became more severe as the day progressed. An ultrasound revealed anteverted uterus with no intrauterine gestational sac and thickened endometrium. Left adnexa with cystic mass measuring 9 mm revealed a gestation of 5 weeks and 6 days. A 4-mm echogenic focus was seen which represented a small fetus corresponding to 6 weeks. Complex fluid was noted in both adnexa and in the pouch of Douglas, possibly a hematoma. The findings suggested a ruptured ectopic pregnancy. A laparoscopy evidenced

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ruptured fallopian tube. Ligation of left Fallopian tube and resection of ectopic pregnancy were performed. The subject received transfusion of 2 units of blood intraoperatively. The event ectopic pregnancy was reported as resolved on 09 January one year after*, and the subject was discharged on 11 January one year after*.

The subject's last dose of evolocumab prior to both the events was on 13 October same year*. Evolocumab was discontinued. As of the data cutoff date of [redacted], the subject was continuing in the study with follow-up visits by telephone.

The investigator reported that there was no reasonable possibility that the events of spontaneous abortion or ectopic pregnancy were related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Parent study: Evolocumab SC Q2W 140 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Osteoarthritis

Subject [redacted] was a 56-year-old white man participating in Study 20110110 who developed osteoarthritis (reported term: gonarthrosis). The subject's medical history included hypercholesterolemia, asthma, hypertension, cholecystectomy, osteoarthritis, knee arthroplasty, spinal operation, and umbilical hernia repair. Concomitant medications included trandolapril, rilmenidine, hydrochlorothiazide, urapidil, ciclesonide, and combination of budesonide and formoterol. Previous and current treatment for hypercholesterolemia was atorvastatin.

The subject was in the parent study from 24 November one year ago* to 28 February same year* and received the last dose of evolocumab in the parent study on 31 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 28 February [redacted].

Approximately 9 months later, on 20 November same year*, the subject was hospitalized for a planned total knee replacement, which was performed on 21 November same year*. Treatment included gabapentin; rivaroxaban; potassium iodide; combination of Vitamin B complex and tocopheryl; ciprofloxacin, combination of caffeine, paracetamol, and propyphenazone; and rehabilitation therapy. On an unspecified date, only basic laboratory tests such as biochemistry and blood cell count were performed and the results were within normal ranges. The event of osteoarthritis was reported as resolved on 15 December same year*, and the subject was discharged from the hospital on the same date after rehabilitation.

The subject's last dose of evolocumab prior to the event was on 06 November same year*. Evolocumab was temporarily withheld and was restarted on 27 December same year*.

As of the data cutoff date of [redacted], the subject was continuing in the study, and received the last dose of evolocumab prior to the data cutoff date on [redacted].

The investigator reported that there was no reasonable possibility that the event of osteoarthritis was related to evolocumab

*新薬承認情報提供時に置き換え

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

Subject [redacted] was a 43-year-old white man participating in Study 20110110 who had a joint dislocation (reported term: dislocation of the right shoulder). The subject's medical history included hypercholesterolemia, coronary artery disease, myocardial infarction, percutaneous coronary intervention, knee surgery, hyperlipidemia, and shoulder operation. Concomitant medications included bisoprolol fumarate, perindopril arginine and acetylsalicylic acid. Previous treatment for hypercholesterolemia included atorvastatin.

The subject was in the parent study from 10 October one year ago* to 02 January same year* and received the last dose of evolocumab in the parent study on 05 December one year ago*. The subject received the first dose of evolocumab in study 20110110 on 25 January [redacted].

After approximately 9 months, on 05 October same year*, the subject experienced dislocation of the right shoulder during a hockey match. The subject was transported by the emergency ambulance with subluxation of the right shoulder; reposition was not successful even after several attempts with diazepam administration. Upon physical examination, subject was conscious and oriented; signs of shock and/or alteration were not present; cardiac and pulmonary functions were controlled; eupneic; and temperature was normal. The subject's right shoulder glenoid fossa was blank; head was palpable on ventrocaudal side and peripheral neural and circulation conditions were good. The subject was hospitalized on the same day (05 October same year*).

On 06 October same year*, the subject underwent reposition of the right shoulder by Kocher's maneuver under general anesthesia; configuration and passive mobility of the glenohumeral joint was restored, and fixated with the orthosis. There was no neural and circulation deficit; orthosis suited; and the subject did not report pain. Treatment medications included diazepam, propofol, and Plasma-Lyte solution (electrolytes). On 06 October same year*, the subject was discharged from the hospital to home care. The event was reported as resolved on 22 October same year*.

*新薬承認情報提供時に置き換え

The subject's last dose of evolocumab prior to the event was on 07 September same year*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject received the last dose of evolocumab on 21 March two years after*.

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

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Parent study: Evolocumab SC Q2W 105 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Muscle rupture, Pulmonary embolism, Pneumonia

Subject [redacted] was a 61-year-old white man participating in Study 20110110 who experienced a muscle rupture (reported term: rupture of the right rectus femoris after trauma of the right knee), pulmonary embolism (reported term: pulmonary embolism), and pneumonia (reported term: pleuropneumonia on the left). The subject's medical history included hypercholesterolemia, hypertension, type 2 diabetes mellitus, metabolic syndrome, pernicious anemia, duodenal ulcer, Gilbert's syndrome, goiter, back pain, axial hernia of esophagus, prostatic disorder, and drug intolerance (to acetylsalicylic acid, rosuvastatin, and atorvastatin). Concomitant medications included ramipril, metoprolol, omeprazole, itopride, metformin, simvastatin, and cyanocobalamin. Previous treatment for hypercholesterolemia included ramipril, metoprolol, omeprazole, itopride, metformin, simvastatin, and cyanocobalamin.

The subject was in the parent study from 10 October one year ago* to 19 January same year* and received the last dose of evolocumab in the parent study on 21 December one year ago*.

On 12 February same year*, the subject was hospitalized due to trauma of the right knee and was diagnosed with muscle rupture. The next day, on 13 February same year*, surgery, revision, and suture were carried out with no complications. An orthesis, verticalization with crutches and rehabilitation were performed. Treatment included enoxaparin, combination of amoxicillin and clavulanate, tramadol, escin, and diazepam. The event of muscle rupture was reported as resolving and the subject was discharged from the hospital on 17 February same year*.

Approximately 6 weeks after the first dose of evolocumab, on 09 March same year*, and after discontinuing anticoagulant therapy with mobilization for muscle rupture, the subject developed dyspnea and noncardiac chest pain on the left side of his chest. The next day, on 10 March same year*, the subject was hospitalized due to pulmonary embolism and pneumonia. A computerized tomography angiogram of the chest showed "pulmonary embolism on both sides, more right (lobar, segmental branches)" with "compensation of parenchyma on the left basal with fluidothorax". Metabolic syndrome and insufficient mobilization were reported as post-operative conditions leading to the development of pulmonary embolism and secondary

*新薬承認情報提供時に置き換え

pneumonia. Laboratory tests revealed creatinine 103 µmol/L, C-reactive protein 26.8 mg/L, D-dimer 20.680 FEU (fibrinogen equivalent units)/mL, hemoglobin 14.7 g/dL, troponin I undetectable, sodium 136 mmol/L, potassium 4.0 mmol/L, and glucose 7.8 mmol/L. Treatment for the events of pulmonary embolism and pneumonia included enoxaparin and combination of amoxicillin and clavulanate. The events of pulmonary embolism and pneumonia were reported as resolved on 19 March same year*, and the subject was discharged from the hospital on the same day.

On 13 June same year*, the subject was hospitalized, and a radiograph of the right knee showed a fracture of the metallic material. The next day, on 14 June same year*, the subject underwent an extraction of the fragmental metal material from the right rectus femoris without complications. On 17 June same year*, INR was 1.16 and on 26 June same year*, the INR was 2.3. Treatment included warfarin and escin. The subject was discharged from the hospital on 26 June same year* and the event of muscle rupture was reported to have resolved on 29 June same year*.

The subject's last dose of evolocumab prior to the event of muscle rupture was on 20 January same year*. The subject's last dose of evolocumab prior to the events of pulmonary embolism and pneumonia was on 20 February [redacted]. Evolocumab was withheld after the dose on 20 February same year* due to anticoagulant therapy, disability, and risk of drug interaction, and restarted on 28 February one year after*.

As of the data cutoff date of [redacted], the subject was continuing in the study, and received the last dose of evolocumab prior to the data cutoff date on [redacted]. The investigator reported that there was no reasonable possibility that the events of muscle rupture, pulmonary embolism, and pneumonia were related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q4W 280 mg Year 1 treatment: Evolocumab SC 420 mg QM + Standard of Care Years 2-5 treatment: Evolocumab SC 420 mg QM + Standard of care
Report: Gastroenteritis

Subject [redacted] was a 48-year-old white man participating in Study 20110110 who developed acute gastroenteritis. The subject's medical history included hypercholesterolemia, hypertension, hyperglycemia, hepatic steatosis, obesity, benign extrasystoles, dry cough following treatment with angiotensin converting enzyme inhibitors (ACEI), gastroesophageal reflux disease, hiatal hernia, irritable bowel syndrome, diverticulosis of the sigmoid, and appendectomy. Concomitant medications included omeprazole, ramipril, omeprazole, amlodipine, losartan, an acetaminophen/salicylate/codeine compound, tizanidine, phenoxymethylpenicillin, ibuprofen, diprospan, bupivacaine, nimesulide, erdosteine, aminophylline, minalgan, Vitamin E, and cefuroxime. Previous and ongoing treatment for hypercholesterolemia included pravastatin and fluvastatin.

The subject received evolocumab in the parent study from 03 November one year ago* to 26 January same year* and received the last dose of evolocumab in the parent study on 28 December one year ago*. The first dose of evolocumab in Study 20110110 was on 26 January [redacted].

The subject developed bursitis of shoulder in November or December one year after* and, at an unknown date near the end of December one year after*, developed a bacterial infection of the respiratory tract and was treated with unspecified antibiotics. On 26 December one year after*, the subject developed acute gastroenteritis and was admitted to the hospital on the following day. Laboratory tests revealed amylase 0.78 µkat/L (46.8 U/L), bilirubin 13.7 µmol/L, alanine aminotransferase 0.78 µkat/L (46.8 U/L), C-reactive protein (CRP) 14 mg/L, leukocyte count 13.21 x 10^9/L, and hemoglobin 160 g/L. Laboratory tests on 30 December one year after* showed leukocyte count of 5.17 x 10^9/L and hemoglobin of 147 g/L. The subject was discharged with the event improving. On 07 January two years after* ultrasonogram revealed edema of the head of the pancreas, and the subject was treated with pancreatin, diclofenac potassium, thiethylperazine, metoclopramide, and electrolites. The event was reported as resolved on 14 January two years after*. A computed tomography (CT) on 20 January two years after* showed normal pancreas and sigmoidal diverticulosis, and 3 days later an ultrasonogram confirmed normal pancreas. The subject's last dose of evolocumab before the event was on 20 December one year after*. As of the data cutoff date of [redacted], the subject was

*新薬承認情報提供時に置き換え

continuing on the study, and the date of the last dose of evolocumab prior to the data cutoff date was [redacted].

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

Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q4W 280 mg Year 1 treatment: Evolocumab SC Q4W 420 mg Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Sinus polyp

Subject [redacted] was a 56-year-old white man participating in Study 20110110 who developed a sinus polyp (reported term: inflammatory polypous in the left maxillary sinus). The subject's medical history included hypercholesterolemia and a prolonged history of sneezing. Concomitant medications included acetylsalicylic acid, losartan, methylprednisolone, trimecaine, budesonide, desloratidine, mometasone, benzodiazepine derivatives, paramax, zolpidem, nadroparin, naphazoline, diclofenac, atropine, naloxone, neostigmine, and pyrazolones.

Previous and ongoing treatment for hypercholesterolemia included atorvastatin.

The subject was in the parent study from 09 November one year ago* to 31 January same year* and received the last dose of evolocumab in the parent study on 04 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 31 January [redacted]. .

Approximately 1 year and 10 months after randomization, on 27 November one year after*, the subject experienced intermittent sneezing that was worsening, and was found to have inflammatory polyps in the left maxillary sinus. On 03 December one year after*, a computerized tomography (CT) scan of the paranasal sinus revealed a retention cyst in the left maxillary sinus. On 07 January two years after*, C-reactive protein (CRP) was 3.8 mg/L (normal 0 to 5 mg/L). The next day on 08 January two years after*, laboratory tests revealed leukocytes 5.8x10^9/L (normal 4 to 10 x10^9/L) and hemoglobin 153 g/L (normal 135 to 175 g/L). The subject was hospitalized on 14 January two years after*. On 15 January two years after*, an antrostomy was performed without complications. The subject was discharged on 17 January two years after*. On 23 January two years after*, the histology from the surgery revealed polypous with signs of chronic inflammation. Treatments reported after the onset of the event included nadroparin, naphazoline, zolpidem, nitrazepam, "paratiax", diclofenac, a caffeine/paracetamol/propyphenazone preparation, electrolytes, atropine, syntostigmin, and naloxone. The outcome of the event of inflammatory polyps in the left maxillary sinus was reported as recovering.

The investigator reported that there was not a reasonable possibility that the event inflammatory polypous in the left maxillary sinus was related to investigational product.

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

Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q2W 70 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Osteomyelitis

Subject [redacted] was a 35-year-old white woman participating in Study 20110110 who developed osteomyelitis (reported term: osteomyelitis of the base distal phalanx finger right upper limb). The subject's medical history included hypercholesterolemia since five years ago* and a burned second finger of right hand on 21 August one year after*. Although diabetes was not included in the available medical history, insulin was reported as a concomitant medication. Concomitant medications included sulfamethoxazole/trimethoprim, Iruxol™ (topical collagenase and protease), colecalciferol, bismuth tribromophenate, heparin, framycetin, povidone iodine, doxycylne, amoxicillin clavulinic, amoxicillin, dexamethasone, human insulin, multivitamin combinations, pyrazolones, nadroparin, meropenem, cefuroxime axetil, antidiarrheal medications, and ascorbic acid. Previous and current treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 15 November one year ago* to 21 February same year* and received the last dose of evolocumab in the parent study on 24 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 21 February [redacted].

The subject burned the second finger of her right hand on 21 August one year after*. After repeated antibiotic therapy for 6 months, the injury did not heal and a purulent infection resulted. On 21 January two years after*, the subject developed osteomyelitis from the base of the distal phalynx to the second finger of right upper limb, and the subject experienced fever, fatigue, and sepsis. The subject was hospitalized on 22 January two years after*. Treatment reported after the onset date of the event included meropenem, nadroparin, a caffeine/paracetamol/propyphenazone preparation, multivitamins, and human insulin.

On 23 January two years after*, following therapy, the subject's condition improved. Laboratory tests revealed C-reactive protein was 190.1 mg/L and procalcitonin was 21.25 ng/mL. A radiographic scan of the finger revealed an osteolytic lesion bearing 2 mm of the finger base. Additional tests including a radiographic scan of the chest, transesophageal echocardiogram and ultrasonography of abdomen, which all revealed normal results. The following day, 24 January two years after*, C-reactive protein was 122.2 mg/L and procalcitonin was 9.22 ng/mL.

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On 30 January two years after*, the subject's C-reactive protein was 1 mg/L. The subject was discharged from the hospital on that date. On 04 February two years after*, magnetic resonance imaging (MRI) of the finger showed inflammation infiltrate without signals of osteomyelitis. Additional treatment reported after the onset of the event included cefuroxime.

The outcome of the event osteomyelitis of the base distal phalanx second right finger upper limb was reported as resolved on 18 February two years after*.

The subject's last dose of open label evolocumab prior to the onset of the event was on 20 December one year after*. Open label evolocumab was temporarily withheld and restarted on unspecified dates.

The investigator reported that there was not a reasonable possibility that the event osteomyelitis of the base distal phalynx second finger of her right hand was related to open label investigational product or device.

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

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Parent Study: Evolocumab SC Q2W 105 mg Year 1 treatment: Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg+ Standard of care
Report: Atrial flutter, Inguinal hernia

Subject [redacted] was a 68-year-old white man participating in Study 20110110 who experienced atrial flutter and inguinal hernia (reported term: right inguinal hernia). The subject's medical history included hypercholesterolemia, previous atrial flutter followed by high frequency ablation in right atrium in December three years ago*.

Concomitant medications included combination of acetylsalicylic acid and glycine, glyceryl trinitrate, tamsulosin, atorvastatin, ramipril, nebivolol, clopidogrel, ramipril, chloroxine, allopurinol and combination of sulfamethoxazole and trimethoprim and Vitamin E. Previous treatment for hypercholesterolemia was not reported.

The subject received evolocumab in the parent study from 18 November one year ago* to 28 February same year*. The subject was randomized to Study 20110110 on 28 February [redacted] and assigned standard of care treatment.

Approximately 1 year after the randomization, on 25 February one year after*, the subject had asymptomatic type I atrial flutter and was started on anticoagulation therapy. On 29 February same year*, a transesophageal echocardiography showed good function of chamber with no intracardiac thrombus. On 28 February one year after*, the subject was hospitalized and underwent a radiofrequency ablation in the right atrium. The procedure had no complications and the arrhythmia was terminated. Treatment for the event included nadroparin followed by warfarin to complete 6 weeks on anticoagulation therapy. The event atrial flutter was reported as resolved on 01 March one year after* and the subject was discharged from the hospital on the same day in good clinical condition. On 04 March one year after*, international normalized ratio was at 1.38.

On 03 March one year after*, the subject was diagnosed with an inguinal hernia. The subject was again hospitalized and received unspecified treatment. The event was reported as resolved on 05 March one year after*. At time of the data cutoff further details were not available.

The event of atrial flutter was reported during the first part of the study in which the subject received standard of care treatment. After the completion of 1 year in the study, he received the first dose of evolocumab on 25 March one year after*.

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As of the data cutoff date of [redacted], the subject was continuing in the study and received last dose of evolocumab prior to the data cutoff date on [redacted]. The investigator reported that there was no reasonable possibility that the events of atrial flutter and inguinal hernia were related to any study activity or procedure.

Subject No: [redacted]
Treatment: Parent study: Evolocumab SC Q4W 350 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Noncardiac chest pain, Appendicitis, Spinal pain

Subject [redacted] was a 64-year-old white woman participating in Study 20110110 who developed non cardiac chest pain, appendicitis, and spinal pain (reported term: vertebral chest pain). The subject's medical history included hypercholesterolemia, chronic venous insufficiency, coronary artery disease, and hypertension. Concomitant medications included capiven, glyceryl trinitrate, trimetazidine, and metoprolol.

Previous and current treatment for hypercholesterolemia was atorvastatin.

The subject was in the parent study from 25 October one year ago* to 18 January same year* and received the last dose of evolocumab in the parent study on 21 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 01 February [redacted].

Approximately 4 months later, on 27 May same year*, the subject developed chest pain apparently caused by the spine. The subject was hospitalized the next day. Upon admission, laboratory tests did not reveal abnormalities and ruled out myocardial infarction: myoglobin 21.5 µg/L, creatine kinase muscle-bone (MB) 2.5 µg/L and troponin I <0.01 µg/L. Electrocardiogram and laboratory testing results showed no signs of cardiac ischemia. The subject was treated with fentanyl, clopidogrel, and fondaparinux. The event was reported to have resolved on 29 May same year* and the subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event was on 22 May same year*. Evolocumab was continued after discharge.

On 05 September same year*, the subject experienced abdominal pain and was hospitalized on the same day. The subject was diagnosed with appendicitis and underwent an appendectomy. The event appendicitis was reported as resolved on 08 September same year* and the subject was discharged from the hospital on the same day. Treatment included enoxaparin, metamizole, and pethidine.

The subject's last dose of evolocumab prior to the event of appendicitis was on 13 August same year*. The subject continued in the study.

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On 1 January two years after*, the subject complained of a novel chest pain event, similar to that reported in May same year*. Troponin I was negative and ECG did not reveal ischemic changes. The subject was diagnosed with vertebral chest pain, and was treated with paracetamol, propyphenazone and bisoprolol. The event resolved the following day on 2 January two years after* and was not considered related to evolocumab.

The subject's last dose of evolocumab prior to the event of vertebral chest pain was on 02 December one year after*. As of the data cutoff date of [redacted], the subject was continuing evolocumab dosing, with the last dose before the cutoff on [redacted].

The investigator reported that there was no reasonable possibility that the events of noncardiac chest pain and appendicitis were related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Parent study: Evolocumab SC Q2W 70 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Musculoskeletal chest pain

Subject [redacted] was a 49-year-old white man participating in Study 20110110 who developed musculoskeletal chest pain (reported term: musculoskeletal chest pain). The subject's medical history included hypercholesterolemia, dyslipidemia, hypertension, cough, back pain, paresthesia, and cholecystectomy. The subject had a family history of pulmonary embolism. Concomitant medications included budesonide, and perindopril arginine. Previous treatment for hypercholesterolemia included atorvastatin.

The subject was in the parent study from 23 November one year ago* to 27 February same year* and received the last dose of evolocumab in the parent study on 31 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 27 February [redacted].

On 08 February one year after*, the subject experienced chest pain described as pressure with radiation to the left shoulder and below the left scapula. The subject reported sweating and mild nausea; and blood pressure (BP) rose to 200/100 mmHg. The subject was hospitalized. On admission, BP was 115/70 mmHg; physical examination revealed symmetric chest, spine was not tender at percussion, breathing was alveolar and auxiliary phenomenon was not present. Echocardiography revealed right ventricle 32 mm, left atrium 42 mm, interventricular septum 9 mm, posterior wall 8 mm, left ventricle in diastole/systole 57/37 mm, aorta 25 mm, and normal aorta/septum. Chambers of the heart were not dilated and borderline size of heart chambers was noted. Segmental contractibility disturbance was not seen. Left ventricular ejection fraction was 63%. Intracardiac formations and pericardial effusion were not present. Evidence of shunt circulation was not seen. Valves-trace regurgitation on all orifices was observed. An electrocardiogram (ECG) showed sinus rhythm 78 per minute, electrical axis was 0, PQ 0.14, QRS 0.08, QT 0.32, ST was isoelectric, negative T wave in III, aVF, transitional zone in thoracic leads V3, 4. The ECG did not show development of ischemia; baseline hypokalemia was substituted. During hospitalization, vital signs showed heart rate of 76 beats per minute, BP of 116/77 mmHg, normal body temperature, and oxygen saturation of 95% without oxygen. Laboratory test results disclosed troponin I of < 0.01 µg/L, creatinine of 96.0 µmol/L, urea of

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6.7 mmol/L, glucose of 5.5 mmol/L and 6.0 mmol/L, aspartate aminotransferase (AST) of 0.36 U/L and 0.27 U/L, alanine aminotransferase (ALT) of 0.57 U/L and 0.48 U/L, total bilirubin of 9.0 mg/dL, alkaline phosphatase of 1.05 U/L, sodium of 137 mEq/L and 138 mEq/L, potassium of 3.32 mEq/L and 4.10 mEq/L, chloride of 104 mEq/L and 106 mEq/L, creatine kinase - muscle and brain (CPK-MB) of 2.80 IU/L, white blood cell (WBC) count of 9.0 x 10^3/µL, red blood cell (RBC) count of 3.99 10^3/µL, hemoglobin of 13.1 g/dL, hematocrit of 0.38 L/L, platelet count of 262 10^9/L, and absolute neutrophil count of 3.80 GI/L. Urinalysis revealed specific gravity 0.1019, pH 7.0, negative protein, glucose, ketones, urobilinogen, bilirubin, blood, leucocytes, and nitrites. Urinary sediment was negative for RBCs, WBCs, granulated casts, hyaline casts, epithelial cells, bacteria, yeasts, and mucosal fibers. The subject did not report any problems during hospitalization; BP values remained low; and laboratory tests were negative for myocardial necrosis. Treatment medication included unspecified fluids; potassium; and combination of gluconate sodium, magnesium chloride hexahydrate, potassium chloride, sodium acetate trihydrate, and sodium chloride. The final diagnosis was reported as musculoskeletal chest pain. On 09 February one year after*, troponin I was <0.01 µg/L. The event was considered resolved on the same day (09 February one year after*) and the subject was discharged from the hospital with controlled cardiac and pulmonary functions.

The subject's last dose of evolocumab prior to the event was on 28 January one year after*. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab on 25 March two years after*.

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

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent Study: Placebo SC Q4W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg+ Standard of care
Report: Pain in extremity

Subject [redacted] was a 65-year-old white woman participating in Study 20110110 who developed pain in extremity (reported term: pain in left lower leg). The subject's medical history included hypercholesterolemia, obesity, hypertension, type 2 diabetes mellitus, asthma, arthralgia, joint injury, and food allergy (shellfish allergy). Concomitant medications while on study included simvastatin, losartan, formoterol, and combination of budesonide and formoterol. Previous and ongoing treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 14 November one year ago* to 07 February same year* and received the last dose of placebo in the parent study on 09 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 07 February [redacted].

Approximately 1 year and 6 months later, on 27 August one year after*, the subject developed pain in her left lower leg and was hospitalized on the same day. The next day, on 28 August one year after*, ultrasound revealed no findings. Laboratory results from 01 August one year after* did not reveal significant abnormalities, except for a glucose level of 8.1 mmol/L. Treatment included tinzaparin, combination of macrogol, potassium chloride, and sodium bicarbonate, paracetamol, indacaterol and glycopyrronium. The subject's left leg pain was not related to the previous left knee injury. The event was reported as resolved on 28 August 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 20 August one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study, and received the last dose of evolocumab prior to the data cutoff on [redacted].

The investigator reported that there was no reasonable possibility that the event pain in extremity was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q4W 350 mg Year 1 treatment: Standard of care Years 2-5 treatment: Evolocumab SC Q4W 350 mg + Standard of care
Report: Colon cancer

Subject [redacted] was a 68-year-old white woman participating in Study 20110110 who was diagnosed with colon cancer. The subject's medical history included hypercholesterolemia, type 2 diabetes mellitus, gastritis, bladder irritation, hypertension, restless legs, hypovitaminosis (Vitamin D), migraines, uterine prolapse, goiter, right breast fribroma, aortic aneurysm, duodenal ileus, and osteoarthritis. Concomitant medications included metformin, lansoprazole, solifenacin, ramipril, pramipexole, and Vitamin D3. Previous and ongoing treatment for hypercholesterolemia included atorvastatin.

The subject was in the parent study from 18 November one year ago* to 10 February same year* and received the last dose of evolocumab in the parent study on 13 January same year*. The subject received standard of care treatment in the first year of Study 20110110 from 10 February [redacted] to 07 March one year after*. The subject received her first dose of evolocumab in the second year of Study 20110110 on 08 March one year after*.

On 08 February one year after*, the subject's hemoglobin level was 110 g/L and she was advised to see her general practitioner. Hemoglobin level at baseline on 18 November one year ago* was 130 g/L. On 03 May one year after*, hemoglobin was 102 g/L. The subject was referred to the hospital and approximately 3 months after the first dose of evolocumab, colonoscopy showed a tumor in the sigmoideum (polyp) on 29 May one year after*. An ultrasound of the abdomen and a gastroscopy were performed on 03 June one year after* and 07 June one year after* respectively, however no results were provided. There were no symptoms of bleeding or other symptoms. On 13 June one year after*, the subject was hospitalized with a diagnosis of colon cancer. On 14 June one year after*, colon sigmoideum was resected by laparoscopy and 40 cm of colon was removed. Postoperative pain medication included ibuprofen. Histology revealed adenocarcinoma; cancer staging at the time of diagnosis was pT2, pN0, pV0. On an unknown date, a biopsy showed no remaining cancer. The event of colon cancer was reported as resolved on 14 June one year after* and the subject was discharged from the hospital on 16 June one year after*. No further treatment was planned. The subject had no history of malignancy.

*新薬承認情報提供時に置き換え

The subject's last dose of evolocumab prior to the event was on 03 May one year after*. Evolocumab was continued.

As of the data cutoff date of [redacted], the subject was continuing on study and the last dose of evolocumab was on 07 March two years after*.

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

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q2W 140 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Coronary artery arteriosclerosis

Subject [redacted] was a 65-year-old Asian man participating in Study 20110110, who developed coronary artery arteriosclerosis (reported term: worsening of coronary arteriosclerosis). The subject's medical history included hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, acute myocardial infarction, coronary atherosclerosis, and type 2 diabetes mellitus. Concomitant medications included salbutamol, tiotropium, a combination of budesonide and formoterol, atorvastatin, losartan, omeprazole, acetylsalicylic acid, and a combination of metformin hydrochloride and vildagliptin. Previous treatment for hypercholesterolemia was not reported.

The subject was in the parent study from 14 October one year ago* to 20 January same year* and received the last dose of evolocumab in the parent study on 28 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 20 January [redacted].

Approximately 10 months later, on 21 November same year*, the subject had chest pain while working in the garden. An electrocardiogram on the same date was found to be normal. The subject was prescribed sublingual glyceryl trinitrate and was referred to a local hospital for additional cardiac evaluation. On 04 January one year after*, an echocardiography revealed left ventricular ejection fraction of 40-45%. On 06 February one year after*, the subject underwent coronary arteriography which revealed coronary stenosis with left main (LM) distal 70%, left anterior descending artery (LAD) with diffuse beginning stenosis in 2+3 segment, plaque distribution (PD) 90%. After coronary arteriography, the subject was transferred to another hospital where he was scheduled to undergo a bypass operation on 28 February one year after*. Additionally, the subject had developed pneumonia from 13 February one year after* to 25 February one year after*, which was successfully treated with intravenous antibiotics.

On 07 March one year after*, the subject underwent a coronary artery bypass operation due to worsening of coronary artery arteriosclerosis without complications. A transesophageal echocardiogram was performed on the same day and showed hypokinesia infero-lateral, and no pathology of

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valves. The subject was treated with phenoxymethylpenicillin, codeine, gentamicin, cefuroxime, paracetamol, fluconazole, metoprolol, and combination of piperacillin and tazobactam. The event of coronary artery arteriosclerosis was reported as resolved, and the subject was discharged on 12 March one year after*.

The subject's last dose of evolocumab prior to the event was on 18 January one year after*. The investigator reported that the subject skipped the administration of evolocumab at week 56 due to hospitalization. As of the data cutoff date of [redacted], the subject was continuing in the study, and received the last dose of evolocumab prior to the data cutoff date on [redacted]. The investigator reported that there was not a reasonable possibility that the event coronary artery arteriosclerosis was related to evolocumab.

*新薬承認情報提供時に置き換え

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

Subject [redacted] was a 66-year-old white woman participating in Study 20110110 who developed diarrhea. The subject's medical history included hypercholesterolemia, hypertension, osteoarthritis, allergy to insect sting, pain in the extremity (left heel), and pain in the upper abdomen. The subject did not have a history of diarrhea.

Concomitant medications included Vitamin E, pantoprazole, glucosamine, and enalapril. Previous and ongoing treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 20 October one year ago* to 20 January same year* and received the last dose of evolocumab in the parent study on 27 December one year ago*.

The subject was randomized to Study 20110110 on 20 January [redacted] and assigned standard of care treatment. While the subject was receiving standard of care, on 18 November same year*, the subject had severe diarrhea while on a holiday and was hospitalized. The hospital discharge summary confirmed the diagnosis of diarrhea. Fecal culture performed on an unknown date was negative. Treatment medications included ciprofloxacin and loperamide. The event diarrhea was reported as resolved on 23 November same year* and the subject was discharged from the hospital.

After completing the first year of the study, she began part 2 and received her first dose of evolocumab on 15 February one year after*. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the cutoff date on [redacted]. The investigator reported that there was no reasonable possibility that the event of diarrhea was related to any study activity, and that there were no co-suspect medications. The investigator reported that diarrhea was probably caused by *Salmonella* infection.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q4W 420 mg Year 1 treatment: Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Chronic lymphocytic leukemia

Subject [redacted] was a 66-year-old white woman participating in Study 20110110 who was diagnosed with chronic lymphocytic leukemia (reported term: CLL [chronic lymphatic leukemia]). The subject's medical history included hypercholesterolemia, hypothyroidism, intervertebral disc protrusion, congenital defect in the right arm, osteoarthritis, pain in the extremity (right leg), muscle spasms, allergy to adhesive tape and rubber, and breast cancer (treatment between eighteen years ago* and fifteen years ago*). The subject had undergone chemotherapy (9 cycles, unknown agents), radiotherapy (20 cycles), and breast reconstruction.

Concomitant medications included Vitamin E, pantoprazole, levothyroxine, paracetamol, tramadol, glucosamine, tiopronin, pectyl, and codeine. Previous and ongoing treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 03 November one year ago* to 26 January same year*, received the last dose of evolocumab in the parent study on 27 December one year ago*, and was randomized to Study 20110110 on 26 January [redacted] and assigned standard of care treatment. On 27 December one year ago*, laboratory test results showed lymphocyte count 4.74 x 10^9/L, neutrophil count 38.0%, lymphocyte percentage 55.0%, hemoglobin 141 g/L, platelet count 182 x 10^9/L, prothrombin time 9.6 seconds, and WBC 8.62 x 10^9/L. At baseline on 03 November one year ago*, lymphocyte count was 1.601 x 10^9/L, with 37.4 % lymphocytes.

On 26 January same year*, the subject was diagnosed with chronic B-cell lymphoma of mild malignancy grade. On the same day, laboratory data showed lymphocyte count 9.61 x 10^9/L, lymphocyte percentage 65.0%, platelet count 228 x 10^9/L, hemoglobin A1c 5.7%, sodium 144 mmol/L, potassium 4.5 mmol/L, chloride 104 mmol/L, hemoglobin 143 g/dL, hematocrit 0.43 (fraction of 1), red blood cell count 4.8 x 10^{12}/L, and white blood cell count (WBC) 14.78 x 10^9/L. On 23 February same year*, blood tests showed hemoglobin 136 g/L, WBC 18.19 x 10^9/L, lymphocyte count 14.37 g/L, neutrophil count 17.0%, lymphocyte percentage 79.0%, and platelet count 211 x 10^9/L. On 26 April same year*, laboratory test results were hemoglobin 126 g/L, WBC 9.85 x 10^9/L, neutrophil count 2.81 x 10^9/L, neutrophil percentage

*新薬承認情報提供時に置き換え

28.5%, lymphocyte count 6.36 x 10^9/L, lymphocyte percentage 64.5%, and platelet count 206 x 10^9/L. The subject did not receive any treatment for the event. There was no contributory family history for the event. There were no other prior malignancies in addition to breast cancer. The subject did not work in any high risk industries and was not exposed to carcinogens or toxic substances, and did not have any developmental or genetic disorders associated with the development of neoplasm. The event was reported as not resolved, as the investigator stated it was a chronic disease.

After completing the first year of the study, the subject began part 2 and received her first dose of evolocumab on 22 February one year after*.

As of the data cutoff date [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the cutoff date on [redacted]. The investigator reported that there was no reasonable possibility that the event of chronic lymphocytic leukemia was related to any study procedure or study activity.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q4W 350 mg Year 1 treatment: Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Aortic valve sclerosis

Subject [redacted] was a 76-year-old white woman participating in Study 20110110 who developed aortic valve sclerosis (reported term: worsening of sclerosis of the aortic valve). The subject's medical history included hypercholesterolemia, aortic valve sclerosis, dyspnea, and hypertension.

Concomitant medications included bendroflumethiazide and potassium chloride, acetylsalicylic acid, enalapril, glucosamine, losartan, calcium D_3, Vitamin D, and Vitamin E. Previous and ongoing treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 27 October one year ago* to 19 January same year* and received the last dose of evolocumab in the parent study on 21 December one year ago*. The subject was randomized to Study 20110110 on 19 January [redacted] and assigned standard of care treatment. While the subject was receiving standard of care, on 01 May same year*, she developed worsening of sclerosis of the aortic valve with a symptom of shortness of breath when walking. On 20 August same year*, the subject was hospitalized for a planned surgery where the aortic valve was replaced with a biological aortic valve. On 27 August same year*, a postoperative echocardiography showed a normal cardiac output, normal pumping function, and the well-functioning of the biological aorta valve prosthesis. Postoperative treatment medications included amiodarone and warfarin. On 28 August same year*, the event worsening of aortic valve sclerosis was resolved and the subject was discharged from the hospital.

After completing the first year of the study, the subject began part 2 and received her first dose of evolocumab on 22 February one year after*. As of the data cutoff date [redacted], she was continuing in the study and received the last dose of evolocumab prior to the cutoff date on [redacted]. The investigator reported that there was no reasonable possibility that the event of aortic valve sclerosis was related to any study activity.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment Parent study: Evolocumab SC Q4W 280 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Chest pain

Subject [redacted] was a 58-year-old white woman participating in Study 20110110 who developed chest pain. The subject's medical history included hypercholesterolemia and stomach ulcer. Concomitant medications included multivitamins, ibuprofen, codeine, paracetamol, glucosamine, simvastatin, and estradiol. Previous treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 02 November one year ago* to 25 January same year* and received the last dose of evolocumab in the parent study on 28 December one year ago*.

On 22 May same year*, the subject had chest pain at work and was admitted to the hospital. Electrocardiogram and cardiac enzymes were reported to be normal. Acute myocardial infarction was not confirmed. The event was reported as resolved on 23 May same year* and the subject was discharged from the hospital. The investigator stated that the subject was later treated for "too much stomach acid".

The subject's last dose of evolocumab prior to the event was on 16 May [redacted]. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab on 19 March two years after*.

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

*新薬承認情報提供時に置き換え

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

Subject [redacted] was a 69-year-old white woman participating in Study 20110110 who developed coronary artery disease (reported term: worsening of coronary heart disease). The subject's medical history included hypercholesterolemia, osteoporosis, arthralgia, coronary artery disease, and myocardial infarction in January one year after* followed by coronary revascularization with 2 stents. Concomitant medications included fish oil, alendronate, selenium, Vitamin D, calcium, ibuprofen, metoprolol succinate, combination of acetylsalicylic acid and magnesium, glyceryl trinitrate, atorvastatin, and clopidogrel. Previous treatment of hypercholesterolemia included simvastatin. Previous and current treatment for hypercholesterolemia included atorvastatin.

The subject was in the parent study from 03 November one year ago* to 09 February same year* and received the last dose of evolocumab in the parent study on 12 January same year*. The subject was randomized to the standard of care arm of Study 20110110 on 09 February [redacted].

On 11 April one year after*, the subject was electively hospitalized for a coronarography as follow up of the myocardial infarction in January. On the same day, percutaneous coronary angioplasty (PTCA) with stent of the right coronary artery (RCA) was performed, which reduced stenosis of the proximal RCA from 85% to 10%. The event was reported as resolved on 12 April one year after*, and the subject was discharged from the hospital on the same date. Rehabilitation follow up was planned.

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

The investigator reported that there was no reasonable possibility that the event of coronary artery disease was related to any study activity.

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Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q2W 70 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Osteoarthritis

Subject [redacted] was a 73-year-old white woman participating in Study 20110110 who developed osteoarthritis (reported term: worsening arthrosis left hip). The subject's medical history included hypercholesterolemia, osteoarthritis, and bone graft. Concomitant medications included simvastatin, levothyroxine, loperamide, unspecified antibiotics, methotrexate, paracetamol, ibuprofen, and bendroflumethiazide with potassium. Previous and current treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 09 November one year ago* to 15 February same year* and received the last dose of evolocumab in the parent study on 18 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 15 February [redacted].

Approximately 2-1/2 months later, on 30 April same year*, the subject had worsening of osteoarthritis. The subject was hospitalized for a planned hip replacement on 20 September same year*. The left hip alloplastic surgery went without any complications. Treatment medications included triamcinolone, oxycodone, and paracetamol. The event of osteoarthritis was reported as resolved on 22 September same year* and the subject was discharged from the hospital on the same day with postoperative pain killers.

The subject's last dose of evolocumab prior to the event was on 11 April same year*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab on 17 January one year after*.

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

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Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q4W 350 mg Year 1 treatment: Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Uterine cancer

Subject [redacted] was a 73-year-old white woman participating in Study 20110110 who was diagnosed with uterine cancer (reported term: cancer uteri). The subject's medical history included hypercholesterolemia, cholelithiasis, and restless legs syndrome. Concomitant medication included simvastatin, estradiol, amlodipine, ibuprofen, and metronidazole. Previous treatment for hypercholesterolemia was not reported.

The subject was in the parent study from 11 November two years ago* to 03 February one year ago* and received the last dose of evolocumab in the parent study on 06 January one year ago*. After completing the first year of the Study 20110110, in which she received standard of care treatment, the subject received the first dose of evolocumab in Study 20110110 on 01 March [redacted].

Approximately 4 months later, on 11 July same year*, the subject was diagnosed with uterine cancer during follow-up for a vaginal infection. The subject was hospitalized on 20 August same year*, and the following day, on 21 August same year*, the uterus was surgically removed. Uterine cancer was confirmed and the diagnosis was corpus cancer uteri, with < 50% growth into the myometrium, grade II; no dissemination. Additional treatment included ibuprofen and magnesium. The event was reported as resolved on 23 August same year*, and the subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event of uterine cancer was on 21 June same year*. Evolocumab product was continued. As of the data cutoff date of [redacted], the subject was continuing in the study, and received the last dose of evolocumab prior the data cutoff date on [redacted].

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

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Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q4W 350 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Uterine cancer

Subject [redacted] was a 67-year-old white woman participating in Study 20110110 who developed uterine cancer (reported term: cancer cavum uteri). The subject's medical history included hypercholesterolemia, asthma, and back muscle pain. The subject was a smoker. Concomitant medications included tiotropium, paracetamol, ibuprofen, terbutaline, and budesonide. Previous treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 18 November one year ago* to 09 February same year* and received the last dose of evolocumab in the parent study on 16 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 09 February [redacted]. On 13 December one year after*, the subject experienced vaginal bleeding and consulted a gynecologist. Biopsies were carried out and cancer was suspected.

On 09 January one year after*, cervical scrape sample showed mucous material, mixed with flakes of cervix mucosa, loose cervix cylinder epithelium without atypia, and small loose flakes of atropic appearing plate epithelium without dysplasia. There were no signs of malignancy. There was no convincing myometrium, so invasion was not demonstrated. Corpus endometrium had minimal complex hyperplasia with atypia, showing highly differentiated endometrioid adenocarcinoma. Cervix cytology sample showed normal cells.

Approximately 11 months after the first dose, on 28 January one year after*, the subject was hospitalized due to uterine cancer. The subject underwent laparoscopic hysterectomy and bilateral salpingo-oophorectomy. There were no post-surgery complications. The magnetic resonance scan showed tumor in cavum uteri (no infiltration in cervix or endometrium was noted) and the macroscopic evaluation showed less than 50% in-growth in the myometrium. The biopsy result revealed uterus with an endometroid adenocarcinoma grade 1, in the endometrium, no myometrial invasion, no cervical or parametrial involvement, both adnexae without malignancy. Microscopy results showed tumor tissue. Section from cervix and the isthmus of the uterus did not show tumor formation. The adnexae did not have metastasis. In one ovary from the left side a simple serous cyst formation was visible. Many sections from the corpus showed an endometrium where in a single area atypical complex hyperplasia was visible, where the

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mucous membrane was also slightly irregular. Other sections show endometrioid adenocarcinoma grade 1 without solid foci, growing in the mucous membrane area, as an exophytic process focally pressing on the underlying myometrium but where there was no convincing basis for myometrial invasion. No tumor tissue in the carbaners was observed. The mymetrium showed some well-defined leiomyomata without atypia or necroses. Macroscopy evalatuation revealed < 50 % myometrial invasion and uterus with both adenaxe. In cavity anterior wall and fundus a protruding tumor was visible. Peritoneal rinsing fluid was clear liquid with no clot produced. The clinical diagnose was corpus cancer. No further treatment was planned. The event uterine cancer was reported to have 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 14 January one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study, and received the last dose of evolocumab prior to the data cutoff date on [redacted]. The investigator reported that there was no reasonable possibility that the event uterine cancer was related to evolocumab. No concomitant medications were considered as co-suspect.

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

Subject [redacted] was a 67-year-old white man participating in Study 20110110 who developed keratitis (reported term: keratitis left eye). The subject's medical history included hypercholesterolemia, corrective lens user, and muscle disorder. Concomitant medications included Vitamin E and combination of acetylsalicylic acid and magnesium oxide. Previous treatment for hypercholesterolemia included rosuvastatin (five years ago* to 26 July same year*); and current treatment included atorvastatin (27 July same year* to ongoing).

The subject was in the parent study from 17 November one year ago* to 23 February same year* and received the last dose of evolocumab in the parent study on 26 January same year*. The subject was randomized to Study 20110110 on 23 February [redacted] and assigned standard of care treatment. Approximately 9-1/2 months later, on 09 December same year*, the subject woke up with infection in the left eye, pain, and reduced vision. He was hospitalized on 13 December same year* due to keratitis. The subject wore contact lenses and had no previous episodes of keratitis. During hospitalization, the subject was pain free but did not really have any sight in the eye. Slit-lamp examination of the left eye performed on an unspecified date showed bulb substantial mixed injection and cornea with central epithelial defect measuring approximately 3.5 x 3.5 mm with underlying infiltrate. Peripherally the cornea was diffusely clouded, no hypopyon was observed inferiorly, and no impression of any severe reaction in the anterior chamber. Iris with substantial hyperemia was noted. Objectively small improvement was observed. Treatment included chloramphenicol, ciprofloxacin, dexamethasone, hyoscine, polyhexanide, propamidine isetionate, and tobramycin. The event of keratitis was reported as resolved on 15 December same year* and the subject was discharged from the hospital on the same day. Upon discharge, reduced vision persisted.

After completing the first year in Study 20110110, the subject began part 2 of the study. The subject received the first dose of evolocumab in part 2 on 21 March one year after*. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff on [redacted].

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

Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q2W 105 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + standard of care
Report: Breast cancer

Subject [redacted] was a 67-year-old white woman participating in Study 20110110 who was diagnosed with breast cancer (reported term: cancer mammae right breast). The subject's medical history included hypercholesterolemia. Concomitant medications included valaciclovir. Previous and ongoing treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 21 November one year ago to 28 February [redacted] and received the last dose of evolocumab in the parent study on 31 January same year*.

On an unknown date, a regular screening mammogram was performed in which cancer of right mammae was suspected. Biopsy and ultrasound were performed (results were not provided). On 28 August one year after* the subject was diagnosed with breast cancer. She underwent lumpectomy as an outpatient. On 07 October one year after*, the subject was hospitalized. Sentinel node biopsy of her right armpit showed no metastatic findings. The histology showed invasive ductal carcinoma grade 2 of 11 mm, HER2 positive. The event of breast cancer was reported as resolved on 07 October one year after*, and the subject was discharged in good condition.

The subject's first and last dose of evolocumab prior to the event of breast cancer was on 28 February same year*. As of the data cutoff date of [redacted], the subject had chosen not to continue treatment with evolocumab; however, she was continuing in the study.

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

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