Subject No: [redacted]
Treatments: Atorvastatin 80 mg PO QD; Placebo SC QM + Placebo PO QD
Report: Myalgia

Subject [redacted] was a 46-year-old white man participating in Study 20110115 who developed myalgia (reported term: myalgia of lower extremities). The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, former cigarette use, proteinuria, and tonsillectomy The subject never experienced myalgia or muscle cramping in the past. Previous and ongoing treatment for hypercholesterolemia and mixed hyperlipidemia included atorvastatin. No other concomitant medications were reported.

After completing the 4-week lipid stabilization period receiving atorvastatin 80 mg daily, the subject received the first dose of placebo in Study 20110115 on 17 June [redacted]. Approximately 3 months later, on 06 September same year*, the subject experienced severe muscle cramps in the lower limbs and was unable to walk. The subject was taken to the hospital in an ambulance. While in the emergency room, the subject was administered intravenous (IV) fluids. The subject had taken no drugs and specifically no cocaine. Laboratory tests revealed increased creatine phosphokinase (CPK) of 803 IU/L. The subject was subsequently hospitalized and treated with oxycodone. Additional laboratory tests on 06 September same year* revealed creatinine of 116 µmol/L, magnesium of 0.72 mmol/L, phosphate of 0.94 mmol/L, potassium of 4 mmol/L, hematocrit of 0.394 L/L, hemoglobin of 134 g/L, neutrophil count of 7.9 x 10^9/L, platelet count of 274 x 10^9/L, red blood cell (RBC) count of 4.54 x 10^{12}/L, and white blood cell (WBC) count of 10 x 10^9/L.

On 07 September same year*, laboratory tests revealed CPK of 946 U/L. The subject had severe bilateral leg cramps and spasms which were better after an hour. Repeat laboratory tests revealed CPK of 1056 U/L. Mild "rhabdo" was noted, which was considered likely to be secondary to atorvastatin. Liver function tests revealed alkaline phosphatase 76 U/L, alanine aminotransferase (ALT) 28 U/L, aspartate aminotransferase (AST) 33 U/L, direct bilirubin <1.7 µmol/L, total bilirubin 10.6 µmol/L, gamma-glutamyl transpeptidase 18 U/L, and lipase 30 U/L. Upon examination, the physician noted tenderness of the calves, temperature of 36.6 C, pulse rate of 80 beats per minute, respiratory rate of 16 breaths per minute, and blood pressure 138/83 mmHg. The repeat CPK value peaked at 1219 U/L despite continued IV fluids.

On 08 September same year*, laboratory tests revealed anion gap of 1 mmol/L, CPK of 988 U/L, creatinine of 98 µmol/L, potassium of 4.6 mmol/L, hematocrit of 0.349 L/L, hemoglobin of 118 g/L, neutrophil count of 3.60 x 10^9/L, platelet count of 211 x 10^9/L, RBC of 4.02 x 10^{12}/L,

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and WBC of 6.8 x 10^9/L. Repeat laboratory test showed CPK level at 978 U/L. The subject was discharged on the same day, 08 September same year*, with residual muscle weakness. At the time of discharge, the subject was still unable to ambulate and had significant, though improved pain; the physician's impression was myopathy, likely to be drug-related. On 18 September same year*, CPK was normal with a value of 187 IU/L. The event of myalgia was reported as resolved on 21 October same year*.

The last dose of placebo (SC) prior to the event of myalgia and in the study was on the same day, 13 August same year*. The subject received the last dose of oral placebo on 16 September same year* and completed the study on the same day (16 September same year*).

The investigator reported that there was a reasonable possibility that the event of myalgia was related to the investigational product. The investigator reported that there was not a reasonable possibility that the event of myalgia was related to device. Atorvastatin was reported as co-suspect medication.

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Subject No: [redacted]
Treatments: Rosuvastatin 40 mg PO QD; Evolocumab SC QM 420 mg
Report: Injury

Subject [redacted] was a 55-year-old white man participating in Study 20110115 who experienced an injury while on study (reported term: trauma). The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, dyslipidemia, chronic low back pain, degenerative changes in lumbar spine, erectile dysfunction, and bronchitis. The subject was a current smoker. He was not receiving any concomitant medications at the time of event. Pervious and current treatment for hypercholesterolemia and mixed dyslipidemia included rosuvastatin.

After completing the 4-week lipid stabilization period receiving rosuvastatin 40 mg daily, the subject received the first dose of evolocumab in Study 20110115 on 21 May [redacted]. Approximately 2 months later, on 20 July same year*, the subject suffered injury secondary to a motorcycle accident and was hospitalized. The subject had no risk factors associated with the event. A computerized tomography (CT) of head, abdomen, and spine performed on the same day showed questionable small pseudoaneurysm. A thoracic aortic angiography done on 21 July same year* ruled out pseudoaneurysm. Repeat CT of the head done on the same day (21 July same year*) was normal. Treatment included acetaminophen. The event of injury was reported to have resolved on 24 July 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 injury was on 17 July same year*, which was also his last dose in the study. The subject completed the study on 14 August same year*. The investigator reported that there was not a reasonable possibility that the event of injury was related to the investigational product or autoinjector.

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Subject No: [redacted]
Treatments: Atorvastatin 80 mg PO QD; Evolocumab SC Q4W 420 mg + Placebo PO QD
Report: Hip arthroplasty

Subject [redacted] was a 57-year-old white woman participating in Study 20110115 who underwent a hip arthroplasty. The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, dyslipidemia, type 2 diabetes mellitus, hypertension, appendectomy, hysterectomy for myoma, spinal surgery, right ankle fracture, and allergy to vildagliptin and penicillin. Concomitant medications included betaxolol, ramipril, metformin, and gliclazide. Previous and current treatment for hypercholesterolemia and mixed hyperlipidemia included atorvastatin.

After completing the 4-week lipid stabilization period receiving atorvastatin 80 mg daily, the subject received the first dose of evolocumab and placebo on 29 May [redacted]. Approximately 2 months and 1 week later, on 07 August same year*, the subject was hospitalized for prolonged pain in the right hip. The subject was diagnosed with primary right coxarthrosis and underwent a hip arthroplasty. Vital signs included blood pressure of 130/85 mmHg, pulse rate of 60 beats per minute, and temperature of 36.6°C. Treatment included combination of caffeine, paracetamol, and propyphenazone, nadroparin, thiethylperazine maleate, paracetamol, rivaroxaban, cefazolin, diclofenac, and piritramide. The event of hip arthroplasty was reported to have resolved on 14 August same year* and the subject was discharged from the hospital on that date.

The subject's last dose of evolocumab prior to the event of hip arthroplasty and in the study was on 24 July same year*. The subject's last dose of placebo was on 21 August same year*; the subject completed the study on 21 August same year*. The investigator reported that there was not a reasonable possibility that the event of hip arthroplasty was related to the investigational product.

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Subject No: [redacted]
Treatments: Atorvastatin 80 mg PO QD; Placebo SC Q2W + Ezetimibe PO QD 10 mg
Report: Bladder neoplasm

Subject [redacted] was a 67-year-old white man participating in Study 20110115 who developed bladder neoplasm (reported term: tumor of the urinary bladder). The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, myocardial infarction, cigarette use, and coronary artery bypass graft. Concomitant medications included acetylsalicylic acid, ramipril, clopidogrel, bisoprolol, and furosemide. Previous and ongoing treatment for hypercholesterolemia and mixed hyperlipidemia included atorvastatin.

After completing the 4-week lipid stabilization period receiving atorvastatin 80 mg daily, the subject received the first dose of ezetimibe and placebo on 17 June [redacted]. Approximately 3 months later, on 17 September same year*, the subject was diagnosed with tumor of the urinary bladder after cystoscopy. The subject's clinical manifestations included hematuria. On 27 September same year*, the subject was admitted to the hospital. The subject underwent an endoresection of the tumor. Histological type of the tumor was not available at the time of this report. The outcome of the event of bladder neoplasm was reported as unknown. The subject was discharged from the hospital on 03 October same year*.

The subject's last dose of placebo prior to the event and in the study was on 27 August same year* and last dose of ezetimibe prior to the event and in the study was on 12 September same year*. The subject completed the study on 25 September same year*. The investigator reported that there was not a reasonable possibility that the event of bladder neoplasm was related to investigational product or the device.

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Subject No: [redacted]
Treatments: Rosuvastatin 40 mg PO QD; Placebo SC Q2W
Report: Cerebrovascular accident

Subject [redacted] was a 65-year-old white man participating in Study 20110115 who developed cerebrovascular accident (reported term: stroke). The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, normal systolic function, left ventricular systolic function greater than or equal to 50%, hypertension, former cigarette use, stroke/cerebral infarction, transient ischemic attack, and carotid and vertebral artery disease. Concomitant medications included metoprolol, telmisartan, hydrochlorothiazide, rilmenidine, and nitrendipine. Previous treatment for hypercholesterolemia and mixed hyperlipidemia included simvastatin.

After completing the 4-week lipid stabilization period receiving rosuvastatin 40 mg daily, the subject received the first dose of placebo on 14 June [redacted]. Approximately 1 month and 2 weeks later, on 29 July same year*, the subject was hospitalized due to a cerebrovascular accident. The presenting neurological symptom was weakness. On an unspecified date, an electrocardiogram showed sinus rhythm and heart rate of 60 beats per minute, without changes. Computerized tomography scan showed only minimal changes and microangiopathy. The subject was treated with his outpatient medications and clopidogrel. No laboratory test results or diagnostic data were reported. The event of cerebrovascular accident was reported as resolved on 02 August same year*, and the subject was discharged on the same day.

The subject's last dose of placebo prior to the event was on 26 July same year*. Placebo was continued. The subject's last dose of placebo in the study was on 26 August same year*, and the subject completed the study on 20 September same year*. The investigator reported that there was not a reasonable possibility that the event of cerebrovascular accident was related to the investigational product.

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Subject No: [redacted]
Treatments: Rosuvastatin 5 mg PO QD; Placebo SC QM
Report: Ovarian cancer

Subject [redacted] was a 67-year-old white woman participating in Study 20110115 who developed ovarian cancer. The subject's medical history included primary hypercholesterolemia, mixed hyperlipidemia, hypertension, smoker, postpartum depression, and postmenopausal symptoms; she had no history of cancer diagnosed. Concomitant medications included, carvedilol, lercanidipine, combination of bendroflumethiazide and potassium, and acetylsalicylic acid. Previous and ongoing treatment for hypercholesterolemia and mixed hyperlipidemia included ezetimibe and rosuvastatin.

After completing the 4-week lipid stabilization period receiving rosuvastatin 5 mg daily, the subject received the first dose of placebo on 25 July [redacted]. Approximately 2 months later, on 23 September same year*, the subject was hospitalized due to abdominal pain. She was diagnosed with ovarian cancer (adenocarcinoma). A hysterectomy with removal of ovaries and appendix was performed. No signs of spreading were noted. Adjuvant chemotherapy was planned. The event was reported to have resolved on 27 September same year*, and the subject was discharged from the hospital on the same date.

The subject's last dose of placebo prior to the event and in the study was on 19 September same year*. The subject completed the study on 21 October same year*.

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

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Subject No: [redacted]
Treatment: Atorvastatin 10 mg PO QD; Evolocumab SC Q2W 140 mg + Placebo PO QD
Report: Acute pyelonephritis

Subject [redacted] was a 68-year-old white woman participating in Study 20110115 who developed acute pyelonephritis. The subject's medical history included primary hypercholesterolemia, mixed hyperlipidemia, family history of premature coronary heart disease (in first degree male relative), arthrosis, back pain, reflux, hysterectomy, and lipid with borderline values. Concomitant medication included pantoprazole. Previous treatment for hypercholesterolemia and mixed hyperlipidemia included atorvastatin.

After completing the 4-week lipid stabilization period receiving atorvastatin 10 mg daily, the subject received the first dose of evolocumab and placebo on 22 July [redacted]. Beginning 01 October same year* the subject developed a continuously rising fever, up to 39.7°C on 05 October same year*. On 06 October same year*, the subject went to the emergency room, where acute pyelonephritis was diagnosed. The subject was hospitalized on the same day. Treatment for the event included sultamicillin and enoxaparin. The event was reported as resolved on 13 October same year* and the subject was discharged on the same day.

The subject's last dose of evolocumab prior to the event was on 30 September same year*. Evolocumab was discontinued due to the event. The subject's last dose of evolocumab in the study was on 30 September same year* and the last dose of placebo was on 31 October same year*. The subject completed the study on 31 October same year*.

The investigator reported that there was a reasonable possibility that the event of acute pyelonephritis was related to investigational product.

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Subject No: [redacted]
Treatment: Simvastatin 40 mg PO QD; Evolocumab SC QM 420 mg
Report: Spinal pain

Subject [redacted] was a 45-year-old white woman participating in Study 20110115 who developed spinal pain (reported term: pain in cervical spine). The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, hypertension, reflux esophagitis, mood swings, cholecystectomy, hysterectomy, and allergy to propanolol. The subject was a tobacco user. Concomitant medications included candesartan, metoprolol, omeprazole, and opipramol. Previous treatment for hypercholesterolemia and mixed hyperlipidemia included simvastatin.

After completing the 4-week lipid stabilization period receiving simvastatin 40 mg daily, the subject received the first dose of evolocumab on 17 June [redacted]. Approximately 2 months later, on 17 August same year*, the subject experienced spinal pain and took diclofenac but the pain did not resolve. The next day, on 18 August same year*, the subject was admitted to the hospital. The subject complained of increasing pain in the cervical spine area expanding to the back of the head and in the right shoulder for a few days. A trauma could not be remembered. A cervical spine examination revealed pressure pain over the dorsal process of the cervical spine; distinct paravertebral myogelosis on both sides; pain-related reduction of motion in all levels; no peripheral reduction of strength; and no paresthesia at examination. Cervical spine radiography showed no pathological findings. During hospitalization, the subject was treated with physiotherapy; other treatment included clotrimazole cream and a combination of caffeine, paracetamol, and propyphenazone. The event of spinal pain was considered resolved on 23 August same year*. The subject was discharged from the hospital on that day.

The subject's last dose of evolocumab prior to the event of spinal pain was on 13 August same year*, which was also her last dose in the study. The subject completed the study on 11 September same year*. The investigator reported that there was no reasonable possibility that the event of spinal pain was related to investigational product or to device.

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Subject No: [redacted]
Treatment: Rosuvastatin 40 mg PO QD; Placebo SC Q2W
Report: Acute myocardial infarction

Subject [redacted] was a 48-year-old white man participating in Study 20110115 who developed acute myocardial infarction (reported term: acute myocardial infarction of anterior wall). The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, angina due to atherosclerotic coronary disease, hypertension, left ventricular systolic function, myocardial infarction, percutaneous coronary intervention, and smoking. The subject had a family history of premature coronary heart disease. Concomitant medications included acetylsalicylic acid, metoprolol, and ramipril. Previous treatment for hypercholesterolemia and mixed dyslipidemia included simvastatin.

After completing the 4-week lipid stabilization period receiving rosuvastatin 40 mg daily, the subject received the first dose of placebo on 04 July [redacted]. One month later, on 04 August same year*, the subject complained of permanent chest pain that had started 1 day before. The subject died before the ambulance arrived on 04 August same year*. Resuscitation was not successful. The cause of death was reported as acute myocardial infarction of the anterior wall, and this was confirmed by autopsy results.

The subject's last dose of placebo prior to the event of acute myocardial infarction was on 18 July same year*.

The investigator reported that there was not a reasonable possibility that the event of acute myocardial infarction was related to investigational product.

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Subject No: [redacted]
Treatment: Rosuvastatin 5 mg PO QD; Evolocumab SC QM 420 mg
Report: Radius fracture

Subject [redacted] was a 72-year-old white woman participating in Study 20110115 who had a radius fracture. The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, hypertension, pain postherpetic, gastroesophageal reflux, appendectomy, total hysterectomy, alcoholic hepatopathy, chronic cardiomyopathy, hyperlipoproteinemia, ulcus ventriculi, polyarticular arthrosis, status post implant total endoprosthesis coxae, and obesity; she had not used tobacco or consumed alcohol in the past few years. Concomitant medications included *Silybum marianum* fruit, famotidine, amitriptyline, metamizole, and vinpocetine. Previous treatment for hypercholesterolemia and mixed hyperlipidemia included atorvastatin.

After completing the 4-week lipid stabilization period receiving rosuvastatin 5 mg daily, the subject received the first dose of evolocumab on 22 July [redacted]. Approximately 2 months later, on 17 September same year*, the subject fell and suffered a fracture of the radius. A plaster cast was applied on 19 September same year*. On 01 October same year*, the subject was hospitalized and radiography showed that the end of the fracture was compressing a vein. Treatment included surgical intervention. The event radius fracture was reported as not resolved; the subject was discharged from the hospital on 02 October same year*.

The subject's last dose of evolocumab prior to the event of radius fracture was on 08 August same year*. Evolocumab was continued. The subject's last dose of evolocumab in the study was on 20 September same year*. The subject completed the study on 31 October same year*.

The investigator did not consider either the radius fracture or the subsequent hospitalization to be related to investigational product.

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Subject No: [redacted]
Treatment: Atorvastatin 10 mg PO QD; Placebo SC QM + Placebo PO QD
Report: Mycoplasmal pneumonia

Subject [redacted] was a 43-year-old white man participating in Study 20110115 who developed mycoplasmal pneumonia (reported term: mycoplasma pneumoniae pneumonia). The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, hypertension, metabolic syndrome, allergy to graminacae, and impaired fasting glucose. The subject had never experienced similar events of mycoplasma pneumonia in the past. Concomitant medications included lercanidipine, ramipril, paracetamol, a combination of amoxicillin and clavulanic acid, and erdosteine. Previous treatment for hypercholesterolemia and mixed hyperlipidemia included atorvastatin.

After completing the 4-week lipid stabilization period receiving atorvastatin 10 mg daily, the subject received the first dose of placebo on 18 July [redacted]. Approximately 2 months later, on 16 September same year*, the subject developed mycoplasmal pneumonia and was hospitalized on the same day. The subject was admitted to the pneumology ward for further diagnosis and treatment of persistent left basal pneumonia with fever. Upon hospitalization, vital signs were stable. Laboratory testing revealed white blood cell (WBC) count of 8770/mmc, neutrophil count of 6450/mmc, fibrinogen of 575 mg/dL, hemoglobin of 14.1 g/dL, alanine aminotransferase (ALT) of 161 U/L, C-reactive protein (CRP) of 2.8 mg/dL, and prothrombin time (PT) of 1.05 second. The following day, on 17 September same year*, laboratory tests revealed WBC count of 8110/mmc, neutrophil count of 4770/mmc, red blood cell (RBC) sedimentation rate (ESR) of 51 mm/hr, ALT of 155 U/L, gamma glutamyl transferase (GGT) of 172 U/L, creatine phosphokinase (CPK) of 93 U/L, alkaline phosphatase (ALP) of 123 U/L, protein of 7.8 g/dL, and α-2 globulin of 16.4%.

The subject underwent a chest contrast computed tomography to analyze the left basal pneumonia and suspected interstitial pneumonia. On an unspecified date, immunoglobulin M serology was positive for mycoplasma pneumonia. Treatment included ciprofloxacin, betamethasone, ranitidin, cetirizine, azithromycin, pantoprazole, moxifloxacin, and doxycycline. On 30 September same year*, the subject was discharged from the hospital in an improved general condition. On 07 October same year*, chest radiograph showed resolution of basal left pneumonia. Additional treatment for the event included levofloxacin, which was completed on

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21 October same year*. On the same day, high-resolution computed tomography of the thorax revealed a complete resolution of interstitial pneumonia. Reportedly, the subject's condition improved, and he had no fever, as verified 3 times a day until 27 October same year*. On an unspecified date, laboratory examinations revealed hemoglobin, WBC count, renal and hepatic function, CRP, and ESR all within normal ranges. The investigator reported that the subject did not have any predisposing risk factors or history of mycoplasmal pneumonia. The event of mycoplasmal pneumonia was reported as resolved on 31 October same year*.

The subject's last dose of placebo prior to the event was on 11 September same year*. Placebo was permanently discontinued and the subject completed the study on 11 October same year*.

The investigator reported that there was no reasonable possibility that the event of mycoplasmal pneumonia was related to investigational product.

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Subject No: [redacted]
Treatment: Atorvastatin 10 mg PO QD; Evolocumab SC QM 420 mg + Placebo PO QD
Report: Breast pain

Subject [redacted] was a 65-year-old white woman participating in Study 20110115 who developed breast pain. The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, type 2 diabetes mellitus, carotid or vertebral artery disease, and hepatic steatosis. The subject had a family history of premature coronary heart disease. Concomitant medications included atorvastatin. Previous treatment for hypercholesterolemia and mixed hyperlipidemia included ezetimibe and simvastatin.

After completing the 4-week lipid stabilization period receiving atorvastatin 10 mg daily, the subject received the first dose of evolocumab and placebo on 18 July [redacted]. Approximately 2 weeks later, on 01 August same year*, the subject presented to the emergency room due to breast pain with dyspnea. The subject reported that the breast pain had started the previous day. Cardiac enzymes were negative; electrocardiogram was normal, and hematologic examination was in range. The investigator reported that the final diagnosis was unknown, and a panic crisis was suspected. The subject had similar episodes of panic crises. The event of breast pain was reported as resolved on 03 August same year*, and the subject was discharged from the hospital on the same date.

The subject's last dose of evolocumab prior to the event was on 18 July same year*. Evolocumab was continued. The subject received the last dose of evolocumab on 17 September same year* and the last dose of placebo on 11 October same year*; she completed the study on 11 October same year*. The investigator reported that there was not a reasonable possibility that the event of breast pain was related to investigational product.

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Subject No: [redacted]
Treatment: Atorvastatin 10 mg PO QD; Placebo SC QM + Placebo PO QD
Report: Drug-induced liver injury

Subject [redacted] was a 66-year-old white woman participating in Study 20110115 who developed drug-induced liver injury (reported term: drug related hepatitis). The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, former cigarette use, rheumatoid arthritis, breast cancer, , hepatic insufficiency due to use of diclofenac, atrial fibrillation, carotid vertebral artery disease, coronary artery bypass graft, myocardial infarction, percutaneous coronary intervention, peripheral arterial disease, permanent pacemaker implant, resynchronization device with defibrillator, stroke, transient ischemic attack, type 2 diabetes mellitus, and alcohol use (1 to 2 glasses per day). No concomitant medications were reported. Previous treatment for hypercholesterolemia and mixed hyperlipidemia included atorvastatin.

On 23 April same year*, baseline liver enzyme levels were: aspartate aminotransferase (AST) 26 U/L, alanine aminotransferase (ALT) 28 U/L, lactate dehydrogenase (LDH) 208 U/L and alkaline phosphatase (ALP) 71 U/L. The investigator confirmed that baseline hepatic function levels were normal after the lipid stabilization period as well.

After completing the 4-week lipid stabilization period receiving atorvastatin 10 mg daily, the subject received the first dose of placebo on 11 June [redacted]. The next day, on 12 June same year*, laboratory tests showed ALT of 2354 IU/L, elevated AST of 1485 U/L, ALP of 157 IU/L, LDH of 819 U/L and uric acid of 297 µmol/L (This was a protocol violation as laboratory tests should have been obtained on study day 1 prior to the first dose of investigational product). On 17 June same year*, the subject presented to the site with no complaints. During physical examination, the liver was not palpable. Repeated laboratory tests disclosed elevated ALT of 3193 IU/L, elevated AST of 1542 U/L, ALP of 223 IU/L, LDH of 597 U/L and gamma-glutamyltransferase (GGT) of 228 U/L. On 19 June same year*, an ultrasound of the liver showed no abnormal findings except some small cysts. On 21 June same year*, laboratory tests showed improvement with ALT 1613 U/L, AST 472 U/L, ALP 178 U/L, GGT 198 U/L, LDH 257 U/L and creatinine 49 µmol/L. Hepatitis A IgM, hepatitis A IgG, hepatitis B surface antigen, hepatitis B core-Ig, hepatitis B surface-Ig, hepatitis C-Ig, cytomegalovirus IgM, cytomegalovirus IgG and Epstein-Barr test results showed that there were no active infections. No treatment was given for the events; expectant policy was followed and liver function was examined weekly. As of 21 June same year*, the

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subject still had no complaints and laboratory tests were improving. Reportedly, the subject continued using atorvastatin.

Laboratory tests done on retrospectively 12 June same year* blood samples showed serological tests negative for hepatitis E IgG and positive for hepatitis E IgM and acetaminophen level was 15 µg/ml.

On 26 June same year*, serological tests showed positive results for hepatitis E IgG and hepatitis E IgM. On 26 June same year* ALP was 130 U/L, GGT 142 U/L, AST 67 U/L, ALT 484 U/L and LDH 194 U/L. As of that day, the subject still had no complaints and laboratory results were still improving. Upon review the subject's liver and spleen were not enlarged, there was adequate perfusion of extremities, and liver enzymes were almost completely recovered.

On 04 July same year*, laboratory tests disclosed red cell distribution width of 16.4, ALT 54 U/L, AST 24 U/L, ALP 100 U/L, bilirubin total 7 µmol/L, and bilirubin direct 2 µmol/L. Serology was positive for hepatitis E IgG, hepatitis E IgM, cytomegalovirus IgG, Epstein-Barr Virus VCA IgG, Epstein-Barr Virus EBNA IgG, and herpes simplex virus type 1/2 IgG.

The investigator reported that the subject had none of the following risk factors that could contribute or could have caused the reported event: alcohol abuse or illicit drug use, use of wild mushrooms, family history of P-450 enzyme abnormalities, or historical exposure to herbal or "nutraceutical" products, selective serotonin reuptake inhibitors (SSRIs), isonicotinylhydrazines (INH), rifampin, oral contraceptives, isotretinoin, methyldopa, valproic acid, methotrexate, antibiotics, non-steroidals (NSAIDs) or halothane anesthesia. There was no family history of liver disease. The subject had not travelled outside of the Netherlands during the previous 2 years, but visited Berlin in two years ago*. The investigator reported that in six years ago* the subject had developed elevated liver enzymes after use of diclofenac with AST 202 U/L, ALT 441 U/L, LDH 281 U/L and ALP 284 U/L.

The event of drug-induced liver injury was reported as resolved on 06 August same year*. The investigator reported there were no co-suspect medications. On 22 August same year*, hepatitis E IgG and hepatitis E IgM were positive. On 13 September same year*, hepatitis E IgG and hepatitis E IgM were positive.

Hepatitis E serology testing was recommended on samples from screening on 23 April same year* and at the end of the lipid stabilization period on 31 May same year*. However, further testing could not be done due to ambient collection of the samples.

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The subject's last dose of placebo prior to the event of drug-induced liver injury was on 11 June same year*, which was also her last dose in the study. The subject completed the study on 13 September same year*. The investigator reported that there was a reasonable possibility that the event of drug-induced liver injury was related to investigational product. The investigator commented that the subject was possibly infected with hepatitis E before the first dose, of investigational product; although it could not be excluded that the infection started after the first dose.

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Subject No: [redacted]
Treatment: Rosuvastatin 40 mg PO QD; Evolocumab SC QM 420 mg
Report: Cholecystitis

Subject [redacted] was a 65-year-old white man participating in Study 20110115 who developed cholecystitis (reported term: acute calculous cholecystitis). The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, angina due to atherosclerotic coronary disease, New York Heart Association (NYHA) class II congestive heart failure, normal systolic function with a left ventricular ejection fraction of 50%, myocardial infarction, hypertension, atrial fibrillation/atrial flutter, varicose veins of the lower extremities, aneurysm of the apex of the left ventricle, and chronic antral erosive gastritis in exacerbation stage. Concomitant medications included metoprolol, losartan, perindopril, torasemide, and combination of diosmin and hesperidin. Previous treatment for hypercholesterolemia and mixed hyperlipidemia included rosuvastatin.

After completing the 4-week lipid stabilization period receiving rosuvastatin 40 mg daily, the subject received the first dose of evolocumab on 08 August [redacted]. Approximately 1.5 months later, on 26 September same year*, the subject felt pain in the right hypochondrium after a high-fat meal and was hospitalized with cholecystitis. The subject was also diagnosed as having cholelithiasis and gallbladder hydrops, which was not serious. Chest and stomach radiograph showed no pathologies.

The following day, on 27 September same year*, a cholecystostomy was done. Additional treatment with metronidazole and ciprofloxacin was started.

On 30 September same year*, laboratory results were: white blood cell (WBC) count 5.9 x 10^9/L, red blood cell (RBC) count 4.22 x 10^{12}/L, hemoglobin 127 g/L, hematocrit 0.398 (fraction of 1), platelet count 236 x 10^9/L, neutrophils 46%, lymphocytes 50%, monocytes 4%, urea 4.4 mmol/L, glucose 5.6 mmol/L, creatinine 70.3 µmol/L, total protein 69.5 g/L, amylase 34 U/L, total bilirubin 10.6 µmol/L, alanine aminotransferase (ALT) 12 U/L, and aspartate aminotransferase (AST) 23 U/L. On 01 October same year*, additional conservative treatments included infusion and spasmolytic therapy, antisecretory medications, anaesthetization, anticoagulation, symptomatic, and anti-inflammatory therapies. Removal of the gallbladder was subsequently scheduled

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within the next 6 months. The event cholecystitis was reported as resolved on 03 October same year* and the subject was discharged from the hospital on the same day in good condition.

The risk factors the investigator considered possibly contributing to the development or worsening of the event included the subject's high-fat diet and statins in frame of the protocol.

The subject's last dose of evolocumab prior to the event was on 04 September same year*. Evolocumab was continued. The subject's last dose of evolocumab in the study was on 09 October same year*. The subject completed the study on 06 November same year*. The investigator reported that there was no reasonable possibility that the event of cholecystitis was related to investigational product or the device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Rosuvastatin 40 mg PO QD; Evolocumab SC QM 420 mg
Report: Acute glomerulonephritis

Subject [redacted] was a 55-year-old white woman participating in Study 20110115 who developed acute glomerulonephritis. The subject's medical history included primary hypercholesterolemia, mixed hyperlipidemia, congestive heart failure (New York Heart Association Class II, mainly caused by arterial hypertension), type 2 diabetes mellitus, hypertension degree III, stroke/cerebral infarction, carotid or vertebral artery disease, mixed goiter, obesity, macular dystrophy, gallbladder shape anomaly, cholelithiasis, chronic calculous cholecystitis, chronic gastritis, fibrocystic "masthopaty", cervical and lumbar osteochondrosis, uterine artery embolization, uterine myoma, chronic pancreatitis, and bilateral myopia. Concomitant medications included indapamide, glimepiride, and metformin. Previous treatment for hypercholesterolemia and mixed hyperlipidemia included atorvastatin.

After completing the 4-week lipid stabilization period receiving rosuvastatin 40 mg daily, the subject received the first and only dose of evolocumab on 31 July [redacted]. Two days later, on 02 August same year*, the subject developed edema. The subject was seen by a cardiologist and treated with spironolactone and hydrochlorothiazide, following which there was no significant improvement. One week later, the subject started experiencing dyspnea with an increase in physical activity. The New York Heart Association classification was changed to Class III. Additional visible reasons for decompensation were not observed.

On 14 August same year*, the subject reported feeling ill after receiving rosuvastatin; edema appeared, and weight increased by 8 kg. Rosuvastatin was withheld on 14 August same year*. Urinalysis revealed light yellow, slightly clear, acidic urine with a specific density of 1016, protein 1.97 g/L, sugar negative, singular pavement epithelium in visual field and white blood cells (WBC) and red blood cells (RBC) from 0 to 1 in visual field. Daily diuresis was 1050 mL and nocturnal diuresis 1500 mL. The subject's oral liquid intake was 1990 mL per 24 hours and amount of urine was 2550 mL per 24 hours. Throughout the day, 14 August same year*, the subject's quantity of urine was between 100 mL and 800 mL, and urine specific gravity was between 5 and 25. On 16 August same year*, urinalysis showed light yellow, cloudy, acidic urine with a specific density of 1010, protein 1.8 g/L, sugar negative, singular pavement epithelium in visual field, WBC 0-3-7, RBC unmodified 0-0-1 in visual field, and a large quantity of bacteria.

*新薬承認情報提供時に置き換え

On 14 August same year*, the subject underwent a physical examination that revealed mild edema of the upper extremities and severe leg edema (two-thirds of hip) and was hospitalized on the same day. The subject was noted to have hypoproteinemia, hyperlipidemia, and proteinuria (urinalysis results showed protein level of 1.97 g/L) while hospitalized. On an unspecified date, laboratory test results revealed creatine phosphokinase MB 9.1 IU/L, glucose 8.93 mmol/L, total protein 52.8 g/L, albumin 29.5 g/L, total cholesterol 6.79 mmol/L, triglycerides 5.35 mmol/L, low-density protein 3.5 mmol/L, creatinine 83.1 mmol/L, potassium 4.34 mmol/L, and sodium 141.8 mmol/L. On 16 August same year*, urinalysis protein level was 1.86 g/L. The subject was diagnosed with acute glomerulonephritis due to the presence of signs of nephrotic syndrome.

Risk factors associated with the event were considered the start of statin therapy. The subject had never experienced glomerulonephritis or other kidney diagnoses in the past. Concomitant medications indapamide and metformin were withheld on 13 August same year*.

The subject was started on insulin on 18 August same year*. On 19 August same year*, the subject presented with edema of face and limbs; additionally, heavy proteinuria, hypoalbuminemia, hypercholesterolemia; lack of effect of diuretic therapy was noted.

On 22 August same year*, nephrologist examination showed acute glomerulonephritis, diabetic nephropathy, and nephrotic syndrome.

The nephrologist recommended discontinuation of rosuvastatin. Treatment included acetylsalicylic acid, bisoprolol fumarate, alpha-lipoic acid, combination of aspartic acid dipotassium and magnesium, prednisolone 40 mg oral and 60 mg intravenous, furosemide, torasemide, and spironolactone. Glimepiride was withheld on 17 September same year*. On 25 September same year*, the subject was discharged from the hospital. The event of acute glomerulonephritis was reported as not resolved at the time of this report.

The subject's first and last dose of evolocumab prior to the event was on 31 July same year*. Evolocumab was discontinued due to the event of acute glomerulonephritis. The subject completed the study on 28 October same year*.

The subject's baseline urinalysis on 31 July same year* prior to the first dose of evolocumab showed 3+ proteinuria. Anti-evolocumab antibodies were evaluated at baseline and week 12 and found to be negative.

*新薬承認情報提供時に置き換え

The investigator reported that there was a reasonable possibility that the event of acute glomerulonephritis was related to investigational product and was not related to the device. Unspecified statin therapy was considered a cosuspect medication.

Subject No: [redacted]
Treatment: Atorvastatin 80 mg PO QD; Evolocumab SC Q2W 140 mg + Placebo PO QD
Report: Coma, Ventricular fibrillation, Pulmonary edema, Myocardial infarction

Subject [redacted] was a 59-year-old white man participating in Study 20110115 who developed pulmonary edema, myocardial infarction (reported term: recidivating myocardial infarction), ventricular fibrillation (reported term: paroxysm of ventricular fibrillation), and coma (reported term: depression of consciousness [coma I]). The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, angina pectoris, congestive heart failure, hypertension, carotid artery disease, peripheral arterial disease, stroke, transient ischemic attack, gastritis, appendectomy, prostatitis, post traumatic arthritis of the left knee, rhinitis, pharyngitis, angina due to atherosclerotic coronary heart disease, unstable stenocardia, pulmonary edema, cardiac defibrillator, pacemaker, coronary arterial bypass graft (4 shunts), mammary-coronary bypass of the front interventricular artery, coronary arterial bypass graft of diagonal artery, obtuse marginal branch, right posterolateral artery and posterior interventricular branch, endarterectomy from both carotid arteries, stenting of one of the coronary shunts, stenting of the left carotid artery, stenting of the cephalic artery, percutaneous coronary intervention, resynchronization device and without defibrillator, permanent pacemaker implant and type 2 diabetes. Concomitant medications included acetylsalicylic acid, clopidogrel, bisoprolol, isosorbide mononitrate, metoprolol, captopril, and amlodipine. Previous treatment for hypercholesterolemia and mixed hyperlipidemia included atorvastatin.

After completing the 4-week lipid stabilization period receiving atorvastatin 80 mg daily, the subject received the first dose of evolocumab and placebo on 17 July [redacted]. Approximately 5 days later, on 23 July same year*, the subject presented to the hospital with shortness of breath and constricting pain behind the breastbone without radiation. Upon admission, the subject was oriented to place and time, and cooperative. Vital signs included respiration rate of 26 per minute, oxygen saturation ($Sp0_2$) of 85%, blood pressure of 180/100 mmHg, and heart rate of 75 per minute. The following day, on 24 July same year* the subject was transferred to the urgent cardiology ward for further treatment. Laboratory testing showed white blood cells (WBC) of 13.8 x 10^9/L, red blood cells (RBC) of 5.01 x 10^{12}/L, hemoglobin of 153.0 g/L, platelets of 240.0 x 10^9/L, glucose of 7.9 mmol/L, creatinine of 70 µmol/L, urea of 5.7 mmol/L, aspartate aminotransferase (AST) of 38 U/L, total bilirubin of 9.5 µmol/L, potassium of 4.58 mmol/L, sodium of 142.0 mmol/L, total protein of 81.8 g/L, creatine kinase of 126 U/L, activated partial

*新薬承認情報提供時に置き換え

thromboplastin time of 30.0 seconds, international normalized ratio (INR) of 1.22, and troponin tests which were performed twice were negative. An electrocardiogram (ECG) showed sinus rhythm, heart rate was 55 to 60 per minute, and dynamics of Q-wave myocardial infarction of the inferolateral left ventricular wall. An echocardiogram performed on 24 July same year*, revealed an ejection fraction of 61%, compressed aorta and aortic ring; induration of the aortic and mitral valves; enlarged left atrium; normal global contractility; disorder of local contractility of left ventricular myocardium (akinesia of posterior wall, hypokinesia of posterior apical and septal segments); diastolic function was not disturbed; and no signs of pulmonary hypertension. A chest radiograph showed some stagnation in lesser circulation. Treatment for the event included morphine, furosemide, nitroglycerin, levofloxacin, clopidogrel, acetylsalicylic acid, bisoprolol, isosorbide mononitrate and amlodipine. On 25 July same year*, laboratory tests showed creatine kinase-MB of 11.9 ng/mL, myoglobin of 109 ng/mL, and troponin of 5.39 ng/mL.

On 30 July same year* the subject was urgently transferred to the post resuscitation intensive care department because of acute loss of consciousness, and a short episode of tonic convulsions of the upper part of the body. Before loss of consciousness, the subject complained about intensive pain behind the breastbone. Nitroglycerine was administered. When being admitted, a vascular fibrillation was registered by oscilloscope of the defibrillator and was eliminated with one 90 Joules biphase discharge. The differential diagnosis was between an acute cerebrovascular event and acute cerebral anoxia as a result of transient circulatory arrest against the background of acute myocardial infarction (AMI), the localization of the AMI according to the ECG was complicated. The subject's consciousness was depressed up to coma I and sopor. Subsequently, consciousness was restored, however there were complaints about dyspnea and pains behind the breastbone.

The subject developed a second episode of AMI with acute left ventricular failure and pulmonary edema on 30 July same year*. The subject also had ventricular fibrillation (cut off with countershock). A computed tomography (CT) scan of the brain revealed a picture of post-ischemic changes in the basis of left and right medial cerebral arteries. The CT data for the new focal pathological process of the brain were not received (CT-negative period). The events of ventricular fibrillation and coma were reported to have resolved on that same day (30 July same year*).

The following day, on 31 July same year*, laboratory testing revealed WBC of 12.71 x 10^9/L, RBC of 4.70 x 10^{12}/L, hemoglobin of 145.0 g/L, platelets of 345.0 x 10^9/L, brain natriuretic peptide (BNP) of 717 ng/mL, glucose of 7.9 mmol/L, creatinine of 98 µmol/L, urea of 5.7 mmol/L, AST of 421 U/L, total bilirubin of 6.7 µmol/L, potassium of 4.58 mmol/L, sodium of 141.0 mmol/L,

*新薬承認情報提供時に置き換え

cholesterol of 2.0 mmol/L, total protein of 70.7 g/L, and creatine kinase of 2486 U/L. A chest radiograph in comparison with the examination dated 24 July same year* showed positive dynamics, symmetric lung pattern moderately deformed by mixed type; no focal infiltrating shadows; structural roots, free sinuses; aorta, heart shadow with no peculiarities; condition after stenting; and coronary artery bypass grafting.

On 06 August same year*, the subject was transferred from the post resuscitation intensive care department to the urgent cardiology ward. Laboratory testing showed WBC 6.3 x 10^9/L, RBC 4.13 x 10^{12}/L, hemoglobin 123.0 g/L, platelets 285.0 x 10^9/L, creatinine 65.7 µmol/L, urea 4.3 mmol/L, potassium 4.6 mmol/L, sodium 141.0 mmol/L, and chloride 104 mmol/L. Additional treatment included morphine, trimeperidine, enoxaparin, furosemide, nitroglycerine, fondaparinux, enalapril, omeprazole, spironolactone, carvedilol, acetylsalicylic acid, clopidogrel, atorvastatin, torasemide, isosorbide mononitrate, and levofloxacin.

The events of myocardial infarction and pulmonary edema were reported to have resolved on 06 August same year* and the subject was discharged from the hospital on that day. Upon discharge, the subject's condition was stable; there was no edema, in the lungs respiration was vesicular, somewhat weakened in lower parts on both sides, and there was no crackling. The subject was discharged with a recommendation of limited physical and emotional activities, diet with restriction of salt and animal fat, and easily digestible carbohydrates.

The subject's last dose of evolocumab prior to the events and the last dose in the study was on 17 July same year*. Evolocumab was discontinued as a result of the adverse events. The subject's last dose of placebo in the study was on 06 August same year*. The subject's last dose of atorvastatin was on 06 August same year* and the subject ended the study on that same day. The investigator reported that there was no reasonable possibility that the events of myocardial infarction, pulmonary edema, ventricular fibrillation, and coma were related to investigational product.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Rosuvastatin 5 mg PO QD; Evolocumab SC Q2W 140 mg
Report: Upper abdominal pain

Subject [redacted] was a 75-year-old white woman participating in Study 20110115 who developed upper abdominal pain. The subject's medical history included hypercholesterolemia, angina due to atherosclerotic coronary disease, hypertension, percutaneous coronary intervention, arthrosis of the knee, restless legs, intolerance to mushrooms, and gallstone; she was a former smoker and had a family history of premature coronary heart disease. Concomitant medications included metoprolol, acetylsalicylic acid, and pramipexole. Previous and ongoing treatment for hypercholesterolemia included rosuvastatin and simvastatin.

After completing the 4-week lipid stabilization period receiving rosuvastatin 5 mg daily, the subject received the first dose of evolocumab on 18 July [redacted]. Approximately 3 weeks later, on 08 August same year*, the subject had a pizza with mushrooms; later the subject developed upper abdominal pain and was admitted to the hospital. The investigator reported the subject did not have itching or rash. The subject had experienced food allergy reactions to mushrooms in the past. Her electrocardiogram was normal. Laboratory tests showed normal results for troponin T, hematology, C-reactive protein, sodium, and potassium. Treatment included lidocaine. On 09 August same year*, the event was reported as resolved and the subject was discharged from the hospital with no symptoms.

The subject's last dose of evolocumab prior to the event was on 01 August same year*. Evolocumab was continued. The subject's last dose of evolocumab was on 26 September same year*. The subject completed the study on 24 October same year*. The investigator reported that there was no reasonable possibility that the event of upper abdominal pain was related to investigational product.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Rosuvastatin PO QD 5 mg; Placebo SC Q2W
Report: Pleomorphic adenoma

Subject [redacted] was a 55-year-old white woman participating in Study 20110115 who developed pleomorphic adenoma. The subject's medical history included hypercholesterolemia, mixed dyslipidemia, hypertension, migraine, intermittent facial abscesses, and obesity. Concomitant medications included lymecycline, metoprolol, paracetamol, and zolmitriptan. Previous treatment for hypercholesterolemia and mixed dyslipidemia included rosuvastatin.

After completing the 4-week lipid stabilization period receiving rosuvastatin 5 mg daily, the subject received the first dose of placebo on 18 June [redacted]. Approximately 1 month later, on 16 July same year*, the subject presented with throat and ear pain around a swollen gland. Computerized tomogram of the upper body performed on 01 August same year* and nuclear magnetic resonance imaging performed on 06 August same year* revealed no other finding and the subject was diagnosed with pleomorphic adenoma. The subject was hospitalized on 08 August same year* and surgery was performed on the same day to remove and classify the adenoma. The adenoma was extirpated along with the surrounding parotid tissue. The surgery was free from complications. The adenoma was classified as malignant but was clearly defined and isolated. Additional treatment included diclofenac, paracetamol, and morphine. On 09 August same year*, the subject was discharged from the hospital. The event of pleomorphic adenoma was reported as not resolved.

The subject's last dose of placebo prior to the onset of the event of pleomorphic adenoma was on 03 July same year*. Placebo was continued. The subject received the last dose of placebo on 27 August same year* and the subject completed the study on 27 September same year*.

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

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Rosuvastatin PO QD 20 mg; Evolocumab SC Q2W 140 mg
Report: Orthostatic hypotension, Dehydration

Subject [redacted] was a 77-year-old white man participating in Study 20110115 who developed orthostatic hypotension and dehydration (reported term: probable dehydration). The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, former cigarette use, left ventricular ejection fraction 50%, myocardial infarction, hypertension, family history of premature coronary heart disease (first-degree male relative), percutaneous coronary intervention, renal impairment, gastrointestinal angiodysplasia, recurrent episodes of macrohematuria, melena, and previous prostatic adenocarcinoma. Concomitant medications included acetylsalicylic acid, ticagrelor, bisoprolol, lercanidipine, hydrochlorothiazide, and pantoprazole. Previous treatment for hypercholesterolemia and mixed dyslipidemia included atorvastatin.

After completing the 4-week lipid stabilization period receiving rosuvastatin 20 mg daily, the subject received the first dose of evolocumab on 22 May [redacted]. Approximately 3 weeks later, on 15 June same year*, the subject developed orthostatic hypotension and dehydration and was hospitalized. Baseline blood pressure prior to the event was 141/59 mmHg. During hospitalization, blood pressure values ranged from 140/51 mmHg to 70/51 mmHg. Laboratory test results showed creatinine 187 µmol/L, glomerular filtration rate 31 mL/min/1.73 m^2, urea 17.8 mmol/L, and hemoconcentration. Treatment included cyanocobalamin, folic acid, thiethylperazine, and hydration. The events orthostatic hypotension and dehydration were reported as resolved on 19 June same year* and the subject was discharged from hospital on that date. The investigator reported that recent history of low water intake was the underlying etiology of the events of dehydration and orthostatic hypotension.

The subject's last dose of evolocumab prior to the events was on 05 June same year*. Evolocumab was continued. The subject's last dose of evolocumab in the study was on 30 July same year*. The subject completed the study on 28 August same year*.

The investigator reported that there was no reasonable possibility that the events of orthostatic hypotension and dehydration were related to investigational product or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Atorvastatin PO QD 80 mg; Placebo SC Q2W + Placebo PO QD
Report: Gastroenteritis

Subject [redacted] was a 53-year-old white woman participating in Study 20110115 who developed gastroenteritis. The subject's medical history included primary hypercholesterolemia, mixed hyperlipidemia, smoking, depression, low back pain, irritable bowel syndrome, anxiety, acid reflux, nervousness, constipation, and cold sores. Concomitant medications included lactulose, diazepam, hyoscine, clobetasol, tramadol, mometasone, trazodone, omeprazole, naproxen, propranolol, mentha X piperita oil, and mebeverine. Previous treatment for hypercholesterolemia and mixed dyslipidemia included atorvastatin.

After completing the 4-week lipid stabilization period receiving atorvastatin 80 mg daily, the subject received the first dose of placebo (injectable and oral) on 12 July [redacted]. Approximately 2 months and 3 weeks later, on 04 October same year*, the subject presented diarrhea and later, on 05 October same year*, abdominal pain and vomiting. On 09 October same year*, the subject was seen by the general practitioner and was started on oral tramadol and electrolyte solution containing combination of glucose, potassium chloride, sodium bicarbonate, and sodium chloride. On 10 October same year*, the subject was admitted to the hospital and treated with intravenous fluids. On the same date, a stool culture was positive for *Campylobacter*. The subject was diagnosed with gastroenteritis. Additional treatment included ciprofloxacin. The investigator reported that the diarrhea stopped on 12 October same year*, and the event of gastroenteritis was reported resolved on the same date. On 14 October same year*, the abdominal pain stopped, and the subject was discharged from the hospital on the same date. The investigator reported that the subject did not have any risk factors that could have contributed to the development and/or worsening of the event of gastroenteritis.

The subject's last dose of injectable placebo prior to the event and in the study was on 20 September same year*. The subject's last dose of oral placebo was on 04 October same year*. The subject completed the study on 30 October same year*.

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

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Rosuvastatin PO QD 5 mg; Evolocumab SC QM 420 mg
Report: Acute myocardial infarction

Subject [redacted] was a 71-year-old white man participating in Study 20110115 who developed acute myocardial infarction (reported term: non-ST segment elevation myocardial infarction). The subject's medical history included hypercholesterolemia, angina due to atherosclerotic coronary disease, hypertension, coronary artery bypass graft, anal fistula, vertigo, gynecomastia, varicose veins, first-degree atrioventricular block, diverticular disease, erectile dysfunction, osteoarthritis, palpitations, impaired fasting glucose, and prostatism. The subject was a former cigarette user and had a family history of premature coronary heart disease and hypercholesterolemia. Concomitant medications included acetylsalicylic acid, atenolol, and lansoprazole. Previous treatment for hypercholesterolemia and mixed dyslipidemia included atorvastatin.

After completing the 4-week lipid stabilization period receiving rosuvastatin 5 mg daily, the subject received the first dose of evolocumab on 10 July [redacted]. Approximately 1 month and 1 week later, on 19 August same year*, the subject was hospitalized due to acute myocardial infarction. His troponin level rose to109 ng/mL. The subject had an angiogram and percutaneous coronary intervention. Additional treatment included clopidogrel, ramipril, and glyceryl trinitrate spray. The event was reported as resolved on 21 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 was on 25 July same year*. Evolocumab was continued. The subject's last dose of evolocumab in the study was on 03 September same year*. The subject completed the study on 01 October same year*.

The investigator reported that there was no reasonable possibility that the event of acute myocardial infarction was related to investigational product or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Simvastatin PO QD 40 mg; Evolocumab SC Q2W 140 mg
Report: Ischemic stroke

Subject [redacted] was a 59-year-old white man participating in Study 20110115 who experienced an ischemic stroke. The subject's medical history included hypercholesterolemia, hypertension, arthritis, headaches, gastroesophageal reflux disease, seasonal allergies, and allergy to iodine and codeine. Concomitant medications included hydrochlorothiazide, dietary fiber, multivitamins, paracetamol, naproxen, atenolol, and omeprazole. Previous treatment for hypercholesterolemia and mixed dyslipidemia included simvastatin.

After completing the 4-week lipid stabilization period receiving simvastatin 40 mg daily, the subject received the first dose of evolocumab on 05 April [redacted]. Approximately 3 weeks later, on 23 April same year*, the subject experienced symptoms of dizziness, nausea, dry vomiting, and loss of balance. The next day, on 24 April same year*, the subject presented to the emergency room and was hospitalized with the diagnosis of life-threatening ischemic stroke. No further information was provided. Treatment included acetylsalicylic acid, lisinopril, enoxaparin, famotidine, and clopidogrel. The subject was discharged from the hospital on 26 April same year*. At the time of discharge, residual symptoms were still ongoing. The event of ischemic stroke was reported as resolved on 15 August same year* and the investigator reported that no additional symptoms reappeared.

The subject's last dose of evolocumab prior to the event and in the study was on 19 April same year*. Evolocumab was discontinued. The subject completed the study on 16 July same year*.

The investigator reported that there was a reasonable possibility that the event of ischemic stroke was related to investigational product; however, there was no reasonable possibility that the event was not related to device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Atorvastatin PO QD 80 mg; Evolocumab SC Q2W 140 mg + Placebo PO QD
Report: Aortic aneurysm

Subject [redacted] was a 67-year-old white man participating in Study 20110115 who developed aortic aneurysm (reported term: abdominal aortic aneurysm). The subject's medical history included primary hypercholesterolemia, mixed hyperlipidemia, angina due to atherosclerotic coronary disease, mild left ventricular systolic dysfunction (left ventricular ejection fraction of 40% - 49%), hypertension, ex-smoker, peripheral arterial disease, intermittent hand dermatitis, abdominal aortic aneurysm, trivial mitral regurgitation, and trivial tricuspid regurgitation. Concomitant medication included ranolazine and lisinopril. The subject did not receive previous treatment for hypercholesterolemia and mixed dyslipidemia.

Prior to the study participation, the subject was diagnosed with abdominal aortic aneurysm, and during enrollment the decision was made to proceed with aortic aneurysm surgery.

After completing the 4-week lipid stabilization period receiving atorvastatin 80 mg daily, the subject received the first dose of evolocumab and the first dose of placebo both on 05 April [redacted]. Approximately 1 month and 2 weeks later, on 24 May same year*, the subject was hospitalized and underwent a planned open retroperitoneal abdominal aortic aneurysm repair. On 27 May same year*, laboratory tests revealed hematocrit of 23.9% and hemoglobin of 8.4 g/dL, but the postoperative anemia was considered as not serious. On 30 May same year*, the event of aortic aneurysm was reported as resolved and the subject was discharged on the same date. The investigator reported that the preexisting condition had not worsened prior to the surgery.

The subject's last dose of evolocumab prior to the event was on 17 April same year*. Evolocumab was continued. The subject's last dose of evolocumab in the study was on 12 June same year* and the last dose of placebo was on 26 June same year*. The subject completed the study on 10 July same year*.

The investigator reported that there was not a reasonable possibility that the event of aortic aneurysm was related to investigational product or placebo.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Atorvastatin PO QD 80 mg; Evolocumab SC Q2W 140 mg + Placebo PO QD
Report: Infected bites

Subject [redacted] was a 53-year-old white woman participating in Study 20110115, who developed infected bites (reported term: cellulitis right elbow secondary to wasp sting). The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, cigarette smoker, diverticulitis, mild occasional headaches, menopause, allergy to iodine (hives), anaphylaxis, allergy to sulfa drugs (swelling/blisters), migraines, seasonal allergies, and chronic cough, Concomitant medications included diclofenac, cyclobenzaprine, chlorphenamine, and a combination of oxycodone and acetaminophen. The subject did not receive previous treatment for hypercholesterolemia and mixed hyperlipidemia.

After completing the 4-week lipid stabilization period receiving atorvastatin 80 mg daily, the subject received the first dose of evolocumab and the first dose of placebo both on 17 April [redacted]. Approximately 2 months later, on 26 June same year*, the subject was stung by a wasp on her right elbow and developed cellulitis. On the same day, the subject presented to the emergency room with a pain level of 5/10 in the right elbow and difficulty in flexing or extending the shoulder due to swelling and pain. The subject was hospitalized. The white blood cell (WBC) count was 12.2 x 10^9/L and radiograph of the right elbow showed soft tissue swelling. Treatment included intravenous vancomycin. On 28 June same year*, WBC count was 8.6 x 10^9/L. The subject was discharged on 28 June same year* and was prescribed a course of oral doxycycline. The infected bite was reported as resolved on 05 July same year*.

The subject's last dose of evolocumab prior to the event was on 26 June same year*, which was also the subject's last dose of evolocumab in the study, and the last dose of placebo was on 10 July same year*. The subject completed the study on 24 July same year*.

The investigator reported that there was no reasonable possibility that the event of infected bites was related to investigational product or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Rosuvastatin PO QD 5 mg; Evolocumab SC Q2W 140 mg
Report: Lung adenocarcinoma metastatic

Subject [redacted] was a 65-year-old white woman participating in Study 20110115 who developed metastatic lung adenocarcinoma. The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, anxiety, cervical cancer, seasonal allergic rhinitis, cholecystectomy, ,gastroesophageal reflux disease, hot flashes, insomnia, migraine headache, herpes simplex, and depression. The subject was a former smoker. Concomitant medications included omeprazole, combination of loratadine and pseudoephedrine, estradiol, multivitamins (combination of ascorbic acid, calcium pantothenate, ergocalciferol, nicotinamide, pyridoxine, retinol, riboflavin, and thiamine), and desvenlafaxine. Previous treatment for hypercholesterolemia and mixed hyperlipidemia included pravastatin.

After completing the 4-week lipid stabilization period receiving rosuvastatin 5 mg daily, the subject received the first dose of evolocumab on 07 June [redacted]. Approximately 3 months after the first dose of evolocumab, on 09 September same year*, the subject fell at home and her right leg became weak. The subject presented to the emergency room with complaints of being off balance, headache, and feeling heaviness in her bilateral lower extremities. The subject also had a productive cough for 3 weeks and hemoptysis the night before. In addition, the subject had a 2-week history of balance problems and increased falls, more to the right side.

On 10 September same year*, the subject was admitted to the hospital. Upon physical examination, lungs were clear to auscultation bilaterally; there were no rales, wheezes or rhonchi; and no dullness or hyperresonance to percussion was observed. Vital signs revealed body temperature of 97.2°F, blood pressure of 150/85 mmHg, heart rate of 73 beats per minute, respiratory rate of 18 per minute, and oxygen saturation of 97%. Laboratory tests showed white blood cell (WBC) count of 7.7 x 10^9/L, hemoglobin of 13 g/dL, hematocrit of 39%, platelets of 242 x 10^9/L, creatine phosphokinase (CPK) of 37 U/L, creatine kinase-muscle and bone (CK-MB) of 1 ng/mL, international normalized ratio (INR) of 1.0, troponin of less than 0.01 ng/mL, C-reactive protein of 1.33 mg/L, and sedimentation rate of 5 mm/hour. Blood cultures (x 3) were performed but the results were not available. A computerized tomography (CT) showed bilateral diffuse cortical edema and lung mass below the carina in the mediastinum.

*新薬承認情報提供時に置き換え

On 11 September same year*, a magnetic resonance (MR) of the brain showed numerous supra- and infratentorial ring enhancing lesions consistent with metastatic disease. A CT of the head revealed extensive bilateral metastatic disease without new hemorrhage or herniation syndrome. On 12 September same year*, a core lung biopsy of the soft tissue mass in the right upper anterior lung was positive for adenocarcinoma. The following day, 13 September same year*, CT of the abdomen revealed no acute findings. Bone scan showed increased uptake at the base of the cervical spine with a possibility of being degenerative. Treatment included intravenous sedation, lidocaine, and dexamethasone. The outcome of the event was reported as not resolved; however, the subject was discharged from the hospital on 16 September same year*.
On 19 September same year* the subject was started on radiation therapy.

The subject's last dose of evolocumab prior to the diagnosis of metastatic lung adenocarcinoma was on 16 August same year*, which was also her last dose in the study. The subject completed the study on 17 September same year*.

The investigator reported that there was no reasonable possibility that the event of lung adenocarcinoma metastatic was related to investigational product or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Atorvastatin PO QD 80 mg; Placebo SC Q2W + Placebo PO QD
Report: Gastrointestinal hemorrhage, Grand mal convulsion, Herpes simplex meningoencephalitis

Subject [redacted] was a 74-year-old white man participating in Study 20110115 who developed gastrointestinal hemorrhage (reported term: acute gastrointestinal [GI] bleed), grand mal convulsion (reported term: grand mal seizure), and herpes simplex meningoencephalitis (reported terms: herpes encephalitis and right temporal lobe brain lesion [herpes encephalitis]). The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, hypertension, gastroesophageal reflux disease, diabetes mellitus type 2, hand osteoarthritis, and allergic rhinitis. Concomitant medications included omeprazole, pioglitazone, glucosamine, glipizide, hydrochlorothiazide, lisinopril, meloxicam, metformin, quetiapine, and a combination of ascorbic acid, retinol, and tocopherol. Previous treatment for hypercholesterolemia and mixed hyperlipidemia included atorvastatin.

After completing the 4-week lipid stabilization period receiving atorvastatin 80 mg daily, the subject received the first dose of placebo on 05 June [redacted]. Approximately 1 month later, on 04 July same year*, the subject was admitted to the hospital due to gastrointestinal hemorrhage. The investigator reported that the subject did not have any prior history of GI bleeding. Meloxicam and nonsteroidal anti-inflammatory drugs were reported as risk factors associated with the event. The following day, on 05 July same year*, the subject had a witnessed grand mal seizure while in the hospital, which led to the diagnosis of herpes encephalitis. Additionally, it was noted that the subject had a large lesion in his right temporal lobe. Treatment included midazolam, phenytoin, etomidate, pantoprazole, insulin aspart, fosphenytoin, lorazepam, acyclovir, vancomycin, ceftriaxone, gadobenic acid meglumine, potassium chloride, magnesium sulfate, fentanyl, cyanocobalamin, furosemide, enoxaparin, quetiapine, enalapril, and paracetamol. On 24 July same year*, the subject was discharged from the hospital to a rehabilitation hospital for complete recovery. The events gastrointestinal hemorrhage and grand mal convulsion were reported to have resolved on 05 July same year*. The event herpes simplex meningoencephalitis (herpes encephalitis and right temporal lobe brain lesion [herpes encephalitis]) remained as unresolved.

The subject's last dose of placebo prior to the event was on 24 June same year*, which was also his last dose in the study. The subject withdrew full consent on 24 July same year*. The investigator

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reported that there was no reasonable possibility that the events of gastrointestinal hemorrhage, grand mal convulsion, and herpes simplex meningoencephalitis were related to investigational product or device.

Subject No: [redacted]
Treatment: Atorvastatin PO QD 10 mg; Placebo SC Q2W + Placebo PO QD
Report: Hiatal hernia

Subject [redacted] was a 52-year-old black woman participating in Study 20110115 who developed a hiatal hernia. The subject's medical history included hypercholesterolemia, mixed dyslipidemia, type 2 diabetes mellitus, hypertension, hysterectomy, anemia, gastroesophageal reflux, obstructive sleep apnea, depression, insomnia, and hiatal hernia; the subject was a smoker. Concomitant medications included glibenclamide, rabeprazole, amlodipine, metformin, conjugated estrogens, and a combination of hydrochlorothiazide and losartan. Previous treatment for hypercholesterolemia and mixed dyslipidemia included pitavastatin.

After completing the 4-week lipid stabilization period receiving atorvastatin 10 mg daily, the subject received the first dose of placebo (injectable and oral) on 26 April [redacted]. Approximately 1 month and 3 weeks later, on 19 June same year*, the subject was admitted to the hospital and underwent a scheduled hernia repair surgery. Laboratory test results were reported as normal. Treatment medications included human insulin, enoxaparin, vicodin, and a combination of hydrocodone bitartrate and paracetamol. The event hiatal hernia was reported to have resolved on 21 June same year* and the subject was discharged from the hospital on the same day.

The subject's last dose of placebo prior to the event was on 18 June same year*. Placebo was continued. The subject's last dose of SC placebo in the study was on 05 July same year* and the last dose of oral placebo was on 19 July same year*. The subject completed the study on 03 August same year*.

The event was considered as preexisting condition and was not aggravated by study procedure or medications. The investigator reported that there was no reasonable possibility that the event of hiatus hernia was related to investigational product or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Atorvastatin PO QD 10 mg; Evolocumab SC Q2W 140 mg + Placebo PO QD
Report: Acute coronary syndrome

Subject [redacted] was a 48-year-old black man participating in Study 20110115 who developed acute coronary syndrome. The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, hypertension (receiving treatment), brain aneurysm, erectile dysfunction, left knee arthroscopic surgery, benign prostatic hypertrophy with lower urinary tract symptoms, seizures, included left shoulder pain, and leg pain. Concomitant medications included combination of hydrochlorothiazide and olmesartan, tadalafil, phenytoin, and dutasteride. Previous treatment for hypercholesterolemia and mixed hyperlipidemia included atorvastatin.

After completing the 4-week lipid stabilization period receiving atorvastatin 10 mg daily, the subject received the first dose of evolocumab and the first dose of placebo both on 20 May [redacted]. Approximately 12 days later, on 01 June same year*, the subject was admitted to the hospital due to an abnormal feeling in the chest and chest pain. Cardiac catheterization was performed and was normal. Electrocardiogram showed normal sinus rhythm. Laboratory data revealed glucose of 131 mg/dL, creatine phosphokinase of 179 IU/L, creatine phosphokinase MB of 3.4%, and troponin of 0.01 ng/mL. The subject's complete blood count was reported as normal. Treatment medications included acetylsalicylic acid, fentanyl, midazolam, heparin, and verapamil. The event of acute coronary syndrome was reported to have resolved on 03 June same year* and the subject was discharged from the hospital on that day.

The subject's last dose of evolocumab prior to the event was on 20 May same year*. Evolocumab was continued. The subject's last dose of evolocumab in the study was on 29 July same year*, and the last dose of placebo was on 12 August same year*. The subject completed the study on 24 August same year*. The investigator reported that there was not a reasonable possibility that the event of acute coronary syndrome was related to investigational product or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Rosuvastatin PO QD 40 mg; Placebo SC QM
Report: Gastrointestinal hemorrhage

Subject [redacted] was a 64-year-old black man participating in Study 20110115 who developed a gastrointestinal (GI) hemorrhage (reported term: GI bleed). The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, type 2 diabetes, hypertension, history of bleeding peptic ulcer, history of asbestos exposure, and impotence. Concomitant medications included sitagliptin, glimepiride, and atenolol. Previous treatment for hypercholesterolemia and mixed dyslipidemia was rosuvastatin.

After completing the 4-week lipid stabilization period receiving rosuvastatin 40 mg daily, the subject received the first dose of placebo on 11 July [redacted]. Approximately 1 month and 2 weeks later, on 28 August same year*, the subject was hospitalized due to an acute grade 3 GI hemorrhage. The subject underwent upper endoscopy with cauterization of bleeding vessel ulcer. The acute GI bleed was reported to be due to a bleeding duodenal ulcer. The investigator reported that the subject had no risk factors for the event. The event of GI hemorrhage was considered resolved on 29 August same year*; however, the subject remained hospitalized at the time the last report was available on 29 August same year*.

The subject's last dose of placebo prior to the event was on 06 August same year*. Placebo was continued. The subject's last dose of placebo in the study was on 06 September same year*. The subject completed the study on 05 October same year*.

The investigator reported that there was no reasonable possibility that the event of gastrointestinal hemorrhage was related to investigational product or device.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Atorvastatin PO QD 10 mg; Evolocumab SC Q2W 140 mg + Placebo PO QD
Report: Affective disorder

Subject [redacted] was a 69-year-old black woman participating in Study 20110115 who developed affective disorder (reported term: mood disorder not otherwise specified [NOS]). The subject's medical history included hypercholesterolemia, mixed hyperlipidemia, anxiety attacks, appendectomy, cholecystectomy, degenerative disc disease, hypertension, hysterectomy, insomnia, seasonal allergies, and vaginal bleeding. Concomitant medications included lisinopril, oxycocet, and trazodone. Previous treatment for hypercholesterolemia and mixed dyslipidemia included simvastatin.

After completing the 4-week lipid stabilization period receiving atorvastatin 10 mg daily, the subject received the first dose of evolocumab and the first dose of placebo both on 28 May [redacted]. Approximately 1 month and 2 weeks later, on 09 July same year*, the subject developed affective disorder and was hospitalized on the same day. According to the investigator, there were no predisposing or risk factors for the event. Unspecified treatment was administered. The event of affective disorder was reported to have resolved on 12 July same year*, and the subject was discharged from the hospital on that day.

The subject's last dose of evolocumab prior to the event of affective disorder was on 11 June same year*. Evolocumab and placebo were continued. The subject received the last dose of evolocumab on 06 August same year* and the last dose of placebo on 21 August same year*. The subject completed the study on 03 September same year*.

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

*新薬承認情報提供時に置き換え