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

Subject [redacted] was a 48-year-old white woman participating in Study 20110110 who developed myalgia. Her medical history included hypercholesterolemia. Concomitant medications included Vitamin E and acetylsalicylic acid/magnesium. Previous and current treatments for hypercholesterolemia included atorvastatin and ezetimibe.

The subject was in the parent study from 06 January same year* to 28 March same year* and received the last dose of placebo in the parent study on 02 March same year*. The subject was randomized to Study 20110110 on 28 March [redacted] and assigned standard of care treatment.

In the morning of 20 November same year*, the subject experienced left arm numbness and chest discomfort. The subject was hospitalized on the same day with myalgic chest pain. On the same day, electrocardiogram was normal and blood analysis showed no findings. Treatment included paracetamol. The event of myalgic chest pain was reported as resolved on 21 November same year* and the subject was discharged from the hospital on the same day.

After completing 1 year in the study, she received the first dose of evolocumab on 08 May one year after*. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff on [redacted].

The investigator reported that there was no reasonable possibility that the event was related to any study procedure or study activity. The investigator reported that a pre-disposing risk factor for the event was that the subject was busy in a full-time job as a caregiver in the community.

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

Subject [redacted] was a 44-year-old man of South African mixed race participating in study 20110110 who developed angina pectoris (reported term: worsening angina pectoris). The subject's medical history included hypercholesterolemia, angina pectoris, coronary artery bypass, stent placement, chest pain, and coronary arteriogram. Concomitant medications included carvedilol, acetylsalicylic acid, enalapril, glyceryl trinitrate, diltiazem, etoricoxib, and isosorbide. Previous and current treatment for hypercholesterolemia included atorvastatin and ezetimibe.

The subject was in the parent study from 18 January same year* to 11 April same year* and received the last dose of evolocumab in the parent study on 15 March same year*. The subject received the first dose of evolocumab in Study 20110110 on 11 April [redacted].

After approximately 1 year and 5 months, on 10 September one year after*, the subject experienced worsening of angina pectoris and was hospitalized. A coronary angiogram showed left coronary normal mainstem, circumflex had significant distal disease; right coronary totally occluded; vein graft to right coronary occluded and internal mammary occluded; angina appeared to be related to distal circumflex. An electrocardiogram (ECG) showed normal sinus rhythm and inferior infarct. Treatment included diltiazem and etoricoxib. The subject was discharged on 01 October one year after* and the event resolved on 03 October one year after*.

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

The investigator reported that there was no reasonable possibility that the event angina pectoris was related to evolocumab.

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Subject No: [redacted]
Treatments: Parent study Placebo SC Q4W Year 1 treatment: Standard of care Year 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Groin abscess

Subject [redacted] was a 25-year-old white man participating in Study 20110110 who experienced a groin abscess (reported term: right groin abscess). His medical history included hypercholesterolemia. Concomitant medications while on study included acetaminophen, paracetamol, loperamide, potassium, zinc, ascorbic acid, aerosolized combination of benzocaine and chlorhexidine digluconate, and Vitamin B complex. Previous and current treatment for hypercholesterolemia included atorvastatin.

The subject was enrolled into the parent study and received the first dose of placebo on 16 January one year ago* and the last dose on 12 March one year ago*. During year 1 of Study 20110110 he was assigned standard of care treatment (13 April one year ago* through 07 May same year*). The subject received the first dose of open-label evolocumab with standard of care treatment on 08 May [redacted].

Approximately 8 months after the first dose of open label evolocumab, on 14 January one year after*, the subject developed a right groin abscess. The subject was hospitalized on 18 January one year after*. He received intravenous amoxicillin/clavulanic acid and remained overnight in the hospital. On 19 January one year after*, the subject was discharged from the hospital on oral amoxicillin/clavulanic acid and analgesics. The following day, on 20 January one year after*, the subject was examined by his general practitioner, was referred to a surgeon for incision and drainage of the groin abscess and returned home in the evening of the same day. The groin abscess was reported as resolving. The last dose of evolocumab prior to the event was on 20 December same year*, and evolocumab was continued after the surgery. The investigator reported that there was not a reasonable possibility that the event right groin abscess was related to investigational product.

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

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

Subject [redacted] was a 32-year-old Asian man participating in Study 20110110 who experienced a toothache. His medical history included hypercholesterolemia and familial hypercholesterolemia. Concomitant medications included Vitamin E and acetylsalicylic acid. Previous and current treatment for hypercholesterolemia included atorvastatin.

The subject was in the parent study from 19 January same year* to 12 April same year* and received the last dose of evolocumab in the parent study on 15 March 2012. The subject was randomized to Study 20110110 on 12 April [redacted] and assigned standard of care treatment.

On 14 August same year*, the subject was admitted to the hospital in order to get his wisdom teeth removed after having a toothache since 09 May same year*. On 15 August same year*, the subject received premedication and general anesthetic for surgical removal of the teeth. Treatment included amoxicillin, ibuprofen, and paracetamol. The event of toothache was reported as resolved on 15 August same year* and the subject was discharged from the hospital on 16 August same year*.

After completing 1 year in the study, the subject received the first dose of evolocumab on 09 May one year after*. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff on [redacted].

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

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

Subject [redacted] was a 54-year-old white woman participating in Study 20110110 who developed gastroenteritis. The subject's medical history included hypercholesterolemia, hypertension, and dyslipidemia. Concomitant medications included irbesartan and Vitamin E. Previous and current treatment for hypercholesterolemia included rosuvastatin.

The subject was in the parent study from 18 November one year ago* to 10 February same year* and received the last dose of evolocumab in the parent study on 13 January same year*. The subject was randomized to Study 20110110 on 10 February [redacted] and assigned standard of care treatment. On 16 December same year*, the subject presented with severe bloody diarrhea and was hospitalized with gastroenteritis for intravenous treatment. Treatment medication included ciprofloxacin, *Saccharomyces boulardii*, and hyoscine. The event was reported as resolved on 20 December 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 gastroenteritis was on 10 February same year* (the last dose in the parent study).

After completing 1 year in the study, the subject received the first dose of evolocumab on 15 March one year after*. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff on [redacted].

The investigator reported that there was no reasonable possibility that the event of gastroenteritis was related to any study procedure or study activity.

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

Subject [redacted] was a 63-year-old white woman participating in Study 20110110 who developed a fecaloma (reported term: fecal impaction). The subject's medical history included hypercholesterolemia and diverticulitis. The subject did not have previous episodes of fecaloma. Concomitant medications included hydrochlorothiazide, salbutamol, ranitidine hydrochloride, and amitriptyline. Previous treatment for hypercholesterolemia was atorvastatin.

The subject was in the parent study from 15 November one year ago* to 06 February same year* and received the last dose of evolocumab in the parent study on 09 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 06 February [redacted].

Approximately 2 months later, on 05 April same year*, the subject was hospitalized due to severe constipation with fecal impaction, also resulting in urinary retention, abdominal pain, and distension. An abdominal radiograph revealed non-specific bowel gas pattern, no air-fluid levels or free air, no ileus or obstruction. The same day, the subject underwent colonoscopy and disimpaction. The following day, on 06 April same year*, the subject was started on combination of macrogol, potassium chloride, and sodium bicarbonate. The event of fecaloma was reported as resolved on 06 April 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 02 April same year*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study, and received the last dose of evolocumab prior to the data cutoff date on [redacted].

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

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

Subject [redacted] was a 67-year-old white man participating in Study 20110110 who developed an appendiceal abscess (reported term: appendix abscess). The subject's medical history included hypercholesterolemia and he had undergone coronary artery bypass. No relevant concomitant medications were reported. Previous treatment for hypercholesterolemia included rosuvastatin and ezetimibe.

The subject was in the parent study from 16 November one year ago* to 06 February same year* and received the last dose of evolocumab in the parent study on 09 January same year*. The subject received the first dose evolocumab in Study 20110110 on 06 February [redacted].

Approximately 1 year and 2 months later, on 23 April one year after*, the subject presented to the general physician with a painful mass in his right iliac fossa, which was suggestive of a possible complicated appendicitis or cecal pathology. On 24 April one year after*, the subject was hospitalized due to ruptured appendix. On the same day, the subject underwent surgery; dense adhesions were present with an intraperitoneal abscess in the paracecal and paracolic area. Postoperatively, the subject continued on intravenous antibiotics. On 30 April one year after*, the subject's wound was debrided and sutured. The subject was discharged from the hospital on 30 April one year after*. Initial progress was uncomplicated, but on follow-up on 06 May one year after*, a large bulge was noticed in the region of the sutures. Needle aspiration performed on the same date confirmed an abscess. The wound was partially opened and the abscess was drained and irrigated. Treatment included levofloxacin, metronidazole, and gentamicin. On 07 May one year after*, the wound had improved, minimal drainage was present and the subject continued with local care. The subject was followed up by telephone on 13 May one year after*, and reported that he was recovering well at home. During the next scheduled visit, on 28 May one year after*, the event of appendiceal abscess was reported as resolved. On the same day, evolocumab administration was re-initiated.

The subject's last dose of evolocumab prior to the event was on 02 April one year after*. Evolocumab was temporarily withheld. As of the data cutoff date of [redacted], the subject was continuing

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

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

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

Subject [redacted] was a 46-year-old white man participating in Study 20110110 who developed atrial fibrillation (reported term: intermittent atrial fibrillation). The subject's medical history included hypercholesterolemia, tonsillectomy, and appendectomy. The subject was a non-smoker. Concomitant medication included Vitamin E. Previous and current treatment for hypercholesterolemia included rosuvastatin.

The subject was in the parent study from 15 November one year ago* to 06 February same year* and received the last dose of evolocumab in the parent study on 10 January same year*. The subject was randomized to Study 20110110 on 06 February [redacted] and assigned standard of care treatment.

On an unspecified date in November one year ago*, an ECG showed sinus rhythm at a rate of 82 per minute with a QRS axis of 77 degrees; the P waves were normal with a PR interval of 168 ms, the QRS complexes were within normal limits with a duration of 104 ms; there were some early repolarization changes inferiorly with no T-wave abnormalities; the QTc measured 408 ms. An exercise test showed sinus rhythm at rest, with a good heart rate at peak exercise but with a single ventricular couplet and no evidence of ischemia or other obvious arrhythmias. Blood tests showed normal renal function and abbreviated liver function tests. The subject's iron levels were found to be low and he underwent colonoscopy and gastroscopy but no obvious abnormalities were noted.

The investigator reported that the subject had brief episodes of recurrent light-headedness, lasting a maximum of 30 seconds, since December one year ago*. The subject was aware of palpitations during the episodes but was not sure which occurred first, or whether the onset of both of these was simultaneous. These episodes occurred approximately twice per week without obvious precipitants and the subject had 1 episode of loss of consciousness. Electrocardiograms (ECGs) were performed, but these were after the episodes had resolved.

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On 30 May same year*, ECG showed sinus rhythm at a rate of 83 beats per minute with a QRS axis of 59 degrees; P waves were normal with a PR interval of 154 ms; QRS complexes were within normal limits with duration of 102 ms; repolarization appeared normal although the QTc was slightly prolonged at 451 ms. On 25 June same year*, the subject underwent a tilt test; following administration of sublingual nitrates, the subject developed progressive hypertension with mild bradycardia and became dizzy with subsequent loss of consciousness.

Approximately 1 month later, on 27 July same year*, the subject arrived at the hospital complaining of his earlier symptoms. An ECG confirmed the presence of atrial fibrillation with an average ventricular response of approximately 118 per minute. The subject was diagnosed with atrial fibrillation. The subject was admitted and given flecainide; during the course of the night he converted back to sinus rhythm. The subject was discharged from the hospital on 28 July same year*. The subject went to a cardiologist on 30 January one year after*; an ECG was performed which was reported as 'clinically not significant'. The subject was advised to come for a follow-up in 1 year.

As of the data cutoff date of [redacted], the event of atrial fibrillation was ongoing. The subject's last dose of evolocumab prior to the event was on 10 January same year* (the last dose in the parent study). The subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff on [redacted].

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

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

Subject [redacted] was a 68-year-old white man participating in Study 20110110 who developed infective bursitis (reported term: infected right iliopsoas bursitis). The subject's medical history included hypercholesterolemia, diabetes mellitus, hypertension, nephrolithiasis, renal colic, joint dislocation, retinal detachment, inguinal hernia repair, and tympanoplasty. Concomitant medications included ibuprofen, paracetamol, tazobactam, metformin, triflusal, a combination of hydrochlorothiazide and valsartan, acetylsalicylic acid, azithromycin, triflusal, and zolpidem. Previous treatment for hypercholesterolemia was not reported. Current treatment for hypercholesterolemia included ezetimibe and simvastatin.

The subject was in the parent study from 05 January same year* to 02 April same year* and received the last dose of placebo in the parent study on 01 March same year*. The subject received the first dose of evolocumab in Study 20110110 on 02 April [redacted].

Approximately 1 year and 3 months later, on 20 July one year after*, the subject was hospitalized due to pain in the right iliac fossa, spasms, colics, and fever for 3 days (38°C). The subject had difficulty walking and walked with short steps. Ultrasound showed a hypoechoic collection in the right inguinal region, suspected to be psoas abscess. A computerized tomogram (CT) of the abdomen revealed hypodense image of oval morphology in the thickness of the right iliac muscle, 60 mm x 30 mm in size, well delimited, no enhancement, consistent with collection, and no changes in the rest of the psoas muscle.

On 23 July one year after*, the subject underwent an ileocolonoscopy that revealed polyps treated with endoscopic polypectomy. On 24 July one year after*, biopsy results of polyps revealed tubular adenoma of the colon, with low-grade dysplasia.

On 25 July one year after*, ultrasound showed an ovoid collection of 14 mm, adjacent to right coxofemoral joint, highly suggestive of iliopsoas bursa or bursitis. Aspiration biopsy of the collection confirmed right iliopsoas bursa. The diagnosis was, nevertheless, confirmed by the

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investigator as psoas muscle abscess. Culture of joint synovial fluid was negative for aerobes and anaerobes; no leukocytes were seen on gram stain. On 29 July one year after*, laboratory tests included C-reactive protein 2.47 mg/dL, treatment medication included intravenous (IV) piperacillin/tazobactam and oral levofloxacin. The subject was recommended functional rest while pain persisted, and nonsteroidal anti-inflammatory drugs (NSAIDs). The subject also reported a scant blackish stool thought to be possible mild upper digestive bleeding related to the use of NSAIDs and antiplatelet agents. The antiplatelet agent was removed. Additional treatment included omeprazole and a combination of amoxicillin and clavulanic acid. Ultrasonography on an unknown date in July one year after* revealed reduction of the lesion size. The event of psoas muscle abscess resolved on 04 September one year after* after 6 weeks of antibiotic therapy, and the subject was discharged from the hospital on the same day. At the time of discharge, the subject continued taking analgesics until the pain completely disappeared.

The subject's last dose of evolocumab prior to the event was on 01 July one year after*. Evolocumab was temporarily withheld and not reinitiated. As of the data cutoff date [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff date on [redacted].

The investigator reported that there was not a reasonable possibility that the event of infective bursitis was related to evolocumab. Hypertension, diabetes mellitus, and underlying dyslipidemia were reported as risk factors associated with the reported event.

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Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q4W 420 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + standard of care
Report: Atrial fibrillation, angina pectoris

Subject [redacted] was a 65-year-old white woman participating in Study 20110110 who had atrial fibrillation and angina pectoris (reported terms, respectively: atrial fibrillation episode and hemodinamic angina). The subject's medical history included familial hypercholesterolemia, coronary heart disease, myocardial ischemia, operated breast neoplasm, vitiligo, systemic lupus erythematosus, cholecystectomy, double bypass (saphenous vein and internal mammary artery to anterior descending) in eighteen years ago*, trigger finger, angina pectoris and paroxysmal atrial fibrillation. Concomitant medications included acetylsalicylic acid, bisoprolol, halazepam, amiloride, omeprazole, bisoprolol, thiamazole, combination of caffeine, nitroglycerin, and phenobarbital, lorazepam, combination of amiloride and hydrochlorothiazide, ramipril, clopidogrel, and isosorbide. Previous treatment for hypercholesterolemia included ezetimibe and rosuvastatin.

The subject was in the parent study from 27 January same year* to 18 April same year* and received the last dose of evolocumab in the parent study on 22 March same year*. The subject received her first dose of evolocumab in Study 20110110 on 18 April [redacted].

On 10 February same year*, she developed chest pain and atrial fibrillation was detected. On 17 February same year*, the subject underwent coronary angiography and ventriculography; results showed ischemic heart disease with single-vessel disease with anterior descending artery (AD) occlusion and a proximal stenosis in the saphenous vein graft to the AD. An internal mammary artery (IMA) to AD was of thin caliber, with very low flow, preserving one collateral; nonenlarged left ventricle, and 80% left ventricular ejection fraction (LVEF). The saphenous stenosis was treated with angioplasty and a drug eluting stent. Sinus rhythm was maintained when she was discharged on 18 February same year*.

Approximately 2 months and 3 weeks after the first dose, on 09 July same year*, the subject presented to her primary care physician with non-irradiating tightening precordial pain associated with sweating, starting 8 hours previously while she was resting. An

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electrocardiogram showed atrial fibrillation and the subject was hospitalized. Laboratory tests were completely normal and enzyme series within normal ranges. A chest radiograph did not show acute abnormalities.

The subject was diagnosed with hemodynamic angina and paroxysmal atrial fibrillation. On 09 July same year*, she underwent synchronized electrical cardioversion, changing to sinus rhythm with no repolarization changes. Treatment for the condition included amiodarone, acetylsalicylic acid and clopidogrel for at least 6 months, and was also prescribed acenocoumarol therapy, which the investigator decided would not be started. The events hemodynamic angina and atrial fibrillation episode were resolved on 09 July same year*. The subject was discharged from the hospital on 10 July same year* and remained asymptomatic.

The subject's last dose of evolocumab before the events was on 19 June same year*. As of the data cutoff date of [redacted], her last dose of evolocumab was on [redacted], and she was continuing in the study.

The investigator reported that there was no reasonable possibility that the events atrial fibrillation and angina pectoris were related to evolocumab.

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

Subject [redacted] was a 49-year-old white woman participating in study 20110110 who was diagnosed with intraductal papilloma of the breast. The subject's medical history included hypercholesterolemia, hyperlipidemia, cerebrovascular accident, renal colic, bladder catheterization, and lithotripsy. Concomitant medications included clopidogrel. Previous and current treatment for hypercholesterolemia included simvastatin.

The subject was in the parent study from 25 January same year* to 18 April same year* and received the last dose of placebo in the parent study on 21 March same year*. The subject received the first dose of evolocumab in Study 20110110 on 18 April [redacted].

On 01 May same year*, the subject was diagnosed with intraductal papilloma of the breast. In June same year*, biopsy confirmed the mass to be an intraductal papilloma. On 07 October same year*, the subject was hospitalized and underwent excision of papilloma. The event was reported to have resolved on 09 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 18 April same year*. As of the data cutoff date [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff date on [redacted].

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

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Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q4W 420 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Chronic obstructive pulmonary disease (COPD), Respiratory tract infection, Drug hypersensitivity, and Lumbar vertebral fracture

Subject [redacted] was a 67-year-old white woman participating in Study 20110110 who experienced chronic obstructive pulmonary disease (reported term: chronic obstructive pulmonary disease re-agudization), drug hypersensitivity (reported term: moxifloxacin allergic episode), lumbar vertebral fracture (reported term: L1 vertebra fracture), and respiratory tract infection. The subject's medical history included hypercholesterolemia, dyslipidemia, angina pectoris, myocardial infarction, coronary artery bypass surgery in three years ago*, hypertension, chronic obstructive pulmonary disease, bronchiectasis, osteoarthritis, anxiety, cholecystectomy, appendicectomy, surgery for herniated disc, peptic ulcer, hiatus hernia, goiter, tuberculosis in childhood, hypersensitivity to Vitamins B and D, and dyspnea. Concomitant medications included tiotropium bromide, acetylcysteine, fluticasone, salmeterol, oxygen, acetylsalicylic acid, ciclesonide, diltiazem, lorazepam, combination of losartan and hydrochlorothiazide, nystatin, indacaterol, pantoprazole, paroxetine, theophylline, torasemide, and corticosteroids. Previous and current treatment for hypercholesterolemia included atorvastatin, rosuvastatin, and ezetimibe.

The subject was in the parent study from 07 February same year* to 02 May same year* and received the last dose of evolocumab in the parent study on 04 April same year*. The subject received the first dose of evolocumab in Study 20110110 on 02 May [redacted].

Approximately 3 months and 2 weeks later, on 14 September same year*, the subject presented with worsened symptoms of COPD not improving with corticosteroids. One week later, on 22 September same year*, the subject was hospitalized for worsened COPD, and respiratory tract infection. On admission, the subject denied orthopnea, decreased diuresis, and peripheral edema. Vital signs were blood pressure of 155/77 mmHg, heart rate of 85 beats per minute, respiratory rate of 30/min, body temperature of 36°C, and oxygen saturation of 90%. Laboratory data showed pH of 7.48, pCO_2 of 39.2 mmHg, bicarbonate of 29.0 mEq/L, total CO_2 of

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30.2 mEq/L, troponin I of 0.01 ng/mL, myoglobin of 18.9 ng/mL, pro B-type brain natriuretic peptide of 161.7 pg/mL, glucose of 212 mg/dL, urea of 40 mg/dL, creatinine of 0.69 mg/dL, chloride of 98 mEq/L, sodium of 141 mEq/L, potassium of 3.1 mEq/L, white blood cell (WBC) count of 25.9 x 10^3/µL, neutrophil count of 20.6 x 10^3/µL, red blood cell (RBC) count of 4.97 x 10^6/µL, hemoglobin of 15.1 g/dL, hematocrit of 45.1%, platelet count of 301 x 10^3/µL, international normalized ratio (INR) of 0.88, fibrinogen of 5.2 g/dL, and D-dimer of 156 µg/L. Pulmonary auscultation revealed rhonchus and wheezing lungs (both fields). There were no signs of deep vein thrombosis (DVT) in the lower extremities. Cardiac auscultation showed rhythmic heart sounds at 85 beats per minute and no murmurs auscultated. Electrocardiogram on 22 September same year* showed sinus rhythm at 60 beats per minute, some ventricular extrasystole, ST depression in V4 <1mm. Chest radiography showed signs of chronic bronchopathy with no evidence of parenchymal condensation. Treatment medication included bi-level positive airway pressure (BiPAP) 12/6 and oxygen, prednisone, theophylline, unspecified bronchodilators first in nebulization and then in inhalation, systemic corticoids, and cefditoren. Monitored cardiorespiratory polygraph identified night hypoventilation.

The events of chronic obstructive pulmonary disease and respiratory tract infection resolved on 01 October same year*, and the subject was discharged from the hospital on the same day with O_2 saturation of 95% with oxygen 2L/min.

The subject's last dose of evolocumab prior to the events chronic obstructive pulmonary disease and respiratory tract infection was on 22 August same year*.

In March one year after*, the subject fell down and was diagnosed with first lumbar (L1) vertebral fracture. The subject was treated with analgesics, but the symptoms did not improve after several months. On 06 November one year after*, a lumbosacral spine radiograph showed persistent L1 fracture. On 18 December one year after*, the subject was hospitalized. On 19 December one year after*, the subject underwent L1 vertebroplasty. The outcome of the event L1 vertebroplasty was reported as resolved on 19 December one year after* and the subject was discharged from the hospital on the same day. The subject's last dose of investigational drug prior to the event was on 12 December one year after*. Investigational drug was continued.

The investigator reported that there was not a reasonable possibility that the event L1 vertebroplasty was related to investigational drug.

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On 25 March two years after*, the subject was prescribed moxifloxacin 400 mg for bronchitis. Approximately 30 minutes after taking the first pill, she experienced an anaphylactic reaction with edema of the lip and pruritis on the face, hands, and feet that became widespread, with inflammatory signs attacking the mouth and tongue. The subject was admitted to the emergency room and kept under observation until the next day for anaphylactic reaction (moxifloxacin allergy) and bronchitis.

The outcome of the event of drug hypersensitivity was reported as resolved on 26 March two years after* and the subject was discharged on the same day. After discharge, the subject was prescribed amoxicillin and clavulanic acid.

The subject`s last dose of evolocumab prior to the event of drug hypersensitivity was 07 March two years after*. As of the data cutoff date [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff date on [redacted].

The investigator reported that there was no reasonable possibility that the events chronic obstructive pulmonary disease, respiratory tract infection, lumbar vertebral fracture, or drug hypersensitivity were related to evolocumab.

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Subject No: [redacted]
Treatments: Parent study: Placebo SC Q4W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Year 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Wrist fracture

Subject [redacted] was a 40-year-old white man participating in Study 20110110 who experienced a wrist fracture (reported term: fracture of both wrists). His medical history included hypercholesterolemia. Concomitant medications while on study included ibuprofen. Previous and current treatment for hypercholesterolemia included atorvastatin and ezetimibe.

The subject was enrolled into the parent study and received the first dose of placebo on 18 January same year* and last dose on14 March same year*. The subject received the first dose of evolocumab with standard of care for Study 20110110 on 16 April [redacted].

Approximately 2 years after the first dose of evolocumab, on 06 March two years after*, the subject fell and fractured both wrists. Until 01 April two years after* treatment was conservative. On 01 April two years after*, the subject was hospitalized and underwent uneventful surgery for his both wrists. The event wrist surgery was reported as resolving. On 02 April two years after*, the subject was discharged from hospital. The event was not considered related to evolocumab.

The last dose of evolocumab prior to the event was on 18 February two years after*. As of the data cutoff date of [redacted], the subject was continuing in the study and the last dose of evolocumab prior to the cutoff date was on [redacted].

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

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

Subject [redacted] was a 31-year-old white man participating in Study 20110110 who was diagnosed with colon cancer. The subject's medical history included hypercholesterolemia, constipation, hypoesthesia, hypertension, astigmatism, myopia, hyperlipidemia, xanthoma, obesity and increased blood creatine phosphokinase (CPK). The subject did not have any previous history of cancer, had no risk factors associated with the event, and had no family history of cancer. Concomitant medications included iron, Vitamin B_{12}, and Vitamin E. Previous and current treatment for hypercholesterolemia included rosuvastatin and ezetimibe.

The subject was in the parent study from 19 August same year* to 11 November same year* and received the last dose of placebo in the parent study on 14 October same year*. The subject was randomized to Study 20110110 on 11 November [redacted] and assigned standard of care treatment.

The investigator reported that from 20 August same year* to 11 September same year*, the subject presented loose stools, abdominal bloating and increased gas. On 01 October same year*, the subject experienced diarrhea. On 14 October same year*, laboratory values included alkaline phosphatase (ALP) of 68 U/L, alanine aminotransferase (ALT) 16 U/L, aspartate aminotransferase (AST) of 29 U/L, creatinine of 1.0 mg/dL, glucose of 99 mg/dL, sodium of 137 mEq/L, potassium of 4.2 mEq/L, chloride of 101 mEq/L, hemoglobin of 13.8 g/dL, hematocrit of 41%, red blood cell (RBC) count of 5.3 x 10^6/µL, white blood cell (WBC) count of 6.08 x 10^3/µL, platelet count of 199 x 10^3/µL , and CPK of 466 IU/L with upper limit of normal (ULN) of 198 IU/L. On 04 May one year after*, laboratory tests showed hemoglobin of 8.6 g/dL, hematocrit of 30%, RBC count of 4.9 x 10^6/µL, WBC count of 4.78 x 10^3/µL, and platelet count of 223 x 10^3/µL.

On 08 May one year after*, following abnormal week-24 hematology laboratory results, the subject was referred to his primary care physician for possible anemia and was found to have a positive test for occult blood in stool.

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On 21 May one year after*, colonoscopy was performed and biopsy from proximal ascending colon showed villous adenoma with high grade dysplasia and possible invasive adenocarcinoma. Some of the pieces showed inflammation and necrosis consistent with mucosal ulceration. The histologic findings were suspicious for invasive adenocarcinoma. An abdomen and pelvis computerized tomography scan with contrast showed a mass in the proximal ascending colon measuring 4 cm x 4 cm with a conglomerate of lymph nodes in the adjacent mesentery measuring 8 mm in the short axis, considered by the reporter to be suspicious for colon carcinoma. There was no evidence of liver metastasis. On 23 May one year after*, the subject was diagnosed with colon cancer. The subject underwent colectomy on 13 June one year after*. The tumor site was the right colon, 2.5 cm distal to ileocecal valve. Pathology results showed a tumor size of 4.0 x 3.5 x 1.3 cm. Histology showed adenocarcinoma, low grade (well differentiated to moderately differentiated); primary tumor was T2 as tumor invaded muscularis propria and extended close to but not into the subserosal fat. Proximal and distal margins were uninvolved by invasive carcinoma; surgical margins of excision were free of tumor. Seven additional lymph nodes were found, and all of them were negative for tumor. The event was reported as resolved on 16 June one year after*.

The event of colon cancer occurred during the first year of the study where subject received standard of care treatment. After completing 1 year in the study, the subject received the first dose of evolocumab on 14 December one year after*. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff on [redacted].

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

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

Subject [redacted] was a 60-year-old white woman participating in Study 20110110 who had a cerebrovascular accident (CVA) reported by the investigator. The subject's medical history included dyslipidemia, hypertension, obesity, depression, anxiety, gastroesophageal reflux disease, gastrointestinal hemorrhage due to clopidogrel, meniscus injury, knee operation, hysterectomy, mitral valve prolapsed, cerebrovascular accident in same year*, asthenia, sleep apnea syndrome, diabetes mellitus, coronary artery disease with stenting in eleven years ago* and six years ago*, transient ischemic attack, drug hypersensitivity, angina pectoris and post menopausal symptoms. Concomitant medications included omeprazole, acetylsalicylic acid, propranolol, paroxetine combination of carbidopa and levodopa, and multivitamins. Previous and ongoing treatment for hypercholesterolemia included atorvastatin and ezetimibe.

The subject was in the parent study from 19 October one year ago* to 11January same year* and received the last dose of evolocumab in the parent study on 14 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 11 January [redacted].

On 06 February two years after*, the subject was hospitalized for chest pressure and heaviness similar to her prior angina for the past weeks. On the same day (06 February two years after*), computed tomography angiography (CTA) of the head and neck with contrast showed that there was no significant common carotid stenosis on either side or internal carotid stenosis. Left internal carotid was mildly ectatic. There was mild stenosis involving the distal right vertebral artery. There was a 3-mm aneurysm extending laterally off of the cavernous portion of the left internal carotid artery. Computed tomography (CT) of the head revealed paranasal sinus disease. The subject's ECG showed sinus bradycardia at 58 beats per minute and nonspecific ST - T wave changes were also noted.

On 07 February two years after*, magnetic resonance imaging (MRI) of the brain without contrast was performed due to left sided weakness. There was faint visualization of suspected 3-mm aneurysm along lateral aspect of cavernous left internal carotid artery. There was no evidence

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of acute intracranial abnormality; no foci of signal abnormality on diffusion images, no abnormal extra-axial fluid collections were identified.

On 09 February two years after*, the subject developed a wide complex tachycardia that lasted 3 seconds as noted on telemetry. The telemetry monitoring showed sinus rhythm converting to a second episode of a wide-complex tachycardia. The subject experienced palpitations and dizziness and nausea.

On 10 February two years after*, the subject underwent cardiac catheterization for her angina-like symptoms. Results revealed left main coronary without significant disease; the left anterior descending artery was seen with a long segment of previously deployed stents and the segment was widely patent. The right coronary artery was a small non dominant vessel, 30% to 40% proximal stenosis was noted.

On the same day (10 February two years after*), echocardiogram showed normal left ventricular size, 60% global ejection fraction, and mild mitral regurgitation with calcification. Trivial aortic regurgitation was present and aortic valve appeared to be mildly sclerotic. There was mild tricuspid valve regurgitation with right ventricular systolic pressure of approximately 44 mmHg. Right atrium was normal in size and trivial pulmonic regurgitation was present. The subject's ECG showed normal sinus rhythm with 1st degree AV block, inferior infarct, and non-specific ST abnormality. The ECG when compared with the previous one showed inferior infarct. The subject was diagnosed with CVA. The event was reported as resolved on 11 February two years after* and the subject was discharged on the same day.

The subject's last dose of investigational product prior to the event was not known. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study, and the last dose of evolocumab prior to the cutoff date was on [redacted].

The investigator reported that there was not a reasonable possibility that the event CVA was related to investigational product.

The Sponsor is aware that a diagnosis of CVA appears inconsistent with the clinical details provided, which are consistent with a coronary event. Upon query to the study site after database lock, the diagnosis was changed to TIA because of the dizziness report. The sponsor is still evaluating the remainder of the report.

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Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q4W 420 mg + Ezetimibe PO QD 10 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care (SOC) Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SOC
Report: Osteoarthritis

Subject [redacted] was a 64-year-old white man participating in Study 20110110 who experienced osteoarthritis (reported term: right knee advanced medial compartment arthrosis). The subject's medical history included hypercholesterolemia, coronary heart disease with previous PCI, road traffic accident (bicycle), dry eye, joint dislocation, corneal erosion, pterygium, osteoarthritis, actinic keratosis, and drug intolerance (statins). Concomitant medications included ademetionine, Vitamin B complex, acetylsalicylic acid, candesartan cilexetil, tadalafil, curcumin, and ophthalmologicals. Current and previous treatment for hypercholesterolemia included fish oil, ezetimibe, and rosuvastatin.

The subject was in the parent study from 13 December one year ago* to 07 March same year* and received the last dose of evolocumab in the parent study on 07 February same year*. The subject received the first dose of evolocumab in Study 20110110 on 29 May [redacted]. Since 16 April one year after*, the subject had been experiencing right knee pain. On 25 March two years after*, the subject was hospitalized and underwent right knee replacement. Treatments reported after the onset of event included cefalexin, enoxaparin, tramadol, paracetamol, oxycodone, and naproxen. On 31 March two years after*, the subject was discharged. The outcome of the event was reported as resolving. The subject's last dose of investigational product prior to the event was on 11 March two years after*. Evolocumab was continued.

As of the data cutoff date of [redacted], the subject was continuing in the study and received the latest dose of evolocumab before the data cutoff date on [redacted]. The investigator reported that there was no reasonable possibility that the event of osteoarthritis was related to evolocumab.

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Subject No: [redacted]
Treatment: Parent study: Ezetimibe PO QD 10 mg + Placebo SC Q4W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Lower limb fracture, Syncope

Subject [redacted] was a 57-year-old white man participating in Study 20110110 who developed syncope (reported term: syncopal episode) and had a lower limb fracture (reported term: fractured tibia and fibula right leg). The subject's medical history included hypercholesterolemia, hypertension, coronary artery disease, low white cell count, low neutrophil count, gout, drug intolerance (statin), and an episode of pre-syncope. Concomitant medications included ramipril, colestyramine, ubidecarenone, acetylsalicylic acid, fish oil, and multivitamins. Previous treatment for hypercholesterolemia included colestyramine.

The subject was in the parent study from 17 January same year* to 10 April same year* and received the last dose of ezetimibe in the parent study on 12 March same year*. The subject received the first dose of evolocumab in Study 20110110 on 10 April [redacted]. Approximately 10-1/2 months later, on 18 February one year after* while riding a bike, the subject had an episode of syncope causing a fall and resulting in right leg fracture and extreme pain. He was able to stay conscious and called an ambulance. The subject was admitted to the hospital on the same day. The record of the subject's heart rate monitor suggested a sudden drop in pulse rate. Syncope was suspected to be the result of cardiac chronotropic insufficiency. No specific procedures were performed for the event of syncope due to subject's immobility and the event resolved on the same day. Radiograph of the right tibia/fibula and ankle revealed a spiral fracture of the distal shaft of right femur and spiral fracture of proximal shaft of the fibula. On 18 February one year after*, laboratory tests showed white blood cell (WBC) count of 7.3 x 10^9/L, hemoglobin level of 140 g/L, red blood cell (RBC) count of 4.1 x 10^{12}/L, sodium of 138 mmol/L, potassium of 3.8 mmol/L, chloride of 105 mmol/L, bicarbonate of 21 mmol/L, and C-reactive protein of 0.5 mg/L. On 20 February one year after*, the subject underwent an open reduction of fracture and internal fixation of the tibia shaft after the initial right lower limb swelling had subsided. There were no intraoperative complications. Treatment medications included enoxaparin, paracetamol, oxycodone, combination of docusate and sennoside A + B, cephalexin, metoclopramide, ramipril, and ubidecarenone. The subject continued to progress and on the day of discharge

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(22 February one year after*) he was mobilizing independently on axillary crutches, compliant with the partial weight bearing status. The event of tibia fracture was reported as resolved on 31 May one year after*.

The subject's last dose of evolocumab prior to the events was on 08 February one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the cutoff date on [redacted].

The investigator reported that there was no reasonable possibility that the events of tibia fracture and syncope were related to evolocumab.

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

Subject [redacted] was a 67-year-old white man participating in Study 20110110 who was diagnosed with prostate cancer (reported term: prostate carcinoma) and underwent radical prostatectomy (reported term: radical prostatectomy for carcinoma). The subject's medical history included hypercholesterolemia and hypertension. Concomitant medications included lansoprazole, prochlorperazine, and olmesartan. Previous treatment for hypercholesterolemia was not reported; ongoing treatment included ezetimibe.

The subject was in the parent study from 11 November one year ago* to 31 January same year* and received the last dose of evolocumab in the parent study on 04 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 29 February [redacted]. Approximately 1 year and 2 months later, on 11 April one year after*, the subject was diagnosed with prostate carcinoma, Gleason score 6 by prostate biopsy. Approximately 4 months later, on 13 June one year after*, the subject was hospitalized to undergo a radical prostatectomy for carcinoma. No additional information was reported. The event was reported as resolved on 15 June one year after* and the subject was discharged from the hospital on the same day.

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

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

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Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q4W 280 mg Year 1 treatment: Standard of care (SOC) Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SOC
Report: Cystitis

Subject [redacted] was a 63-year-old white woman participating in Study 20110110 who developed cystitis. The subject's medical history included hypercholesterolemia, hypothyroidism, post-menopause symptoms and chronic allergy (middle ear). Concomitant medications included acetylsalicylic acid, prochlorperazine, levothyroxine, loratadine, clopidogrel and pantoprazole. Current and previous treatment for hypercholesterolemia included fish oil and ezetimibe.

The subject was in the parent study from 18 January one year ago* to 12 April one year ago* and received the last dose of evolocumab in the parent study on 19 March one year ago*. The subject enrolled in Study 20110110 on 09 January [redacted]. Approximately 1 year after enrollment in Study 20110110, on 11 January one year after*, the subject was hospitalized for cystitis. Computerized tomography of the kidney, ureter, and bladder did not reveal calculus in the urinary system or alternative pathology to account for symptoms. Urine analysis showed protein ++. Urine culture showed presence of *Escherichia coli*. On 12 January one year after*, the subject was discharged from the hospital. Gentamicin and cefalexin were used for the treatment of cystitis. Cystitis was reported as resolved on 22 January one year after*.

The subject started evolocumab dosing after the event of cystitis on 05 February one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study and the last recorded dose of evolocumab before the data cutoff date was on [redacted]. The investigator reported that there was no reasonable possibility that the event of cystitis was related to evolocumab.

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Subject No: [redacted]
Treatment: Parent study: Evolocumab SC Q4W 280 mg Year 1 treatment: Standard of care
Report: Pancreatitis

Subject [redacted] was a 66-year-old Asian man participating in Study 20110110 who developed pancreatitis (reported term: gallstone pancreatitis). The subject's medical history included hypercholesterolemia and cholecystitis. Concomitant medications included Vitamin E, metformin, ramipril, rabeprazole, acetylsalicylic acid, paracetamol/codeine, and ciprofloxacin/dexamethasone. Previous and continuing treatment for hypercholesterolemia included ezetimibe.

The subject was in the parent study from 19 September same year* to 14 December same year* and received the last dose of evolocumab in the parent study on 14 November same year*. Subsequently, on 15 December [redacted], the subject was randomized to standard of care in Study 20110110.

Approximately 3 months later, on 16 March one year after*, the subject developed pancreatitis due to gallstone migration and was hospitalized. On 03 May one year after*, a laparoscopic cholecystectomy was performed. The subject tolerated the procedure well and blood loss was minimal. The event of pancreatitis was reported to have resolved on 04 May one year after*; the subject was discharged from the hospital on the same date and had been well since. Approximately 1 month after surgery, on 08 June one year after*, the subject went to the clinic for a post-surgery evaluation. The subject felt well and had no further pain. He was eating and drinking well. The investigator reported that all the incisions were healed; the subject's pathology showed chronic cholecystitis.

The subject's last dose of evolocumab prior to the event of pancreatitis was on 14 November same year* (the last dose in the parent study). As of the data cutoff date of [redacted], the subject was lost to follow-up. The investigator reported that there was no reasonable possibility that the event of pancreatitis was related to evolocumab.

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Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q4W 280 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Intervertebral disc protrusion

Subject [redacted] was a 70-year-old white woman participating in Study 20110110 who developed intervertebral disc protrusion (reported term: cervical discus prolapsus). The subject's medical history included hypercholesterolemia, spinal column stenosis, myalgia, and surgery. Concomitant medications included bendroflumethiazide and losartan. Previous treatment for hypercholesterolemia was not reported.

The subject was in the parent study from 14 October one year ago* to 27 December one year ago* and received the last dose of evolocumab in the parent study on 09 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 12 March [redacted].

On an unspecified date, the subject was seen by a neurologist for muscle pain in the calves and stiffness in the hands and was diagnosed with intervertebral disc protrusion. The subject did not have any previous episodes of prolapsed cervical discs or other pre-disposing risk factors that would have caused prolapsed cervical disc. Approximately 4 months after the first dose of evolocumab, on 18 July one year after*, the subject was hospitalized for surgery and underwent decompression and corpectomy of C5 without any complications. Treatment medication included pantoprazole, ibuprofen, and paracetamol. The event of intervertebral disc protrusion resolved on 18 July one year after*, and the subject was discharged from the hospital on 19 July one year after*.

The subject's last dose of evolocumab prior to the event was on 01 July one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff date on [redacted].

The investigator reported that there was not a reasonable possibility that the event of intervertebral disc protrusion was related to evolocumab. The investigator reported there were no co-suspect medications.

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Subject No: [redacted]
Treatment: Parent study: Ezetimibe PO QD 10 mg + Placebo SC Q4W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Angina pectoris

Subject [redacted] was a 59-year-old white woman participating in Study 20110110 who developed angina pectoris (reported term: stable angina pectoris). The medical history included dyslipidemia, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, allergy to dust, allergy to dogs, fracture of left ankle, retinal detachment in right eye, and sterilization. Concomitant medications included amlodipine, cetrizine, and tiotropium bromide inhaler. Previous treatment for the condition under study included ezetimibe (in the parent study). Current treatment for the condition under study included rosuvastatin.

The subject was in the parent study from 23 November one year ago* to 15 February same year* and received ezetimibe and placebo. The subject received the first dose of evolocumab in Study 20110110 on 15 February [redacted].

On 23 March two years after*, the subject developed chest pain and was hospitalized. Laboratory tests and ECG did not confirm acute myocardial infarct. Echocardiogram showed normal findings. Treatment medications reported after the onset of event included atorvastatin and acetylsalicylic acid. The outcome of the event stable angina pectoris was reported as resolved on 24 March two years after* and the subject was discharged from the hospital on the same day. Outpatient coronary arteriography was planned.

The subject's last dose of evolocumab prior to the event was not known. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff date on [redacted].

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

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Subject No: [redacted]
Treatment: Parent study: Ezetimibe PO QD 10 mg + Evolocumab SC Q4W 420 mg Year 1 treatment: Standard of care Years 2 to 5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Dizziness

Subject [redacted] was a 65-year-old white woman participating in Study 20110110 who developed dizziness (reported term: worsening of dizziness). The subject's medical history included hypercholesterolemia, neck injury, and dizziness since 27 April same year*. Concomitant medications included Vitamin E, acetylsalicylic acid/magnesium oxide, omeprazole, citalopram, magnesium hydroxide, estradiol, and viscous eye drops. Previous and continuing treatment for hypercholesterolemia included fish oil.

The subject was in the parent study from 11 January same year* to 03 April same year*, and received the last dose of evolocumab in the parent study on 07 March same year*, and the last dose of ezetimibe in the parent study on 03 April same year*.

The investigator reported that the subject began experiencing dizziness on 27 April same year*. The subject was randomized to the standard of care arm in Study 20110110 on 23 May [redacted]. A few days later, on 30 May same year*, the subject's dizziness worsened and the she was hospitalized. The subject developed chest pain and was moved to the cardiology ward. Reportedly, troponins, coronary angiography, echocardiography, and chest radiograph were normal. Additionally, laboratory values (liver and kidney infection parameters, D-dimer, and glucose) were normal. The investigator reported that the subject was referred to an ear-nose-throat specialist for further evaluation. The subject received no treatment for the event. The event of dizziness was reported as resolved on 01 June same year* and the subject was discharged from the hospital on the same day.

As of the data cutoff date of [redacted], the subject was continuing in the study. The investigator reported that there was no reasonable possibility that the event of dizziness was related to evolocumab.

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

Subject [redacted] was a 65-year-old white woman participating in Study 20110110 who developed gastritis (reported term: worsening of intermittent gastritis) and spinal osteoarthritis (reported term: chest pain [due to spondylosis]). The subject's medical history included hypercholesterolemia, intermittent gastritis, type 2 diabetes mellitus, hay fever symptoms, common cold, hypertension, osteoarthrosis of the hips, vaginal dryness, urinary incontinence, intermittent joint pain, intermittent lower back pain, sinusitis, pain in legs and back, and drug allergy to trospium chloride and oxycodone. Concomitant medications included losartan; combination of acetylsalicylic acid and magnesium oxide, omeprazole, combination of bendroflumethiazide and potassium chloride, oxybutynin, estradiol, levocabastine, paracetamol, liraglutide, benzocaine, chlorhexidine, metformin, amoxicillin, and glimepiride. The subject did not receive any previous treatment for hypercholesterolemia.

The subject was in the parent study from 19 December one year ago* to 13 March same year* and received the last dose of evolocumab in the parent study on 14 February same year*. The subject received the first dose of evolocumab in Study 20110110 on 13 March [redacted].

Approximately 2 months later, on 06 May same year*, the subject was admitted to the hospital with suspected acute coronary syndrome. Acute coronary syndrome was later eliminated since the subject had a normal echocardiogram, coronary markers, and electrocardiogram. The subject complained of pain mostly in the epigastrium with upward retrosternal radiation. The subject had a prolonged history of pressing chest pain that was epigastric, accompanied with nausea. The subject did not have any heartburn or vomiting. Symptoms began in conjunction with the start of liraglutide. The subject had been taking omeprazole because of nausea, and gastritis was suspected. Biochemistry tests were normal and did not suggest gastrointestinal bleeding. Omeprazole dosage was doubled. The event of gastritis was reported as resolved on 07 May same year* and the subject was discharged. Gastroscopy that was performed on 16 May same year* was normal.

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The subject's last dose of evolocumab prior to the event of gastritis was on 11 April same year*. Evolocumab was continued.

Approximately 1 year and 3 weeks after the first dose, on 07 April one year after*, the subject experienced chest pain (due to spondylosis) and was hospitalized. The subject felt pain in the chest and a tingling and stabbing pain while walking; she contacted the doctor and was referred to the hospital because she was at a risk due to her history of diabetes and hypertension. At the hospital, myocardial infarction and angina were eliminated. Laboratory tests were performed and were normal. On 08 April one year after*, a computerized tomography of the aorta and echocardiogram were performed and were normal. A radiograph of the thorax showed spondylosis. The subject did not receive any new medication or undergo any surgery. The event was reported to have resolved on 09 April one year after* and the subject was discharged from the hospital. The investigator reported that chest pain was likely the result of the subject's condition of thoracic spondylosis. On 24 May one year after*, myocardial scintigraphy was normal according to the subject.

The subject's last dose of evolocumab prior to the event of spinal osteoarthritis was on 14 March one year after*. Evolocumab was continued.

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

The investigator reported that there was no reasonable possibility that the events of gastritis and spinal osteoarthritis were related to evolocumab.

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

Subject [redacted] was a 46-year-old white man participating in Study 20110110 who was diagnosed with B-cell lymphoma (reported term: large cell B-cell lymphoma). The subject's medical history included hypercholesterolemia. Concomitant medications included combination of codeine and acetaminophen. Previous and ongoing treatment for hypercholesterolemia included omega-3 fish oil, ezetimibe, unspecified herbal, colestyramine, and colesevelam hydrochloride.

The subject was in the parent study from 03 November two years ago* to 26 January one year ago* and received the last dose of evolocumab in the parent study on 29 December two years ago*. The subject was randomized to Study 20110110 on 26 January one year ago* and assigned standard of care treatment. After completing the first year of the study, he began part 2 and received his first dose of evolocumab on 28 February [redacted]

On 26 November same year*, the subject developed right sided back pain. On an unknown date, a nuclear magnetic resonance (NMR) showed an extradural tumor located at fourth-fifth lumbar vertebra marginally affecting the corpus of left pedicle and inter-vertebral foramen. On 27 December same year*, the subject was hospitalized and the tumor was removed from neural channel. Biopsy revealed large cell B cell lymphoma. The subject was discharged from the hospital on 28 December same year*. On 30 December same year*, total body computed tomography (CT) and positron emission tomography (PET), confirmed that there was no lymphonodular disease except the tumor.

On 20 January one year after*, treatment medication included cyclophosphamide, doxorubicin, rituximab and high dose of prednisolone. The event was ongoing at the time of this report and the investigator confirmed that the subject's cytostatic treatment was continued.

The subject's last dose of investigational product prior to the event was 09 January one year after*. Evolocumab was withheld due to the event. As of the data cutoff date of [redacted], the

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

The investigator reported that there was not a reasonable possibility that the event large cell B cell lymphoma was related to the investigational product.

Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q4W 280 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Positional vertigo, Esophageal carcinoma

Subject [redacted] was a 56-year-old white woman participating in Study 20110110 who had positional vertigo (reported term: benign paroxysmal positional vertigo), and esophageal carcinoma (reported term: carcinoma oesophagi). Her medical history included hypercholesterolemia and statin intolerance. She had a history of depression, insomnia, long time gastric acid reflux type symptoms and hyperthyroidism. Concomitant medications included quetiapin, zolpidem, esomeprazole, ibuprofen, levothyroxine, trazodone, and fish oil. Previous treatment for hypercholesterolemia included simvastatin and atorvastatin.

The subject was in the parent study from 05 January same year* to 29 March same year* and received the last dose of evolocumab in the parent study on 06 March same year*. The subject received the first dose of evolocumab in Study 20110110 on 29 March [redacted].

On 12 February one year after*, the subject developed vertigo and was hospitalized on 01 March one year after* with a diagnosis of benign paroxysmal positional vertigo. The subject did not have a history of previous episodes of vertigo. Upon admission to the hospital, physical examination corroborated the diagnosis. The subject was discharged from the hospital on 02 March one year after*. On 04 April one year after*, the investigator reported that at week 52 (end of study), the subject did not present with any symptom s associated with vertigo. No co-suspect medications were reported. The event was reported as resolved on 04 April one year after*.

On 06 February two years after*, the subject underwent gastroscopy due to the long time gastric acid reflux type symptoms, which showed a suspected tumor at the distal esophagus. Results of the biopsy dated 12 February two years after* revealed squamous cell carcinoma. The investigator added that for esophageal cancer, cytostatic therapy was planned as a long term treatment. The outcome of the event of esophageal carcinoma was reported as ongoing.

The last dose of evolocumab prior to the event of positional vertigo was on 08 February one year after*. Evolocumab was continued following this event. The subject discontinued from

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Study 20110110 following the event of esophageal carcinoma, and her last dose of evolocumab was 06 February two years after*.

The investigator reported that there was no reasonable possibility that the events of positional vertigo or esophageal carcinoma were related to evolocumab.

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

Subject [redacted] was a 64-year-old white woman participating in Study 20110110 who experienced a femur fracture (reported term: pretrocanterea broken right femur) and wrist fracture (reported term: right wrist scaphoid fracture). The subject's medical history included hypercholesterolemia, menopause symptoms, overweight, dyslipidemia, and hypothyroidism. There were no known drug allergies. Concomitant medications included levothyroxine, hydrochlorothiazide, clebopride, simeticone, ibuprofen, esomeprazole, alprazolam, and citalopram. Previous and current treatment for hypercholesterolemia and dyslipidemia included pravastatin and ezetimibe.

The subject was in the parent study from 09 November two years ago* to 01 February one year ago* and received the last dose of evolocumab in the parent study on 04 January one year ago*. The subject was randomized to standard of care in the first year of Study 20110110, and received the first dose of evolocumab in Study 20110110 on 15 March [redacted].

Approximately 2 years and 4 months later, on 04 March one year after*, the subject experienced a fall that caused pertrochanteric fracture of the right femur and right wrist scaphoid fracture. The subject was admitted to the hospital. The investigator confirmed that the fracture occurred due to the fall. Radiograph of the pelvis showed intertrochanteric break. The radiograph of the right wrist showed scaphoid fracture. The final diagnosis included right pertrochanteric fracture and right scaphoid fracture.

On 07 March one year after*, the subject underwent osteosynthesis. The subject showed good postoperative outcome and she was moved to the sociosanitary unit for continued convalescence. Treatment medications reported after the onset of the event included levothyroxine, pantoprazole, metamizole magnesium, heparin, metoclopramide, alprazolam, tramadol, citalopram, atorvastatin, diazepam, paracetamol, ibuprofen, lorazepam, and magnesium hydroxide. The subject was discharged from the hospital on 13 March one year after*.

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The last dose of evolocumab prior to the event was on 12 February one year after*. The investigator reported that evolocumab was not administered on the day of the week-108 visit as the subject was in the hospital. Evolocumab was temporarily withheld. The subject was unable to visit the center to restart evolocumab.

The last dose of evolocumab prior to the event was on 12 February one year after*. As of the data cutoff date of [redacted], the subject was continuing in the study, and received the last dose of evolocumab prior to data cutoff on [redacted].

The investigator reported that there was not a reasonable possibility that the events femur fracture and wrist fracture were related to evolocumab or to the study conduct.

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Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q4W 350 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Pyelonephritis, Urinary tract infection (2 episodes of each)

Subject [redacted] was a 65-year-old white man participating in Study 20110110 who developed pyelonephritis and urinary tract infection (2 episodes of each event). The subject's medical history included hypercholesterolemia, chronic obstructive pulmonary disease, bronchial hyperreactivity, angina pectoris, allergy to arthropod sting, urosepsis, bacterial prostatitis, and drug intolerance (statins). Concomitant medications included isosorbide mononitrate, glyceryl trinitrate, a combination of budesonide and formoterol, enalapril, alfuzosin, methenamine hippurate, finasteride, acetylsalicylic acid and vaccine for tick borne encephalitis. Previous treatment for hypercholesterolemia included ezetimibe.

The subject was in the parent study from 13 December one year ago* to 05 March same year* and received the last dose of evolocumab in the parent study on 08 February same year*. The subject received the first dose of evolocumab in Study 20110110 on 05 March [redacted].

Approximately 7 months later, on 30 October same year*, the subject experienced fever, low abdominal pain, malaise, shivering, burning on micturition, and frequent urges. A urine strip was positive for blood. On 01 November same year*, a urine culture was positive for *Enterococcus faecalis*. The subject was diagnosed with probable pyelonephritis and treated with ciprofloxacin. The symptoms worsened. On 03 November same year*, the subject presented debilitated to the emergency room. Additionally, he had respiratory symptoms including dry cough and basal expiratory rhonchi on the right side, and experienced difficulty in eating. Vital signs included an oxygen saturation of 94%, a respiratory rate of 22 breaths per minute and pure breathing sounds bilaterally, a body temperature of 38.9°C, blood pressure of 150/70 mmHg, and regular heart rhythm with a rate of 104 beats per minute. Laboratory tests showed creatinine 105 µmol/L, C-reactive protein (CRP) 178 mg/L, hemoglobin 155 g/L, and WBC count 16.4 x 10^{12}/L. Blood and urine cultures were negative. The subject was given a gentamicin injection and a supporting intravenous (IV) drip in the emergency room. Subsequently, the subject was hospitalized, and the treatment was changed to a combination of piperacillin and tazobactam IV, followed by amoxicillin. On 04 November same year*, chest radiography revealed no

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infiltrates and no heart enlargement or stasis. On 06 November same year*, laboratory tests showed creatinine 84 µmol/L, CRP 61 mg/L, hemoglobin 153 g/L, and WBC count 8.9 x 10^{12}/L. The event of pyelonephritis resolved on 07 November same year*, and the subject was discharged on the same date.

The subject's last dose of evolocumab prior to the first event of pyelonephritis was on 22 October same year*. Evolocumab was continued. The investigator reported that there was not a reasonable possibility that the first event of pyelonephritis was related to evolocumab.

The subject had pyelonephritis from 09 April one year after* to 23 April one year after* associated with a growth of *Enterococcus faecalis* on culture. He was also diagnosed with prostatitis during this period. The subject was treated by a combination of sulfamethoxazole and trimethoprim without hospitalization.

Approximately 1 year and 4 months after the first dose of evolocumab on Study 20110110, on 01 May one year after*, the subject developed fever and pain in the back and went to the emergency department. A urine culture showed *Escherichia coli*. Subsequently, the subject was hospitalized on 02 May one year after*. On 03 May one year after*, laboratory test results included CRP of 91 mg/L and LPK of 14.1. On 04 May one year after*, CRP was 39 mg/L. During hospitalization, a computerized tomogram of the urinary tract revealed a concretion of 3 mm in the mid part of right calyx group, and a 3-cm large cortical cyst laterally in the left kidney. The subject was diagnosed with urinary tract infection. Treatment medications included cefotaxime sodium. The event of urinary tract infection resolved on 05 May one year after*, and the subject was discharged with ciprofloxacin and alfuzosin.

The subject's last dose of evolocumab prior to the third event of urinary tract infection was on 30 April one year after*. Evolocumab was continued. The investigator reported that there was not a reasonable possibility that the first event of urinary tract infection was related to evolocumab. No medications were considered co-suspect.

Approximately 1 year and 8 months after the first dose of evolocumab on Study 20110110, on 28 July one year after*, the subject was hospitalized with high fever, pain, and frequent urge to urinate. The subject had fever over 39°C and back pain for the prior 3 days. Laboratory tests revealed CRP 87 mg/L, WBC of 13.4 x 10^{12}/L, sodium of 136 mmol/L, and hemoglobin of 159 g/L. On admission, urinalysis revealed fairly thin sediment, where WBCs and nitrite were negative. Urine culture showed no growth. The subject was diagnosed with another event of pyelonephritis and started on ciprofloxacin and a combination of piperacillin and tazobactam.

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The subject became afebrile and was discharged from the hospital on 30 July one year after* with ciprofloxacin. The fourth event of pyelonephritis resolved on 15 August one year after*.

The subject's last dose of evolocumab prior to the fourth event of pyelonephritis was on 15 July one year after*. Evolocumab was continued. The investigator reported that there was not a reasonable possibility that the second event of pyelonephritis was related to evolocumab.

Approximately 1 year and 9 months after the first dose of evolocumab, on 17 September one year after*, the subject was diagnosed with urinary tract infection and hospitalized. Laboratory testing revealed CRP of 27 mg/L, and WBC 13.3 x 10^{12}/L. On 18 September one year after*, laboratory tests showed CRP of 57 mg/L. Treatment medications included ciprofloxacin, gentamicin, cefotaxime, and paracetamol. The subject was discharged on 18 September one year after*. The fifth event of urinary tract infection resolved on 9 October one year after*.

The subject's last dose of evolocumab prior to the fifth event of urinary tract infection was on 16 September one year after*. Evolocumab was continued. As of the data cutoff date [redacted], the subject was continuing in the study, and received the last dose of evolocumab prior to data cutoff date on [redacted]. The investigator reported that there was not a reasonable possibility that this event of urinary tract infection was related to evolocumab.

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