Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Evolocumab SC QM 420 mg Year 1: Standard of Care
Report: Unstable angina, Bradycardia, Dyspnea, Hypertension

Subject [redacted] was a 45-year-old white man participating in Study 20120138 who experienced unstable angina (reported term: probable unstable angina), bradycardia, dyspnea, and hypertension. The subject's medical history included dyslipidemia, coronary artery disease with a history of non ST-segment elevation myocardial infarction in ten years ago* and coronary artery bypass grafting surgery in October ten years ago*. Concomitant medications included mesalazine and acetylsalicylic acid. Previous and ongoing treatment for hyperlipidemia included rosuvastatin.

The subject received evolocumab in the parent study from 29 July same year* to 23 September same year*. He was enrolled in Study 20120138 on 25 November [redacted] and was assigned to the standard of care treatment. Approximately 10 weeks later, on 04 February one year after*, the subject developed dyspnea, bradycardia and hypertension and was hospitalized. On 05 February one year after*, he underwent coronography which showed right coronary artery venous bypass with 60% stenosis. Cerebral computed tomography (CT) was negative on the same day. Troponin levels were not increased during hospitalization. The final discharge diagnosis was probable unstable angina. Treatments included ticagrelor. No actions were taken with the standard of care medication. The events of angina unstable, bradycardia, dyspnea, and hypertension resolved on 12 February one year after*, 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 events of unstable angina, bradycardia, dyspnea, and hypertension were related to study conduct.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Placebo SC Q2W + Ezetimibe PO QD 10 mg Year 1: Standard of Care
Report: Pneumonia, Pulmonary embolism, Hepatic enzyme increased

Subject [redacted] was a 65-year-old white man who developed pneumonia, pulmonary embolism, and increased hepatic enzyme (reported term: elevated liver enzymes). The subject's medical history included dyslipidemia, aortic aneurism, cardiomyopathy and ulcerative colitis. Concomitant medications included enalapril, felodipine, paracetamol and acetylsalicylic acid. Previous treatment for dyslipidemia was not reported; ongoing treatment included simvastatin.

The subject received placebo and ezetimibe in the parent study from 04 July same year* to 25 September same year*. He was enrolled in Study 20120138 on 10 October [redacted] and was assigned to the standard of care treatment. Approximately 12 weeks later, on 02 January one year after*, the subject experienced right-sided chest pain, and was hospitalized the same day. C-reactive protein was 125 mg/L, and chest computed tomography (CT) showed pulmonary emboli in all lobes of the right lung, and pneumonia in the right lung. The subject was treated with amoxicillin for the pneumonia, and warfarin and tinzaparin for the pulmonary emboli. No actions were taken with the standard of care medication. The event of pulmonary embolism resolved on 04 January one year after*, and the subject was discharged from the hospital on the same day. The event of pneumonia was resolved on 11 January one year after*.

Three days after discharge from the hospital, on 07 January one year after*, the subject experienced elevated liver enzyme levels with laboratory tests showing alanine aminotransferase (ALT) of 194 IU/L, aspartate aminotransferase (AST) of 162 IU/L, alkaline phosphatase (ALP) of 136 IU/L, and lactate dehydrogenase (LDH) of 267 IU/L. Previous levels on 25 September same year* showed ALT of 72 IU/L, AST of 43 U/L, ALP of 100 IU/l, and LDH of 236 U/L. No treatment was reported for the event of elevated liver enzymes, and no action was taken with the standard of care medication. On 14 January one year after*, follow-up laboratory testing showed ALT of 84 IU/L and AST of 38 U/L. On 16 January one year after*, ALT was 66 IU/l and AST was 41 U/L. The event of elevated liver enzymes was reported as resolved on 16 January one year after*.

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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 events of pneumonia, pulmonary embolism and elevated liver enzymes were related to study conduct. The investigator stated that the treatment of pneumonia with amoxicillin was a possible cause of elevation of liver enzymes.

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

Subject [redacted] was a 66-year-old white man participating in Study 20120138 who developed pleurisy. The subject's medical history included dyslipidemia, hypertension, obstructive cardiomyopathy, and hypercholesterolemia. Concomitant medications included losartan. Previous treatment for dyslipidemia was not reported; ongoing treatment included atorvastatin.

The subject received evolocumab in the parent study from 24 June same year* to 17 September same year*. He received the first dose of evolocumab in Study 20120138 on 30 September [redacted]. Approximately 1 month later, on 30 October same year*, the subject developed pleuritis. Evolocumab was temporarily withheld. Chest computed tomography (CT) on 12 November same year* revealed left pleural fluid, some emphysematous changes and isolated pleural plaques on the right. The subject underwent pleurocentesis on 02 December same year* and 16 December same year*, removing 1.7 and 1.2 L of fluid, respectively. On 30 December same year* he was hospitalized for a biopsy, which occurred the next day. Biopsy results showed inflammation and fibrosis, but no malignant cells. No treatments were given for the event, and evolocumab continued to be withheld. On 07 January one year after*, the subject was discharged from the hospital. The event of pleurisy was reported as ongoing.

Biopsy from 30 January one year after* did not reveal malignancy, and a chest CT from 6 March one year after* did not show significant alterations besides left pleural thickening and pleural fluid.

According to the investigator, the subject's last dose of evolocumab prior to the event was on 30 September same year*. As of the data cutoff date of [redacted], the last in-clinic dose of evolocumab was documented on 7 December same year* and the subject was continuing in the study.

The investigator reported that there was not a reasonable possibility that the event of pleuritis was related to evolocumab or device. Per the investigator, viral etiology was suspected.

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

Subject [redacted] was a 66-year-old white woman participating in Study 20120138 who developed abnormal hepatic function (reported term: liver function abnormality). The subject's medical history included primary hyperlipidemia, unexplained jaundice event in six years ago*, and recurrent urinary tract infections. Concomitant medications included candesartan, nitrofurantoin in chronic (6 months before the event) use for recurrent urinary infections, ramipril, gabapentin, diclofenac, omeprazole, aluminum hydroxide magnesium carbonate, electrolytes with macrogol, codeine,paracetamol, salbutamol, budesonide, pseudoephedrine, fexofenadine, and mometasone. Previous and ongoing treatment for primary hyperlipidemia included simvastatin.

The subject received placebo in the parent study from 21 May same year* to 16 July same year*. She received the first dose of evolocumab in Study 20120138 on 09 October [redacted]. On 13 August same year* the subject's laboratory tests included aspartate aminotransferase (AST) 22 U/L and alanine aminotransferase (ALT) 20 U/L. On 09 December same year*, the subject experienced dyspepsia. On 20 December same year*, the subject developed liver function abnormality with ALT 794 U/L, AST 562 U/L, and alkaline phosphatase 158 U/L. On 23 December same year*, the subject's laboratory tests included total bilirubin of 25 µmol/L, ALT of 817 U/L, gamma glutamyltransferase (GGT) of 326 U/L, and alkaline phosphatase (ALP) of 156 U/L. Treatment after the onset of the event of liver function abnormality included domperidone and cholestyramine. Evolocumab and simvastatin were discontinued.

On 27 December same year*, results were negative for hepatitis B surface antigen and hepatitis C. On the same day, results included total bilirubin of 23 µmol/L, ALT of 896 U/L, AST of 736 U/L, alkaline phosphatase of 157 U/L, iron of 36 µmol/L, and transferrin saturation of 60%. On 30 December same year*, total bilirubin was 20 µmol/L, antinuclear antibody (ANA) showed 1/40 homogeneous pattern, which was very weakly positive. ALT was 940 U/L, AST was 765 U/L, ALP was 150 U/L and serum ferritin was 1599 µg/L. On 03 January one year after*, the subject was tested for hereditary hemochromatosis, which was negative. On 06 January one year after*, results included total bilirubin of 26 µmol/L, ALT of 1052 U/L, AST of 959 U/L, and ALP of 172 U/L.

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Laboratory values on 10 January one year after* showed AST and ALT decreasing to levels of 884 U/L and 854 U/L, respectively, total bilirubin was 30 µmol/L and ALP was 176 U/L.

On 15 January one year after*, the subject underwent an abdominal ultrasound, which showed no abnormalities. There was no change from the previous ultrasound on 28 March same year*. On 22 January one year after*, the subject underwent endoscopy and gastroscopy due to dysphagia, nausea and/or vomiting, which showed a normal upper gastrointestinal tract. On 30 January one year after*, laboratory values included immunoglobulin A of 5.2 g/L, iron of 37 µmol/L, total bilirubin of 230 µmol/L, ALT of 636 U/L, AST of 833 U/L, ALP of 266 U/L, transferrin saturation of 64%, albumin of 28 g/L, and alpha fetoprotein of 39 Ku/L.

On 03 February one year after*, the subject's coagulation screening showed a thrombin time of 19 seconds. On 06 February one year after* laboratory values included C-reactive protein of 15 mg/L, chloride of 109 mmol/L, total bilirubin of 271 µmol/L, ALT of 509 U/L, AST of 593 U/L, ALP of 263 U/L, glomerular filtration rate of 53 mL/min and albumin of 27 g/L. On 07 February one year after*, the subject underwent a liver biopsy. Biopsy results showed lobular inflammation consisting of lymphocytes, polymorphonuclear leukocytes, and a few eosinophils. The portal tracts were expanded by chronic inflammatory cell infiltrate consisting of lymphocytes, histiocytes, and eosinophils. There was no evidence of ductular damage or granulomata. There was ductular reaction. There was focal zone 3 necrosis along with areas of portal to central bridging confluent necrosis. A few foci of spotty necrosis were seen. There were areas of dilated sinusoids within the necrotic component. Special stains Van Gieson (VG) and Martius, Scarlet and Blue ("MSB") showed focal mild fibrosis within necrotic component and mild fibrous expansion of portal tracts. There was no evidence of bridging fibrosis. Pearls, orcian, and periodic acid-schiff diastase (PASD) stains did not reveal any evidence of increased iron, copper associated protein or PASD inclusions. Negative screening for autoantibodies and negative viral screening was noted. The features were those of acute hepatitis with confluent necrosis and focal bridging necrosis with exclusion of viral and autoimmune etiology. The clinical diagnosis was drug-induced acute hepatitis.
On 04 April one year after*, liver function tests were normalized with values of ALT 21 U/L, AST 27 U/L, albumin 33 g/L, alkaline phosphatase 108 U/L, and total bilirubin 20 µmol/L. The outcome of the event liver function abnormality was reported as resolved on 09 April one year after*, and the subject was discharged from the hospital on an unknown date. Evolocumab and simvastatin continued to be withheld.

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The subject's last dose of evolocumab prior to the event was on 04 December same year*. As of the data cutoff date of [redacted], evolocumab was still being withheld and the subject was continuing in the study.

The investigator reported that there was a reasonable possibility that the event of abnormal liver function was related to evolocumab but was not related to the device. The investigator noted that medications such as simvastatin, nitrofurantoin, diclofenac and ramipril may have contributed to the liver dysfunction.

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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: Myocardial infarction

Subject [redacted] was a 52-year-old white man participating in Study 20120138 who experienced a myocardial infarction (reported term: anterior myocardial infarction). The subject's medical history included dyslipidemia, fibromyalgia, tobacco use, and joint pain. He also had a family history of ischemic heart disease. Concomitant medications included ibuprofen. Previous and ongoing treatment for dyslipidemia included atorvastatin.

The subject received evolocumab in the parent study from 27 June same year* to 19 September same year*. He received the first dose of evolocumab in Study 20120138 on 24 October [redacted]. Approximately 2 months later, on 29 December same year*, the subject was hospitalized with symptoms of severe central chest pain at rest, radiating to the neck, along with sweating and nausea. Electrocardiogram (ECG) that day revealed possible early changes of acute anterior myocardial infarction. The baseline troponin I level was 0.04 ng/mL. The next day, on 30 December same year*, ECG showed a completed anterior and anterolateral wall infarct. Troponin I level that day was 28.5 ng/mL. Other laboratory values that day included aspartate aminotransferase (AST) at 91 U/L, potassium at 3.4 mmol/L, and C-reactive protein at 35 mg/mL (normal values 0-10). Echocardiogram that day showed apical wall hypokinesia, mild left ventricular systolic dysfunction and an ejection fraction of 45% to 50%. That same day, the subject tolerated a modified exercise tolerance test; without complications. The subject received acute coronary syndrome (ACS) treatment, including acetylsalicylic acid, glycerine trinitrate, ramipril, and ticagrelor. Evolocumab dosing was temporarily withheld. On 03 January one year after*, the subject was discharged from the hospital.

On 15 January one year after*, the subject underwent coronary angiography and successful angioplasty with drug-eluting stent placement for severe stenosis in the left anterior descending (LAD) coronary artery, and bare metal stent placement for severe stenosis in the first obtuse marginal coronary artery. The event of myocardial infarction was ongoing at that time.

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The subject's last dose of evolocumab prior to the event was on 21 November 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 February one year after*.

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

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Subject No: [redacted]
Treatments: Parent Study: Study 20110115; Evolocumab SC Q4W 420 mg Year 1 treatment: Standard of care (SOC)
Report: Angina pectoris

Subject [redacted] was a 60-year-old white woman participating in Study 20120138 who developed angina pectoris (reported term: worsening of angina control). The subject's medical history included dyslipidemia, type II diabetes mellitus, angina, microvascular coronary artery disease, asthma, depression and anxiety disorder, and migraine. In eleven years ago*, a coronary angiogram showed minor coronary disease with a maximal 50% to 60% stenosis and dobutamine stress echocardiogram showed normal results. Concomitant medications included fluoxetine, carbamazepine, alendronic acid, salbutamol, amitriptyline, montelukast, combination of budesonide and formoterol, acetylsalicylic acid, metformin, diltiazem, esomeprazole, morphine, ranolazine, and tramadol. Previous treatment for hypercholesterolemia included rosuvastatin.

The subject received evolocumab in the parent study from 17 July same year* to 11 September same year*. The subject was randomized to standard of care in Study 20120138 on 11 November [redacted].

Approximately 37 days after the last dose of evolocumab on the parent study, on 18 October same year*, and prior to randomization into Study 20120138, the subject was hospitalized due to angina pectoris. The angina was treated with glyceryl trinitrate and the subject continued in the study. The investigator reported that the event was not considered related to evolocumab. At the time of this report the event was ongoing.

The subject's last dose of evolocumab was in the parent study (11 September same year*). As of the data cutoff date [redacted], the subject was continuing in the study and was receiving standard of care therapy.

The investigator reported that there was not a reasonable possibility that the event of angina pectoris was related to study activity.

On 01 April one year after*, [redacted], the subject was again hospitalized due to worsening angina. Electrocardiography (ECG) results were within normal limits. She had isolated T wave inversion inferiorly. Her angiogram results showed significant left anterior descending disease,

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a non diseased first obtuse marginal but significantly diseased second obtuse marginal, and a diseased right coronary artery. Echocardiogram was performed and results were normal.

Information received after the data cutoff date revealed that on [redacted], the subject underwent elective coronary artery bypass grafts x 3 with left internal mammary artery (LIMA), right internal mammary artery (RIMA) and radial grafts. The post-operative period was uneventful and the subject was placed on prophylactic antibiotics. Six days later on [redacted], the subject was discharged from the hospital. The outcome of the event was reported as resolving. The investigator reported that there was not a reasonable possibility that the event selective coronary artery bypass surgery x 3 was related to study procedure/activity.

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Evolocumab SC Q2W 140 mg Year 1: Evolocumab SC 140 mg + Standard of care
Report: Peripheral arterial occlusive disease

Subject [redacted] was a 54-year-old white man participating in Study 20120138 who developed peripheral arterial occlusive disease (reported term: worsening of peripheral artery disease – worsening atherosclerosis of left femoral artery). The subject's medical history included peripheral arterial occlusive disease, dyspepsia, carpal tunnel syndrome, hearing loss, pure hypercholesterolemia, renal colic, temporomandibular joint disorder, tonsillectomy, and metabolic syndrome. Concomitant medications included acetylsalicylic acid, bisoprolol, lansoprazole, and metformin. No previous treatment for hypercholesterolemia was reported; ongoing treatment included atorvastatin and ezetimibe.

The subject participated in the parent study (Study 20110115) from 23 July same year* to 01 November same year* and received the last dose of evolocumab in the parent study on 01 October [redacted]. The subject received the first dose of evolocumab in Study 20120138 on 14 November same year*.

On 14 February one year after*, the subject experienced worsening peripheral artery occlusive disease of left femoral artery. On 05 May one year after*, the subject was hospitalized for percutaneous transluminal angioplasty of femoral artery. Treatment medication reported after the onset of the event included metformin and telmisartan. The subject was discharged from the hospital on 07 May one year after*. The outcome of the event worsening peripheral artery disease of left femoral artery was reported as resolving. Open-label investigational drug was continued.

The subject's last documented in-clinic dose of evolocumab, which was also his last known dose prior to the event, was on 11 February one year after*. The subject was continuing home dosing as of the data cutoff date of [redacted].

The investigator reported that there was not a reasonable possibility that the event peripheral arterial occlusive disease was related to the investigational product.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Placebo SC Q2W + Ezetimibe PO QD 10 mg Year 1: Evolocumab SC 140 mg Q2W+ Standard of Care
Report: Bladder transitional cell carcinoma

Subject [redacted] was a 66-year-old white man participating in Study 20120138 who developed bladder cancer. Relevant medical history included current smoking, ATII intolerance, spondylosis, and previous spine surgery. Concomitant medications included amlodipine, codeine, metformin, and sertraline. Previous treatment for hyperlipidemia was not reported; ongoing treatment included atorvastatin.

The subject received placebo and ezetimibe in the parent study from 26 June same year* to 09 September same year*. He received the first dose of evolocumab in Study 20120138 on 06 November [redacted]. Approximately 5 months after the first dose, on April one year after*, the subject developed multifocal transitional cell carcinoma of bladder. No action was taken with evolocumab. The subject was hospitalized on 16 April one year after* and discharged the next day. No treatment was reported. Re-hospitalization was planned for 9 June one year after*. The event was ongoing at the time of this report.

The subject's last dose of evolocumab prior to the event was not known. The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose of evolocumab was documented on 29 January one year after*.

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

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Evolocumab SC QM 420 mg Year 1: Standard of Care
Report: Bile duct stone, Chronic cholecystitis

Subject [redacted] was a 74-year-old white woman participating in Study 20120138 who was diagnosed with a bile duct stone (reported term: choledocholithiasis) and chronic cholecystitis. The subject's medical history included hyperlipidemia, mixed dyslipidemia, chronic obstructive pulmonary disease, mesenteric ischemia, aortic bypass graft, hypertension, coronary artery disease, myocardial infarction, gastroesophageal reflux disease, depression, hypokalemia, angina, hysterectomy, and small bowel resection. She had no previous history of cholecystitis. Concomitant medications included a combination of fluticasone and salmeterol, ipratropium, pantoprazole, acetylsalicylic acid, glyceryl trinitrate, carvedilol, valsartan, potassium, magnesium, salbutamol, amlodipine, sertraline, and combination of calcium and colecalciferol. Previous and ongoing treatment for primary hyperlipidemia or mixed dyslipidemia included atorvastatin.

The subject received evolocumab in the parent Study 20110115 from 02 May same year* to 26 June same year* and was randomized to standard of care in Study 20120138 on 20 September [redacted].

Approximately 10 days later, on 01 October same year*, the subject developed abdominal pain, nausea, and vomiting. On 04 October same year*, the subject presented to the emergency room with worsening of symptoms with diffuse, moderate to severe, nonradiating abdominal pain with nausea and vomiting. The subject denied any fever, hematemesis, diarrhea, constipation, or melena. Liver function tests were abnormal and laboratory investigations revealed alanine aminotransferase (ALT) of 339 IU/L, aspartate aminotransferase (AST) of 220 IU/L, alkaline phosphatase (ALP) of 224 IU/L, bilirubin of 5.5 mg/dL, glucose of 114 mg/dL, white blood cell (WBC) count of 15.3 K/µL, hemoglobin of 11.9 g/dL, platelet count of 155 K/µL, albumin of 3.5 g/dL, lipase of 32 U/L, troponin of 0.02 ng/mL, and lactate of 1 mg/dL. Computerized tomography (CT) scan of the abdomen showed heterogeneous liver parenchyma, periportal edema, moderate intrahepatic biliary ductal dilation, extrahepatic biliary ductal dilation, and distended gallbladder with some stones in the gallbladder and cystic duct stone.

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On 05 October same year*, the subject was admitted to the hospital. Vital signs were normal, with the exception of hypertension, with blood pressure of 170/62 mmHg, and repeat of 148/68 mmHg. Laboratory tests revealed ALT of 254 IU/L, ammonia level of 55 µmol/L, AST of 156 IU/L, direct bilirubin of 3.2 mg/dL, albumin of 2.8 g/dL, ALP of 189 IU/L, total bilirubin of 4.7 mg/dL, gamma glutamyltransferase of 248 IU/L, total protein of 5.1 g/dL, and C-reactive protein of 2 mg/L. Ultrasound of the abdomen showed gallstones within the normal appearing gallbladder. A slight distention of the common bile duct of uncertain etiology was noted. A biliary scan revealed failure of tracer to be extended from the liver during the usual time interval, which was consistent with either common duct obstruction or hepatic failure. Magnetic resonance without contrast showed cholelithiasis. There was moderate intrahepatic periportal edema, which could have been from an increased transudative state, a cholangitis, or hepatic cellular disease. Common bile duct at the upper limits was normal for age. There was no evidence for intraductal calculus.

On 06 October same year*, laboratory values were: ALT 191 IU/L, AST 125 IU/L, direct bilirubin 2.5 mg/dL, albumin 2.5 g/dL, ALP 206 IU/L, and total bilirubin 4.2 mg/dL. On 07 October same year*, laboratory values were: ALT 148 IU/L, AST 87 IU/L, albumin 2.4 g/dL, ALP 219 IU/L, and total bilirubin 4.9 mg/dL. An endoscopic retrograde cholangiopancreatography was performed and the common biliary duct, which showed choledocholithiasis, was treated with endoscopic technique.

On 08 October same year*, laboratory values were: ALT 129 IU/L, AST 76 IU/L, direct bilirubin 3.1 mg/dL, albumin 2.7 g/dL, ALP 266 IU/L, and total bilirubin 5.4 mg/dL. On 09 October same year*, laboratory values were: ALT 111 IU/L, AST 71 IU/L, direct bilirubin 2.2 mg/dL, albumin 2.5 g/dL, alkaline phosphatase (ALP) 256 IU/L, total bilirubin 4.1 mg/dL, hematocrit 30.2%, hemoglobin 9.8 g/dL, and WBC count 6.1 K/µL. No renal function abnormality was detected during hospitalization. Hepatitis panels were negative and F-actin antibody was negative. During the event, the subject received morphine and combination of hydrocodone and paracetamol for pain, ondansetron for nausea, ceftriaxone, levofloxacin, combination of piperacillin with tazobactam, and metronidazole for sepsis, temazepam for insomnia, docusate, lactulose for prophylaxis of constipation, phosphorus as a dietary supplement, hydralazine for blood pressure, and iodixanol heparin. A low fat diet was recommended. The investigator reported possible chronic cholecystitis with choledocholithiasis, and leukocytosis due to sepsis. The subject was discharged from the hospital on 09 October same year* with normal vital signs,

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hypertensive (165/68 mmHg) and with elevated liver function tests. As per the verbal report provided by the subject, these values improved.

On 07 November same year*, a planned outpatient laparoscopic cholecystectomy was carried out. The subject was recovering well from surgery, and both the events of bile duct stone and chronic cholecystitis were reported as resolved on 07 November same year*.

On 12 December same year*, ALT was 14 IU/L, AST 14 IU/L, ALP 81 IU/L, total bilirubin 0.4 mg/dL, and direct bilirubin 0.2 mg/dL.

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

The investigator reported that there was not a reasonable possibility that the events of bile duct stone and chronic cholecystitis were related to any study activity/procedure.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Placebo SC QM Year 1: Evolocumab SC Q2W 140 mg + Standard of care
Report: Multiple fractures

Subject [redacted] was a 59-year-old white man participating in Study 20120138 who experienced multiple fractures. The subject's medical history included hyperlipidemia, mixed dyslipidemia, hypertension, type 2 diabetes, reflux esophagitis, and cataract surgeryThe subject had a family history of hypertension, heart disease, and diabetes. Concomitant medications included labetalol, lisinopril, hydrochlorothiazide, pioglitazone, metformin, glipizide, diltiazem, acetylsalicylic acid, and insulin detemir. Previous treatment for primary hyperlipidemia and mixed dyslipidemia included fluvastatin, simvastatin, and rosuvastatin; ongoing treatment included atorvastatin.

The subject received placebo in the parent study from 21 March same year* to 22 May same year*. He received the first dose of evolocumab in Study 20120138 on 12 July [redacted]. Approximately 3 months later, on 17 October same year*, the subject presented to the emergency department with level II trauma. The subject, a roofer/mason, had slipped and fallen from a roof. He was hospitalized and radiographic evaluation disclosed pelvic, costal, and right humeral fractures. Computerised tomography (CT) of head disclosed no acute intracranial process and CT of cervical, thoracic, and lumbar spine disclosed no evidence of fracture or static instability. The bones appeared osteopenic. The subject stated that the fall was purely mechanical and not due to a syncopal episode. The subject had no history of alcohol abuse, sedating medications or recreational drugs, any hypotension, episodes of low blood glucose, impaired hearing, vision, balance or muscle strength or other co-morbities that would have contributed to an injury. The subject also had no prior history of falls, accidents or injuries. An electrocardiogram showed normal sinus rhythm and nonspecific T-wave abnormality. Treatment included docusate, enoxaparin, famotidine, insulin lispro, hydromorphone, acetaminophen, a combination of docusate and senna alexandrina, naloxone, ondansetron, cefazolin, omeprazole, metoprolol, oxycodone, morphine, fentanyl, and sodium chloride.

On 20 October same year*, the subject underwent an open reduction with internal fixation of the right proximal humerus fracture and a percutaneous fixation of right posterior pelvic ring and sacrum fracture. The subject was discharged from the hospital on 23 October same year* to a skilled nursing

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facility in stable condition. Discharge medications included morphine, insulin, macrogol, omeprazole, diltiazem, rosuvastatin, and a combination of oxycodone hydrochloride, oxycodone terephthalate, and paracetamol. As of the data cutoff date of [redacted], the event of multiple fractures was ongoing.

The subject's last dose of evolocumab prior to the event of multiple fractures was on 09 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 30 December same year*.

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

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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 QM + Standard of Care
Report: Tendon rupture

Subject [redacted] was a 71-year-old white woman participating in Study 20120138 who experienced a tendon rupture (reported term: ruptured tendon left foot). The subject's medical history included primary hyperlipidemia/mixed dyslipidemia, diabetes type II, hypercholesterolemia, chronic back pain (sclerosis), irritable bowel syndrome, essential hypertension, osteoarthritis, esophagitis, and major depressive disorder. Concomitant medications included bisacodyl, benzonatate, esomeprazole, sertraline, desloratadine, ergocalciferol, nirvaxal, guaifenesin/pseudoephedrine, calcium, multivitamins combinations, furosemide, glimepiride, amlodipine besilate/hydrochlorothiazide/olmesartan, fluticasone propionate, diphenhydramine chloride/ibuprofen, and melatonin. Previous and ongoing treatment for hyperlipidemia included atorvastatin.

The subject received evolocumab in the parent study from 24 May same year* to 19 July same year*. She received the first dose of evolocumab in Study 20120138 on 06 November [redacted].

Approximately 2 months and 2 weeks later on 20 January one year after*, the subject tripped and fell. Left foot radiograph revealed a bone fracture and later a ruptured foot tendon was diagnosed. Surgical repair was performed on 26 March one year after*. The outcome of the event was reported as resolving and the subject remained hospitalized. No action was taken with evolocumab or standard of care treatment.

The subject's last dose of evolocumab prior to the event was on 26 February 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 26 February one year after*.

The investigator reported that there was not a reasonable possibility that the event of tendon rupture 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: Evolocumab SC QM 420 mg + Standard of Care
Report: Aortic stenosis, Coronary artery disease

Subject [redacted] was an 80-year-old white man participating in Study 20120138 who was diagnosed with aortic stenosis and coronary artery disease (reported terms: moderate aortic stenosis and severe coronary artery disease). The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, overweight, hypertension, previous smoking and severe peripheral vascular disease. Concomitant medications included acetylsalicylic acid, diltiazem, , furosemide, vitamin D, valsartan, and hydrochlorothiazide. Previous and ongoing treatment for hyperlipidemia included rosuvastatin.

The subject received evolocumab in the parent study from 25 July same year* to 03 October same year*. He received the first dose of evolocumab in Study 20120138 on 01 November [redacted]. Approximately 8 weeks later, on 26 December same year*, the subject was diagnosed with coronary artery disease and aortic stenosis. On 20 January one year after*, positron emission tomography (PET) with rubidium showed inferior wall abnormality consistent with ischemia. Additional treatments were not reported and no action was taken with evolocumab or standard of care treatment. On 07 February one year after*, the subject underwent coronary angiography, which revealed 90% occlusion of the left main coronary artery, 100% occlusion of the right coronary artery, 75% occlusion of the left anterior descending (LAD) coronary artery and moderate aortic stenosis. On 09 February one year after*, the subject was hospitalized for coronary artery bypass surgery and aortic valve replacement. Hospital discharge date was not reported. The events aortic stenosis and coronary artery disease were reported as ongoing.

The subject's last dose of evolocumab prior to the event was on 01 November same year*. The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose was documented on 23 January one year after*.

The investigator reported that there was not a reasonable possibility that the events of aortic stenosis and coronary artery disease were related to evolocumab or to 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 + Placebo PO QD Year 1: Standard of Care
Report: Ataxia, Headache

Subject [redacted] was a 55-year-old white man participating in Study 20120138 who developed ataxia and headache. The subject's medical history included hyperlipidemia, depression, coronary artery disease, and coronary artery bypass surgery. Concomitant medications included benzonatate, venlafaxine, and acetylsalicylic acid. Previous and ongoing treatment for hyperlipidemia included rosuvastatin.

The subject received evolocumab in the parent study from 06 May same year* to 01 July same year*. He was enrolled in Study 20120138 on 07 November [redacted] and was assigned to the standard of care treatment.

Approximately 5 weeks later, on 16 December same year*, the subject developed headache and ataxia during a stressful situation. The next day, on 17 December same year*, he went to the emergency department and was hospitalized for further evaluation. On the same day, magnetic resonance imaging (MRI) of the head and neck showed no evidence of acute infract. Computed tomography (CT) scan of head showed no evidence of hemorrhage. Headache was managed with standard medical care and no interventions were reported, moreover no action was taken with standard of care lipid lowering treatment. The event of headache was reported as resolved that same day. On 19 December same year*, the subject was discharged from the hospital. The event of ataxia was reported as ongoing.

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 events of headache and ataxia were related to study conduct.

*新薬承認情報提供時に置き換え

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

Subject [redacted] was a 76-year-old white man participating in Study 20120138 who developed ventricular tachycardia. The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, bilateral carotid bruit, hypertension, type 2 diabetes mellitus, coronary artery disease, stent placement, peripheral arterial disease, atherosclerosis, atrial fibrillation, peripheral vascular disease, cardiomyopathy, left great toe ulcer, left leg pain, low back pain, and a large ventral hernia. Concomitant medications included acetylsalicylic acid, warfarin, metoprolol, furosemide, lisinopril, metformin, nateglinide, allopurinol, ergocalciferol, and digoxin. No previous treatment for primary hyperlipidemia and mixed dyslipidemia was reported; ongoing treatment included atorvastatin.

The subject participated in the parent study from 10 April same year* to 01 July same year*. He received the first dose of evolocumab in Study 20120138 on 01 July [redacted]. Approximately 2.5 months later, on 12 September same year*, the subject developed symptoms of sustained palpitations with diaphoresis, chest discomfort, and dizziness. He was found to be in sustained monomorphic ventricular tachycardia (VT) upon paramedic arrival; VT terminated spontaneously. Cardiovascular work-up showed ischemic cardiomyopathy with left ventricular ejection fraction of approximately 40% and severe 3-vessel coronary artery disease. The subject underwent coronary artery bypass graft surgery, which went well. On 24 September same year*, an electrophysiological (EP) test was performed.

Based on EP test findings, the subject had indications for secondary prevention implantable cardioverter-defibrillator (ICD), and underwent implantation of biventricular ICD. The subject left the EP laboratory in stable condition with proper device function. The outcome of the event was reported as resolved on 25 September same year*, and the subject was discharged from the hospital to an extended care facility in good condition on the same day. Discharge medications included unspecified antibiotics, unspecified beta-blocker, combination of hydrocodone and paracetamol, macrogol, potassium chloride, amlodipine, and colecalciferol.

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The subject's last dose of evolocumab prior to the event was on 01 July 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 02 December same year*.

The investigator reported that there was not a reasonable possibility that the event of ventricular tachycardia 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 + Placebo PO QD Year 1: Standard of Care
Report: *Clostridium difficile* infection

Subject [redacted] was a 73-year-old white man participating in Study 20120138 who developed *Clostridium difficile* infection (reported term: Clostridium difficile). The subject's medical history included hyperlipidemia, mixed dyslipidemia, hypertension, atherosclerosis, angina pectoris, myocardial infarction, coronary artery disease, osteoarthritis, obesity, and allergy to penicillin. Concomitant medications included diclofenac, metoprolol, isosorbide, nifedipine, multivitamins, and acetylsalicylic acid. Previous treatment for primary hyperlipidemia and mixed dyslipidemia was not reported by the investigator; current treatment included atorvastatin.

The subject received evolocumab and placebo in the parent study (Study 20110115) from 16 April same year* to 09 July same year*. The subject was randomized to the standard of care arm in Study 20120138 on 12 July [redacted]. The subject developed *Clostridium difficile* infection on 03 September same year* and was hospitalized on 07 September same year* for further evaluation and treatment.

According to a family member the subject had a viral eye infection, was placed on antibiotics, and developed *Clostridium difficile* colitis. He had been hospitalized previously in August (date unknown) and readmitted at the beginning of September same year*. The subject developed ascites and the abdominal fluid was removed once. He was evaluated for cancerous cells and lymph nodes were to be evaluated. No additional information was available at the time of this report. The subject died on 07 September same year* and the cause of death was reported as *Clostridium difficile* colitis.

The investigator reported that there was no reasonable possibility that the event of *Clostridium difficile* infection was related to any study activity.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Evolocumab SC QM 420 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Convulsion

Subject [redacted] was a 74-year-old white man participating in Study 20120138 who experienced a convulsion (reported term: new onset seizures). The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, head trauma in two years ago*, chronic right shoulder pain, benign prostatic hyperplasia symptoms, left knee replacement, hypertension, osteoarthritis, right foot drop, right hearing loss, gastroesophageal reflux disease,pernicious anemia, colonic polyps, diverticulosis, esophageal stricture post dilatation, hiatal hernia, antral gastritis, obesity, coronary artery disease, left inguinal hernia repair, coronary artery bypass graft, left shoulder rotator cuff, ex-smoker and alcohol consumer. Concomitant medications included tamsulosin, vitamin D, omeprazole, lisinopril, nicotinic acid, milk thistle, ferrous sulfate, vitamin B12, acetylsalicylic acid, and hydrochlorothiazide. On 12 October same year* he received an influenza vaccine injection. Previous treatment for hyperlipidemia included ezetimibe, nicotinic acid and simvastatin; ongoing treatment included rosuvastatin.

The subject received evolocumab in the parent study from 12 July same year* to 06 September same year*. He received the first dose of evolocumab in Study 20120138 on 18 October [redacted]. Approximately 5 weeks later, on 23 November same year*, the subject developed new onset seizures and was admitted to the hospital. The subject had came to the emergency room after waking up at 2:00 am that day with left-sided back pain radiating to his left anterior chest. Electrocardiogram (ECG) showed first degree AV block, but was otherwise unremarkable. Laboratory results included albumin 3.1 gm/dL, calcium 7.8, creatine phosphokinase (CPK) 463 U/L, creatinine 0.66, glucose 145 mg/dL, magnesium 2.2, potassium 4.2 mEq/L, sodium 138 mEq/L, thyroid stimulating hormone 1.62 mU/L, granulocytes 84%, hematocrit 36, hemoglobin 12, INR 1.09, platelet count 204, troponin-I lower than 0.015 ngm/mL and white blood cell count (WBC) 11 x 10^9/L. Liver function tests were normal. Chest radiograph showed stable chronic change with evidence of possible fibrosis in each lung.

While in the emergency department, the subject had 2 witnessed generalized tonic-clonic seizures. He was treated with lorazepam. During both seizures, normal vital signs and normal

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sinus rhythm were reported. After each seizure, he woke up alert and oriented. Head computerized tomogram (CT) scan revealed sinus disease but no acute intracranial abnormality. Physical examination was unremarkable. Additional treatment reported included levetiracetam, glyceryl trinitrate, and sodium chloride. No action was taken with evolocumab or standard of care treatment. The event of convulsion was reported as resolved on 24 November 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 15 November 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 10 January one year after*.

The investigator reported that there was not a reasonable possibility that the event of convulsion was related to evolocumab or to device. Head trauma was identified as a possible risk factor for the event.

*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 PO QM + Placebo PO QD Year 1: Standard of Care
Report: Pulmonary embolism

Subject [redacted] was a 63-year-old white man participating in Study 20120138 who developed pulmonary embolism (reported term: pulmonary embolus). The subject's medical history included dyslipidemia, hyperlipidemia, insulin-dependent diabetes, hypertension, alcoholism, spinal stenosis, shoulder surgery, obesity, sleep apnea, and lower extremity edema. Concomitant medications included ramipril, fluoxetine, cetirizine, vardenafil, metformin, insulin lispro, insulin glargine, and acetylsalicylic acid. Previous and ongoing treatment for dyslipidemia included atorvastatin.

The subject received placebo in the parent study from 23 July same year* to 15 October same year*. He was enrolled in Study 20120138 on 07 November [redacted] and was assigned to standard of care treatment.

Approximately 4.5 months later, on 23 March one year after*, the subject experienced moderate dyspnea on exertion. He was hospitalized on the same day and diagnosed with bilateral pulmonary emboli. Laboratory values included prothrombin time (PT) 12 seconds, international normalized ratio (INR) 1.2, activated partial thromboplastin time (PTT) 34.3 seconds, troponin-I 0.09 µgm/L, B-type natriuretic peptide 225 ng/L, hemoglobin 15-15.7 g/dL, hematocrit 44-45.9%, sodium 141 mEq/L, potassium 3.7 mEq/L, chloride 108 mEq/L, carbon dioxide 23 mEq/L, blood urea nitrogen (BUN) 10 mg/dL, creatinine 0.9 mg/dL, ionized calcium 1.19, D-dimer 4.20 µgm/mL, white blood cell (WBC) $10x10^9$/L, red blood cell (RBC) 5.35 x 10^6/µL, mean cell volume (MCV) 85.8, mean cell hemoglobin (MCH) 34.3, mean cell hemoglobin concentration (MCHC) 13.7, platelet count $140x10^9$/L, mean platelet volume 10.6, nucleated RBC percent 0.2, absolute neutrophil 6.6, oxygen saturation 95%. Blood pressure was 140/81 mmHg, and heart rate was 113 beats per minute (bpm).

On the same day, electrocardiography (EKG) noted absence of acute ischemia with heart rate of 112 bpm. Additionally, the EKG showed sinus tachycardia, first degree atrioventricular block, and left axis deviation with ST deviation in lead V2 (which did not meet ST-segment elevation myocardial infarction criteria). Repeat EKG showed no acute ischemia, with heart rate of

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104 bpm. Chest radiograph showed no acute disease and normal lung markings. Non-contrast chest computed tomography (CT) showed multiple large emboli in the right and left pulmonary arteries, and the bilateral upper and lower lobar and segmental arteries. There was a focal wedge-shaped density in the upper lobe posterior segment thought to be due to consolidation or pulmonary infracts. No pleural effusions were seen. Computer tomography angiography (CTA) of the pulmonary arteries showed findings consistent with multiple bilateral pulmonary emboli with involvement of all lobar arterial branches and large embolus load. Focal air space disease was seen in the superior segment of the right lower lobe. Transthoracic echocardiography showed mild concentric left ventricular hypertrophy, with decreased left ventricular cavity size, normal left ventricular function, trace to mild mitral valve regurgitation, increased ventricular wall thickness, and a mildly dilated right ventricle. Nuclear myocardial studies demonstrated a low risk scan for significant ischemia, gated SPECT ejection fraction was normal at 60%. Treatments for the event of pulmonary emboli included enoxaparin sodium, acetylsalicylic acid, warfarin sodium, and rivaroxaban. No action was taken with the standard of care medication. The outcome of the event of pulmonary embolism was reported as ongoing. The subject was discharged from the hospital on 26 March one year after*.

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

The investigator reported that there was not a reasonable possibility that the event of pulmonary emboli was related to study conduct. Obesity was considered as a risk factor for the deep vein thrombosis (DVT) and pulmonary embolism.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Placebo SC Q2W + Ezetimibe PO QD 10 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Abdominal pain, Duodenitis

Subject [redacted] was a 45-year-old white woman participating in Study 20120138 who developed abdominal pain and duodenitis. The subject's medical history included primary hyperlipidemia, mixed dyslipidemia, hypercholesterolemia, depression, gastroesophageal reflux disease, seasonal allergy, asthma, borderline diabetes and fibromyalgia (FM). Concomitant medications included gabapentin, hydrocodone bitartrate, paracetamol, omeprazole, ibuprofen, and citalopram hydrobromide, lidocaine hydrochloride, and metaxalone. Previous and ongoing treatments for dyslipidemia were not reported.

The subject received placebo in the parent study from 16 May same year* to 08 August same year*. She received the first dose of evolocumab in Study 20120138 on 22 August [redacted]. Approximately 2 months later, on 25 October same year*, the subject developed sharp left lower abdominal pain with movement and was hospitalized. She underwent endoscopy and colonoscopy on an unspecified date, which revealed no significant findings. The subject had a frontal plain radiograph of abdomen which revealed stool in the ascending colon. Laboratory values included white blood cell (WBC) count 8.1 ml, red blood cell count (RBC) 4.39 ml, hemoglobin 13.5 dl, amylase 26 U/L, lipase 15 U/L and elevated C-reactive protein. Esophagogastroduodenoscopy showed gastritis. On 26 October same year*, laboratory values were reported as WBC 6.5 ml, RBC 4.26 ml, and hemoglobin 13.2 dl. Computerized tomogram (CT) of the abdomen showed mild fat stranding in the right lower quadrant mesentery. On 28 October same year*, colonoscopy was performed and revealed hemorrhoids and colon polyps which were removed and sent to pathology. On 29 October same year*, laboratory results showed a WBC count of 6.4 ml, RBC count 3.93 ml and hemoglobin 11.9 dl. Treatment for the event of abdominal pain also included morphine, odansetron, metronidazole, bisacodyl and levofloxacin. No action was taken with evolocumab or standard of care treatment. The outcome of the event was reported as resolved on 30 October same year*, and the subject was discharged from the hospital on the same day.

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The subject's last dose of evolocumab prior to the event was on 17 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 14 November same year*.

The investigator reported that there was not a reasonable possibility that the event duodenitis was related to evolocumab or to 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: Chest pain

Subject [redacted] was a 59-year-old black woman participating in Study 20120138 who developed chest pain. The subject's medical history included hyperlipidemia, hypertension, anxiety, depression and angiotensin-converting enzyme (ACE) inhibitor allergy. Concomitant medications included losartan potassium, and sertraline hydrochloride. Previous treatment for hyperlipidemia was not reported; ongoing treatment included rosuvastatin.

The subject received evolocumab in the parent study from 18 May same year* to 27 July same year*. She was enrolled in Study 20120138 on 14 December [redacted] and was assigned to standard of care treatment. Approximately 1 month later, during screening on 15 January one year after*, the subject developed chest pain and was hospitalized on the same day. She underwent a stress test which showed normal results. The investigator considered the chest pain to be non-cardiac. Treatment after the onset of chest pain included paracetamol, acetylsalicylic acid, and glyceryl trinitrate. No action was taken with the standard of care lipid lowering treatment. The outcome of the event of chest pain was reported as resolved on 15 January one year after*, 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 on the standard of care arm.

The investigator reported that there was not a reasonable possibility that the event of non-cardiac chest pain 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: Standard of Care
Report: Vascular graft complication, Peripheral ischemia

Subject [redacted] was a 69-year-old white man participating in Study 20120138 who developed vascular graft complication and peripheral ischemia (reported terms: bypass graft stenosis and leg ischemia). The subject's medical history included dyslipidemia, and percutaneous transluminal angioplasty. Concomitant medications included carvedilol, insulin glargine, acetylsalicylic acid, dyazide, lisinopril, clopidogrel bisulfate, furosemide, and diclofenac. Previous treatment for dyslipidemia was not reported; ongoing treatment included simvastatin.

The subject received evolocumab in the parent study from 26 June same year* to 21 August same year*. He was enrolled in Study 20120138 on 26 September [redacted] and was assigned to standard of care treatment.

Approximately 10 weeks later, on 04 December same year*, the subject underwent a percutaneous transluminal angioplasty procedure on the same day for the elective management of chronic peripheral vascular disease per the investigator. The subject had an angiogram showing stenosis in his left femoral popliteal bypass graft with significant stenosis in the left common femoral artery and popliteal artery. The subject was diagnosed with vascular graft complication on the same day. Additional treatments were not reported. No action was taken with the standard of care treatment. He underwent an additional percutaneous transluminal angioplasty procedure on 04 February one year after*. The outcomes of the events of vascular graft complication and peripheral ischemia were reported as resolved on the same day.

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

The investigator reported that there was not a reasonable possibility that the event bypass graft stenosis with ischemia of left lower extremity was related to study conduct.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Placebo SC QM + Ezetimibe PO QD 10 mg Year 1: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Esophageal ulcer hemorrhage

Subject [redacted] was a 73-year-old white man participating in Study 20120138 who developed an esophageal ulcer hemorrhage (reported term: bleeding esophageal ulcer).

The subject's medical history included hyperlipidemia, hypertension, metabolic syndrome, severe chronic obstructive pulmonary disease, obesity, lichen planus, allergic rhinitis, left hip replacement, squamous cell carcinoma, drug allergy to amlodipine, shellfish allergy, ex-smoker (cigarette use until 10 years ago), and alcohol use.

Concomitant medications included atenolol, acetylsalicylic acid, a combination of fluticasone and salmeterol, atorvastatin, albuterol, lisinopril, mometasone furoate, ascorbic acid, calcium, and multivitamins.

Previous treatment for hyperlipidemia included atorvastatin and ezetimibe.

The subject received placebo and ezetimibe in the parent study (20110115) from 24 April same year* to 16 July same year*. The subject was randomized into the evolocumab treatment arm of Study 20120138 on 10 September [redacted] and received the first dose on that date.

Approximately 3 months after randomization on 08 December same year*, the subject experienced shortness of breath upon waking up with gradually worsening symptoms for one week. The subject became dizzy, suffered a syncopal episode, hit his head but denied losing consciousness, and was hospitalized. The subject's initial blood pressure was 84/62 mmHg, which increased to 110/64 mmHg after administration of IV fluids. The results of laboratory tests on 08 December same year* were hematocrit 24.3%, hemoglobin 6.6 to 7.6 g/dL, mean cell hemoglobin concentration (MCHC) 31.3 g/dL, neutrophil count 14.4 x 10^9/L, platelet count 408 x 10^9/L, red blood cell (RBC) count 2.80 x 10^9/L, white blood cell (WBC) count 17.5 x 10^9/L, alanine amino transferase 34 IU/L, and aspartate aminotransferase 28 IU/L. The subject developed crackles in the right lung base, left leg swelling, low grade fever, and productive

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cough, but denied chest pain. An endoscopy performed on 08 December same year* revealed a duodenal ulcer without active bleeding.

The following day, on 09 December same year*, laboratory results were hematocrit of 22.9% to 24.9%, hemoglobin of 7.4 to 8.3 g/dL, RBC of 2.99 x 10^6/µL, troponin I of 0.06 ng/mL, and WBC of 15.4 x 10^3/µL. Similar results were observed until discharge. On 14 December same year*, the subject was discharged from the hospital and the outcome of the event was reported as resolved.

Treatment medications reported after the onset of the event included salbutamol, azithromycin, docusate, oseltamivir, pantoprazole, phenylephrine, ceftriaxone, levofloxacin, epinephrine, methylprednisolone, and sodium bicarbonate.

The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose was documented on 04 December same year*.

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

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Subject No: [redacted]
Treatments Parent study and regimen: Study 20110115, Evolocumab SC QM 420 mg Year 1: Standard of care
Report: Unstable angina

Subject [redacted] was a 60-year-old white man participating in Study 20120138 who developed unstable angina. The subject's medical history included dyslipidemia, valvular heart disease, hypertensive cardiovascular disease, coronary artery disease with previous angioplasty and stent of the left anterior descending artery, tonsillectomy, allergy to animals, seasonal allergy, degenerative joint disease with surgeries in knee and ankle, sleep apnea, hepatitis B, cervical myelopathy, basal cell carcinoma excision, and rotator cuff repair. The subject had a family history of coronary artery disease (multiple family members). Concomitant medications included acetylsalicylic acid, carvedilol, and olmesartan. Previous treatment for primary hyperlipidemia or mixed dyslipidemia included fish oil; ongoing treatment included atorvastatin and fish oil.

The subject received evolocumab in the parent study (Study 20110115) from 24 May same year* to 16 July same year*, and was randomized to standard of care in Study 20120138 on 20 August [redacted].

In March one year ago*, the subject's echocardiogram showed normal left ventricular wall motion and function with mild concentric left ventricular hypertrophy and stage I diastolic dysfunction.

In November same year*, the subject developed unstable angina. On 18 November same year*, a stress test was positive for ischemia and showed an early ST segment depression in anterolateral leads.

On 27 November same year*, an angiogram revealed an occlusion of the proximal portion of the circumflex marginal artery. A second stenosis of the posterior descending artery was also noted. A previously placed stent in the left anterior descending artery displayed minimal restenosis. On the same day, total cholesterol was 102 mg/dL, triglycerides 152 mg/dL, high density lipoprotein (HDL) 37 mg/dL, and low density lipoprotein (LDL) 118 mg/dL.

Approximately 10 days after the angiogram, on 11 December same year*, the subject underwent successful and non-complicated stenting of the mid circumflex artery. Cineangiograms showed normal left main coronary artery with mild irregularity. The left anterior descending artery,

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where the previous stent was placed, was widely patent. The proximal segment of circumflex artery was normal. There was 30% stenosis observed in proximal mid segment before the takeoff of the large obtuse marginal artery. The continuation of the circumflex artery was mildly tortuous. The obtuse marginal artery was occluded in a very proximal segment. Faint collateral to the distal was observed. Right coronary artery showed mild disease in the mid segment. There was 80% stenosis observed in the distal posterior descending artery.

Treatment of the event included glicalzide, glyceryl trinitrate, prasugrel, heparin and lidocaine and lisinopril. The event of unstable angina was reported as resolved on 11 December same year*.

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

The investigator reported that there was not a reasonable possibility that the event of unstable angina 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: Evolocumab SC Q2W 140 mg + Standard of Care
Report: Bipolar I disorder

Subject [redacted] was a 58-year-old white man participating in Study 20120138 who developed bipolar I disorder (reported term: bipolar disorder-manic). The subject's medical history included hypercholesterolemia, hernia surgery, lymphadenectomy, cardiac catheterization, substance abuse including alcohol, influenza vaccine, and tobacco use (2 packs per day).

Concomitant medications included acetylsalicylic acid, glyceryl trinitrate, omeprazole, escitalopram, acamprosate, ascorbic acid, tocopherol, and multivitamins.

Previous and ongoing treatment for hyperlipidemia included atorvastatin.

The subject received evolocumab and placebo in the parent Study 20110115 from 08 April same year* to 02 July same year*. The subject was randomized into the evolocumab arm of Study 20120138 on 22 July [redacted] and received the first dose of evolocumab on that date.

Approximately 8 months after starting evolocumab, on 28 March one year after*, the subject visited an emergency room with complaints of suicidal ideation. The subject apparently had been behaving inappropriately with increasing irritability, excessive spending, and sleeplessness, and was obviously manic and agitated. The subject was diagnosed with bipolar I disorder and was admitted to the hospital.

On the same day, review of systems revealed that the subject did not have cardiorespiratory, gastrointestinal, genitourinary, or neurologic symptoms. Mental status results revealed that the patient was oriented to time, place and person, affect was labile, mood was expansive, and speech was pressured. The results of a physical examination were normal. Urine tests for drugs of abuse were positive for marijuana, and the urinalysis results were normal. No other significant abnormalities were found in laboratory tests. The subject's family reported that the subject had been depressed and anxious since the death of his uncle 1 week ago and there

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was a recent attempted robbery of his car. The subject denied homicidal or delusional ideation or hallucinations. Treatment after the onset of the event included a combination of aluminium hydroxide, magnesium and acamprosate.

The subject was continuing home dosing as of the study cutoff date of [redacted], and the last in-clinic dose was documented on 14 October same year*. The outcome of the event bipolar disorder was reported as unknown, as the subject was still hospitalized at the time of this report. The investigator reported that there was not a reasonable possibility that the event of bipolar I disorder was related to the investigational study drug.

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Subject No: [redacted]
Treatments: Parent study and regimen: Study 20110115, Evolocumab SC QM 420 mg Year 1: Evolocumab SC 140 mg Q2W + Standard of care
Report: Osteoarthritis

Subject [redacted] was a 59-year-old white man participating in Study 20120138 who had osteoarthritis (reported term: worsening of osteoarthritis pain left knee). The subject's medical history included hyperlipidemia, osteoarthritis, severe obstructive sleep apnea, allergy to morphine, and hypertension. Concomitant medications included hyaluronate, simvastatin, benazepril, and paracetamol. Previous and ongoing therapy for hyperlipidemia included simvastatin.

The subject received evolocumab in the parent study from 01 May same year* to 29 June same year*. He received the first dose of evolocumab in Study 20120138 on 30 July [redacted].

On 05 March one year after*, the subject was evaluated for left knee pain. The subject had a history of knee pain (1 year) and a previous left medial compartment unicondylar arthroplasty. Radiology of the left knee showed severe joint space narrowing, sclerosis, osteophyte, and cyst formation. Patello-femoral articulation was satisfactory. The anterior cruciate ligament was preserved and lateral compartment visualization was also satisfactory. On 19 March one year after* the subject had worsening left knee pain (osteoarthritis) and was hospitalized. On the same day, the subject underwent total left knee replacement surgery with successful pain relief. The pre- and post-operative diagnosis was left knee antero-medial osteoarthritis.

The event was reported as resolved on 19 March one year after* and the subject was discharged from the hospital on 21 March one year after*. Evolocumab was continued and the subject continued the study.

The subject's last dose of evolocumab prior to the event was not known. The subject was continuing home dosing as of the data cutoff date of [redacted], and the last in-clinic dose was documented 22 October same year*.

The investigator reported that there was not a reasonable possibility that the event of osteoarthritis 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 + Placebo PO QD Year 1: Evolocumab SC 140 mg Q2W + Standard of care
Report: Osteoarthritis

Subject [redacted] was a 53-year-old white man participating in Study 20120138 who had osteoarthritis (reported term: worsening of osteoarthritis left knee). The subject's medical history included primary hyperlipidemia, gout, gastroesophageal reflux disease, overactive bladder, porphyria cutanea tarda, chronic non-allergic rhinitis, hypertension, obesity, and osteoarthritis in the left knee. Concomitant medications included amlodipine, atorvastatin, and benazepril. Previous treatment for primary hyperlipidemia included atorvastatin.

The subject received evolocumab in the parent study from 29 May same year* to 20 August same year*. He received the first dose of evolocumab in Study 20120138 on 20 August [redacted].

Approximately 3 month after the first dose, on 12 November same year*, the subject had worsening of osteoarthritis in his left knee. On 22 November same year*, the subject was hospitalized for increased discomfort and severe pain. On the same day, the subject underwent a total left knee arthroplasty. The postoperative diagnosis was osteoarthritis of the left knee.

Treatment medications reported after the onset of the event included celecoxib, acetylsalicylic acid, gabapentin, oxycodone, tramadol, gentamicin, tranexamic acid, methylprednisolone, morphine, paracetamol, cefazolin, dexamethasone, cyanocobalamin, folic acid, polysaccharide-iron complex, amlodipine, lisinopril, metoclopramide, docusate, sennoside a+b, hyoscine, rivaroxaban, ondansetron, hydrocodone, and hydromorphone.

The outcome of the event of worsening of osteoarthritis of the left knee was reported as resolved on 22 November same year* and the subject was discharged from the hospital on 23 November same year*. Evolocumab was continued and the subject continued the study.

The subject's last dose of evolocumab prior to the event was 12 November 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 20 August same year*.

*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 worsening of osteoarthritis of the left knee was related to evolocumab or device.