Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus, diet; atorvastatin 80 mg, ezetimibe 10 mg)
Report: Angina pectoris, Hypotension, Ventricular extrasystoles

Subject [redacted] was a 58-year-old white man participating in Study 20110109 who developed angina pectoris (reported term: atypical cardiac chest pain), hypotension, and ventricular extrasystoles (reported term: premature ventricular contraction). The subject's medical history included hypercholesterolemia, coronary artery disease, back pain, neck pain, spinal fusion surgery, intervertebral disc disorder, compression fracture (lumbar spine), osteoarthritis, knee arthroplasty, constipation, exposure to communicable disease (tuberculosis), benign breast neoplasm, mastectomy, nephrolithiasis, appendicectomy, cholecystectomy, and remote tobacco and alcohol abuse. His family history included premature coronary heart disease (myocardial infarction and bypass surgery in father) and diabetes mellitus and malignant neoplasm in mother.

Concomitant medications included meloxicam, oxycodone terephthalate/paracetamol, acetylsalicylic acid, tramadol, cyclobenzaprine, bisacodyl, docusate, and multivitamins. Previous treatment for hypercholesterolemia included fish oil, ezetimibe and atorvastatin.

The subject received the first dose of atorvastatin and ezetimibe on 11 June same year* and of evolocumab on 25 July [redacted]. Blood pressure was 120/88 mmHg on 25 July same year*, 118/74 mmHg on 22 August same year*, and 126/78 mmHg on 19 September same year*. Approximately 2 months after the first dose of evolocumab, on 20 September same year*, the subject presented to the emergency room (ER) complaining of a 5-day history of chest pain, located in the anterior substernal chest. The subject stated that while driving he felt a constant pressure of a squeezing sensation in his chest. The degree of pain at onset was moderate and did not increase in intensity. The subject denied shortness of breath or diaphoresis and was admitted with some fluttering sensation in his chest. A Holter monitoring showed no abnormalities. In the ER, the subject had premature ventricular contractions (PVCs) on his telemetry. The subject was hypotensive with a systolic blood pressure of 99 mm Hg at 1 point during his stay in the ER. At 15:50 hour, his vitals included weight of 89 kg, body temperature of 98.2 F, O_2 saturation of 99%, respiratory rate of 22/min, heart rate of 75 bpm, and systolic blood pressure of 149/80 mmHg. Subsequently, systolic blood pressure was 126/57 mmHg at 17:00 hour, 101/67 mmHg at 18.00 hour, 100/62 mmHg at 19.00 hour, and 89/56 mmHg at 20.00 hour. Physical examination revealed subject had low back pain; heart had regular rhythm, no

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murmurs, rub, or gallop; lungs were bilaterally clear to auscultation, without wheezes, rales or rhonchi. Radiography of chest showed no acute processes. Electrocardiogram (ECG) revealed normal sinus rhythm and no acute changes. Serial troponin T was < 0.01 ng/dL, fasting lipid panel was in good control, and serial cardiac enzymes were negative. Additional blood tests included white blood cell count (WBC) 6.9 $x10^3$/µL, red blood cell count (RBC) 4.29 x 10^6/µL, hemoglobin (Hgb) 13.8 g/dL, hematocrit 40.4%, sodium 140 mmol/L, potassium 3.7 mmol/L, chloride 102 mmol/L, CO_2 26 mmol/L, glucose 85 mg/dL, blood urea nitrogen (BUN) 10.0 mg/dL, creatinine 0.72 mg/dL, calcium 9.7 mg/dL, albumin 4.9 g/dL, total protein 5.9 g/dL, alkaline phosphatase 97 U/L, aspartate aminotransferase (AST) 18 U/L, alanine aminotransferase (ALT) 26 U/L, and bilirubin total 0.5 mg/dL. Initial diagnoses included chest pain syndrome with significant cardiac risk factors, including family history, hypercholesterolemia, age, coronary artery disease, and thoracic artery disease. The subject continued to be slightly hypotensive, with on and off chest pain continuing after nitroglycerin and metoprolol. Prior to metoprolol, the subject had one 3 beat episode of ventricular tachycardia. The subject was taken to the intensive care unit (ICU). During hospitalization, systolic blood pressure ranged between 200 mmHg and 89 mmHg while diastolic blood pressure ranged from 86 mmHg to 62 mmHg.

On 21 September same year*, an echocardiogram was performed showing mild mitral regurgitation; mild tricuspid regurgitation; the estimated pulmonary artery systolic pressure was 22 mmHg; normal left ventricular dimensions with normal left ventricular global and regional systolic function. The subject underwent stress test (adenosine Cardiolite stress test) and a baseline ECG showed normal sinus rhythm with occasional PVCs. During the adenosine infusion, there was no complaint of chest pain; and maximum blood pressure was 125/55; resting blood pressure was 125/69; baseline PVCs persisted throughout the infusion; no other arrhythmias were seen. The nuclear portion of the test reported that stress/rest perfusion was normal; there were no reversible or fixed defects were not seen; LV function was normal at 54% with normal wall motion. The final impression was that there were no electrocardiographic changes consistent with ischemia; normal perfusion study with normal LV functions. During hospitalization, the subject was hemodynamically stable, did not have any chest pain, shortness of breath or any fluttering sensation. The subject was kept on cardiac diet, and no changes were made to home medications, as test results showed the subject was in good control of hyperlipidemia. Final diagnoses were angina pectoris, hypotension, ventricular extrasystoles with negative stress test and chronic back pain. Treatment medications also included enoxaparin sodium. Discharge laboratory results included negative serial troponin. The events

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of hypotension, ventricular extrasystoles and angina pectoris resolved on 22 September same year*, and the subject was discharged from the hospital on the same day in stable condition.

The subject's last dose of evolocumab prior to the event was on 19 September same year*. Evolocumab, atorvastatin, and ezetimibe were continued. The investigator reported that there was no reasonable possibility that the events angina pectoris, hypotension, and ventricular extrasystoles were related to the evolocumab. Reportedly, the cause of the hypotensive excursions was unknown by the investigator. The investigator reported that subject seemed to think it was caused by a medication administered during hospitalization.

The subject's last dose of evolocumab, atorvastatin, and ezetimibe in the study was on 26 June one year after*. The subject completed the study on 24 July one year after*.

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Subject No: [redacted]
Treatment: Placebo SC QM (plus diet, atorvastatin 80 mg)
Report: Spinal osteoarthritis

Subject [redacted] was a 65-year-old white woman participating in Study 20110109 who developed spinal osteoarthritis (reported term: worsening of osteoarthritis in spine). The subject's medical history included hypercholesterolemia, hypothyroidism, menopausal symptoms, cholecystectomy, hysterosalpingo-oophorectomy, presbycusis, ulna fracture, plantar fasciitis, sciatica, knee arthroplasty, arthralgia, and osteoarthritis.

Concomitant medications included naproxen, levothyroxine, diltiazem, lisinopril, bisoprolol/hydrochlorothiazide, calcium, magnesium, potassium, metaxalone, and multivitamins. Previous treatment for hypercholesterolemia included atorvastatin.

The subject received the first dose of atorvastatin on 19 January same year* and the first dose of placebo on 02 March [redacted]. Approximately 8 months later, on 13 November same year*, the subject was hospitalized because osteoarthritis of the spine was causing pain, resulting in a need for surgery. On the same day, the subject underwent an L3-L4 transforaminal lumbar interbody fusion. The event spinal osteoarthritis was reported as resolved on 16 November 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 05 November same year*. Both atorvastatin and placebo were continued; the subject received the last dose of placebo on 31 January one year after*, and atorvastatin on 28 February one year after*.

The investigator reported that there was not a reasonable possibility that the event of spinal osteoarthritis was related to placebo. The subject completed the study on 28 February one year after*.

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Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet)
Report: Cholelithiasis

Subject [redacted] was a 64-year-old white man participating in Study 20110109 who developed cholelithiasis (reported term: worsening of chronic cholecystitis with cholelithiasis). The subject's medical history included hypercholesterolemia, hyperlipidemia, hypertension, tobacco user, overweight, tonsillectomy, nasal polyps, allergic sinusitis, eye operation, joint dislocation, ankle operation, peripheral edema, gastroesophageal reflux disease, colelithiasis, hemangioma of liver, vasectomy, removal of 3 colon and rectal polyps, arthritis, back pain, osteoarthritis, and congenital hyperbilirubinemia.

The subject had no previous treatment for hypercholesterolemia. Concomitant medications included antacids.

The subject received the first dose evolocumab on 28 March [redacted]. Approximately 10 months later, on 29 January one year after*, the subject had pain in the upper right quadrant of the abdomen. Two days later, on 31 January one year after*, the subject presented to the clinic complaining of pain. On 01 February one year after*, the subject went to the emergency room (ER) and was admitted to the hospital on 02 February one year after*, with a history of abdominal pain mainly in the right upper quadrant for several days. The subject's liver function tests were elevated and he was found to have gallstones. At the time of admission, the subject was feeling better and was felt to have most likely passed a gallstone. Physical examination showed the abdomen to be soft and non-tender; there was no guarding or rebound. Laboratory tests showed a normal white blood cell count. A computerized tomography scan revealed evidence of hemangiomas in the liver, though no evidence of choledocholithiasis. The impression was cholelithiasis with an episode of choledocholithiasis. On 04 February one year after*, the subject underwent a laparoscopic cholecystectomy, and the postoperative diagnosis was chronic cholecystitis with cholelithiasis. Treatment for the event included hydrocodone and paracetamol. On 05 February one year after*, the gallbladder was sent to pathology and on 06 February one year after* the report revealed that the gallbladder measured 9.5 x 2.5 x 2 cm. A large amount of sludge and stone-like material was seen within the lumen; the gallbladder wall was moderately thickened at 0.3 cm. The event was reported as resolved on 04 February one year after*. The subject was discharged from the hospital on 05 February one year after*.

The subject's last dose of evolocumab prior to the event was on 31 January one year after*. Evolocumab was continued. The subject's last dose of evolocumab in the study was on 28 February one year after*.

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The investigator reported that there was no reasonable possibility that the event of cholelithiasis was related to evolocumab. The subject completed the study on 16 April one year after*.

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Subject No: [redacted]
Treatment: Placebo SC QM (plus diet, atorvastatin 80 mg, ezetimibe 10 mg)
Report: Convulsion, Skull fracture

Subject [redacted] was a 75-year-old white man participating in Study 20110109 who developed convulsion (reported term: seizure) and skull fracture.

The subject's medical history included hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, hypertension, metabolic syndrome, obesity, angina, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, past episode of atrial fibrillation/flutter, glaucoma, surgery for liver abscess, alcohol use (4 to 5 times per week), benign prostate hyperplasia, inguinal hernia, hip arthroplasty, arthralgia, osteoarthritis, musculoskeletal pain, cataract operation, and drug hyper sensitivity (to penicillin).

Concomitant medications included acetylsalicylic acid, amlodipine, tamsulosin, losartan, brimonidine, latanoprost, multivitamins, metoprolol, macrogol, vitamin B, and ibuprofen. Previous treatment for hypercholesterolemia included fish oil, atorvastatin and ezetimibe.

The subject received the first dose of atorvastatin and ezetimibe on 23 April same year* and of placebo on 07 June [redacted]. On 04 February one year after*, the subject fell in his house while drinking alcohol, fractured his skull with some bleeding and was hospitalized on the same day. Vital signs showed normal blood pressure, pulse, respiratory rate, and oxygen saturation. Physical examination revealed a 5-cm laceration horizontally on the external portion of the scalp but no obvious focal neurologic deficits were noted. The other body systems were normal. Laboratory tests revealed creatinine level of 2.3 mg/dL, serum ethanol of 265 mg/dL, glucose of 125 mg/dL, blood urea nitrogen of 34 mg/dL, white blood cell (WBC) count of 6.2 x 10^3/µL, red blood cell (RBC) count of 3.45 x 10^6/µL, platelet count of 116 x 10^3/µL, hematocrit of 36%, hemoglobin of 12.4 g/dL and mean cell volume of 105 fL. ECG revealed normal sinus rhythm, axis normal, no ectopy, conduction normal, ST segments with no acute change, T waves with no acute change and no Q waves.

The CT of the head showed small subdural hematomas over the frontal convexities which were greater towards the right side than left as well as the right extending over the temporal convexity. No midline shift; scattered subarachnoid hemorrhage in the anterior frontal regions were observed. Small scattered contusions involving the anterior frontal lobes; frontal bone fracture just right of midline extending to the vertex and involving the parietal bone was seen. The subject underwent a laceration repair procedure which was well tolerated. Treatment for the event included tetanus vaccine, octocaine with epinephrine, levetiracetam, bacitracin,

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oxycodone, oxycodone/paracetamol, diphtheria vaccine, pertussis vaccine, and sodium chloride. The event was reported as resolved on 20 February one year after*.

On 19 May one year after*, the subject presented to the emergency department with an apparent seizure. At home, the subject had been alert and oriented. However during transportation, he experienced a generalized seizure and was given diazepam. The subject was reported to have no past history of seizures. Upon arrival, the subject was having respiratory depression possibly due to his post-ictal status and a nasal trumpet was inserted. Physical examination revealed coarse breath sounds bilaterally, decreased respiratory effort, and Glasgow Coma Score of 3. Vital signs included blood pressure 139/51 mmHg, pulse rate 88/min, respiratory rate 13/min, and oxygen saturation 99%. Laboratory results showed the following: RBC count 4.19 x 10^6/µL, mean cell volume 103 fL, mean cell hemoglobin 35 pg, platelet count 115 x 10^3/µL, absolute lymphocyte count 4.6 x 10^3/µL, absolute basophil count 0.0 x 10^3/µL, blood urea nitrogen 32 mg/dL, carbon dioxide 13 mEq/L, random glucose 166 mg/dL, creatinine 1.58 mg/dL, glomerular filtration rate 43 mlL/min/1.73 sq meter, ethanol level 28 mg/dL, ammonia 184 µmol/L, aspartate aminotransferase 43 IU/L, alanine aminotransferase 26 IU/L, and troponin I of 0.01 ng/mlL.

A computerized tomographic (CT) scan of the head demonstrated mild chronic age-related atrophic cerebral and degenerative white matter change probably a small area of right subfrontal chronic cortical infarction; no evidence of an intracranial mass, hemorrhage, or subacute cortical infarction. The chest radiograph was unremarkable. The electrocardiogram (ECG) revealed evidence of sinus rhythm with a first degree atrioventricular (AV) block, PR 161, normal QT interval; minimal ST segment depression in lead 2, no evidence of ST segment elevation, and slightly widened QRS complex.

The emergency department physician noted that the subject appeared to have hepatic encephalopathy, which may have been the cause of the seizures. The subject was given intravenous levetiracetam in sodium chloride, diazepam, and started on lactulose. His mental status improved and he became more awake. The physician's final impression was new onset seizure disorder and hepatic encephalopathy. Further treatment medications included topiramate. On 20 May one year after*, the glucose level was 160 mg/dL. The event was reported as resolved on 21 May one year after* and the subject was discharged on the same day.

The subject's last dose of placebo prior to the event of skull fracture was on 17 January one year after*, and prior to the event of convulsion was on 10 May one year after*. Atorvastatin, ezetimibe, and placebo were continued. The investigator reported that there was no reasonable possibility that the

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events of skull fracture and convulsion were related to placebo. The investigator reported there were no co-suspect medications. The subject's last dose of placebo in the study was on 10 May one year after*. The subject received the last dose of atorvastatin and ezetimibe on 14 June one year after*. The subject completed the study on 14 June one year after*.

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Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 10 mg)
Report: Asthma

Subject [redacted] was a 61-year-old white woman who was participating in Study 20110109 and developed asthma (reported term: worsening of asthma). The subject's medical history included hypercholesterolemia, hyperlipidemia, asthma, chronic obstructive pulmonary disease, hypothyroidism, gastroesophageal reflux disease (GERD), dyspepsia, anxiety, depression, sleep disorder, hysterectomy, bilateral salpingo-oophorectomy, hernial repair, appendicectomy, scoliosis, arthritis, alcohol use, and mycotic allergy. Concomitant medications included levothyroxine, omeprazole, enoxaparin, pantoprazole, calcium, potassium, multivitamins, docusate, cimicifuga racemosa extract, melatonin, valeriana officinalis root, naproxen, and citalopram. She had not received previous treatment for hypercholesterolemia.

The subject received the first dose of atorvastatin on 06 March same year* and the first dose of evolocumab on 10 April [redacted]. Approximately 11 months after receiving the first dose of evolocumab, on 08 March one year after*, the subject presented to the hospital with shortness of breath, cough, chest pain, and reported that her GERD flared up along with her asthma. Asthma exacerbation and viral upper respiratory infection were diagnosed. Physical examination at the hospital showed a body temperature 37.5°C, blood pressure 126/50 mmHg, heart rate 129 beats per minute, respiratory rate 31 breaths per minute, and oxygen saturation 98%.

On 12 March one year after*, laboratory testing revealed hemoglobin 10.8 g/dL, hematocrit 32%, red blood cell count 3.9 x 10^6/µL, white blood cell count 9.00 x 10^3/µL, neutrophils 87.0%, lymphocytes 7.9%, monocytes 3.8%, eosinophils 1.2%, basophils 0.1%, platelets 247 x 10^3/µL, and glomerular filtration rate 63.4 mL/minute/1.73m^2.

Lungs were clear to auscultation, respirations were non-labored, and breath sounds were equal. Her chest radiograph was negative for acute abnormality. Laboratory test results showed troponin levels of 0.0 and D-dimer < 200 ng/mL. Treatment included salbutamol sulfate, fluticasone propionate/salmeterol xinafoate, hydrocodone, loratadine, potassium chloride, prednisone, azithromycin, influenza virus vaccine, and pneumococcal 23-valent vaccine. Additional treatment included methylprednisolone sodium succinate and guaifenesin cough syrup. On 11 March one year after*, the subject was discharged from the hospital. The event was reported to be resolved on 01 April one year after*.

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The investigator reported that the subject's history of asthma was an etiological or predisposing risk factor associated with the event.

The subject's last dose of evolocumab prior to the event was on 13 February one year after*. Evolocumab was withheld. Her last dose of atorvastatin was on 09 April one year after*, and she completed the study on this date.

The investigator reported that there was no reasonable possibility that the event asthma was related to evolocumab and there were no co-suspect medications.

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Subject No: [redacted]
Treatment: Placebo SC QM (plus diet, atorvastatin 80 mg)
Report: Pulmonary embolism

Subject [redacted] was a 64-year-old white man who was participating in Study 20110109 and developed pulmonary embolism.

The subject's medical history included hypercholesterolemia, cardiac murmur, hypertension, type 2 diabetes mellitus, diabetic neuropathy, colon adenoma, edema, erectile dysfunction, drug hypersensitivity, osteoarthritis, rhinitis seasonal, hematuria, nephrolithiasis, meniscus operation (left knee partial medial), and joint arthroplasty. The subject was a tobacco user (chewing tobacco and smoking cigars); he quit smoking on 01 November same year*.

Concomitant medications included hydrochlorothiazide/triamterene, sildenafil, ibuprofen, psyllium hydrophilic mucilloid, acetylsalicylic acid, neomycin, polymyxin B, and ranitidine. Previous treatment for hypercholesterolemia included rosuvastatin.

The subject received the first dose of atorvastatin on 17 May same year* and the first dose of placebo on 21 June [redacted]. Approximately 10 months after receiving the first dose of placebo, on 12 April one year after*, the subject noted chest pressure while walking up some stairs; the pressure was substernal and associated with shortness of breath, improved with rest and lasted only a few minutes. Later that day, the subject was walking when he experienced an abrupt onset of shortness of breath associated with profound diaphoresis, with some chest pressure at the time but no nausea. The subject denied recent prolonged travel and other risk factors for pulmonary embolism. On 12 April one year after*, he presented to the hospital with shortness of breath associated with diaphoresis and some chest pressure; there was no radiation from the discomfort, but he felt slightly disoriented. The subject was found to be hypoxic; and cardiac examination showed regular rate and rhythm, without murmurs, gallops, or rubs. He received intravenous heparin, oxygen therapy, acetylsalicylic acid, and clopidogrel. Troponin levels were as follows: at baseline 0.33 ng/mL; at 90 minutes 0.68 ng/mL; and at 6 hours 1.07 ng/mL. A Doppler ultrasound of his legs showed thrombus within the left posterior tibial veins from the left of the knee to the ankle.

An electrocardiogram (ECG) showed some premature ventricular contractions in a pattern of bigeminy, sinus rhythm, otherwise there was no evidence of ST-segment elevation or depression. A repeat ECG showed sinus rhythm with frequent premature ventricular complexes; junctional ST depression and prolonged QT interval or fusion. A chest radiograph

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showed clear lungs; heart size and pulmonary vascularity were within normal limits; no evidence of pneumothorax or pleural effusion; no acute infiltrates were identified; and negative for acute pulmonary disease. The subject was kept on heparin 100 units/hour. On 12 April one year after*, the subject's vital signs were body temperature 98.1 degrees Fahrenheit, respiratory rate 14 breaths per minute, blood pressure 157/79 mmHg, pulse rate 98 beats per minute, and oxygen saturation of 95%.

A coronary angiography was performed due to abnormal troponin in the context of symptoms suggesting possible non-ST segment elevation myocardial infarction. The coronary angiography showed no obstructive disease and normal left ventricular function.

The subject was diagnosed with pulmonary embolism through symptoms of shortness of breath, chest pain, and signs of deep vein thrombosis with left lower extremity edema, and was started on enoxaparin and warfarin. He also received metoprolol and lisinopril for high blood pressure. Acetylsalicylic acid and nonsteroidal anti-inflammatory drugs were stopped. The event of pulmonary embolism resolved on 13 April one year after*, and the subject was discharged from the hospital on the same date.

The subject's last dose of placebo prior to the event was on 28 March one year after*. Both atorvastatin and placebo were continued and his last dose of placebo was on 23 May one year after*. His last dose of atorvastatin was on 20 June one year after*, and he completed the study on this date.

The investigator reported that there was no reasonable possibility that the event of pulmonary embolism was related to placebo.

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Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 10 mg)
Report: Positional vertigo

Subject [redacted] was a 48-year-old black woman participating in Study 20110109 who developed positional vertigo (reported term: benign paroxysmal positional vertigo). Her medical history included hypercholesterolemia, benign pituitary tumor, Rathkes cleft cyst, status post transsphenoidal surgery, road traffic accident with multiple ankle surgeries, vision blurred, type 2 diabetes mellitus, menopause, arthritis, and tobacco use.

Concomitant medications included metformin and naproxen. The subject had no previous treatment for hypercholesterolemia.

The subject received the first dose of atorvastatin on 29 March same year* and the first dose of evolocumab on 03 May [redacted]. On 21 January one year after*, the subject developed benign paroxysmal positional vertigo which was reported to have resolved. On 23 January one year after*, the subject experienced dizziness. She presented to the emergency department with dizziness, unsteady gait, frequent falls, forgetfulness, slurring of speech for 2 months, and vaginal bleeding for 1 to 2 days. She had dizziness as well as vertigo and her symptoms were exacerbated with ambulating as well as bending over. The symptoms were not constant and were waxing and waning; she had no headache, visual changes, weight loss, night sweats, chest pain, shortness of breath, cough, or any vaginal itching or dryness. On admission, vital signs included a temperature of 97.1 degrees Fahrenheit, heart rate of 58 beats per minute, respirations of 15 breaths per minute, blood pressure of 121/74 mmHg, and oxygen saturation of 100% on room air. Laboratory testing was unremarkable.

On examination, cranial nerves II-XII were intact, there was 5/5 strength in all 4 extremities. The subject had grossly intact sensation; gait without ataxia; +2 deep tendon reflexes to bilateral lower extremities; normal finger to nose. Regarding her gait instability, frequent falls, and dizziness, though possibly related to her pituitary mass, it was reported as unlikely. Computerized tomographic (CT) scan of the head showed a 12-mm suprasellar remnant as seen on postoperative magnetic resonance imaging (MRI) from three years ago*.

The MRI during hospitalization showed residual/recurrent pituitary tumor with superior sellar extension which appeared to be stable in size; mass effect on optic chiasm was unchanged. The subject reported being dizzy constantly which had gotten worse over the past 2 months. The CT of her head showed no sign of infarct or hemorrhage. The electrocardiogram (ECG)

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showed sinus bradycardia with first degree atrioventricular (AV) block. Dix Hallpike maneuver was negative; however, her symptoms appeared to be consistent with benign paroxysmal positional vertigo.

The subject was placed on cardiac monitoring during her stay; heart rate ranged from 40 to 60 bpm consistently, with the ECG showing first-degree AV block.

The subject reported having multiple falls over the past 2 months; she was found to be neurologically intact with the exception of decreased sensation on the medial aspect of her right foot that was thought to be contributing to her possible impaired proprioception leading to her falls. Her treatment included heparin, dextrose, and insulin lispro. The subject was discharged from the hospital on 26 January one year after*.

The last dose of evolocumab prior to the event and in the study was on 16 October same year*, and the last dose of atorvastatin was on 05 November same year*. Evolocumab and atorvastatin were discontinued due to other reason (due to change in job hours, the subject could not continue to keep appointments). The subject completed the study on 20 June one year after*.

The investigator reported that there was no reasonable possibility that the event positional vertigo was related to evolocumab or atorvastatin.

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Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet; atorvastatin 80 mg)
Report: Back pain

Subject [redacted] was a 55-year-old white man participating in Study 20110109 who developed back pain (reported term: acute back pain). The subject's medical history included hypercholesterolemia, depression, hiatal hernia, and hyperlipidemia.

Concomitant medications included acetylsalicylic acid, clopidogrel, losratan, esomeprazole, and escitalopram. Previous treatment for hypercholesterolemia included atorvastatin.

The subject received the first dose of atorvastatin on 10 August same year* and the first dose of evolocumab on 08 October [redacted]. Approximately 5 months later, on 26 March one year after*, the subject developed back pain that subsequently became worse. He was seen by an orthopedic surgeon and was scheduled for a back operation. Approximately 7 months after the first dose of evolocumab, on 08 May one year after*, the subject was admitted to the hospital for back pain and underwent a planned, unspecified back operation on the same date. The event of back pain was reported to have resolved on 17 May one year after*.

The subject's last dose of evolocumab prior to hospitalization was on 22 April one year after*. Both atorvastatin and evolocumab were continued; the subject's last dose of evolocumab in the study was on 10 September one year after* and last dose of atorvastatin in the study was on 15 July one year after*. The investigator reported that there was no reasonable possibility that the event of back pain was related to evolocumab. The subject completed the study on 07 October one year after*.

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Subject No: [redacted]
Treatment: Placebo SC QM (plus diet, atorvastatin 80 mg, ezetimibe 10 mg)
Report: Joint injury

Subject [redacted] was a 61-year-old man participating in Study 20110109 who developed joint injury (reported term: left shoulder injury). The subject's medical history included hypercholesterolemia.

Concomitant medications while on study included allopurinol, amlodipine, lisinopril, pentoxifylline, human insulin, calcium dobesilate, carvedilol, amiloride, hydrochlorothiazide, insulin, acetylsalicylic acid, pioglitazone, ranitidine, and metformin. Previous treatment for hypercholesterolemia included atorvastatin.

The subject received the first dose of atorvastatin and ezetimibe on 19 June same year* and of placebo on 25 July [redacted]. Approximately 9 months later, on 15 April one year after*, the subject experienced joint injury while exercising. One month and 1 week later, on 24 May one year after*, the subject was hospitalized. Surgery of acromioclavicular (AC) joint excision acromioplasty and rotator cuff repair was performed on the same day (24 May one year after*). Additional treatment included ibuprofen and paracetamol. The event resolved on 25 May one year after*, and the subject was discharged from the hospital on the same day. The subject's last dose of atorvastatin and ezetimibe prior to the event was on 03 April one year after*. The subject's last dose of placebo prior to the event was on 03 May one year after*, which was also the last dose in the study.

The investigator reported that there was no reasonable possibility that the event joint injury was related to placebo, and there were no co-suspect medications. The subject completed the study on 23 July one year after*.

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Subject No: [redacted]
Treatment: Placebo SC QM (plus diet; atorvastatin 80 mg)
Report: Chest pain

Subject [redacted] was a 60-year-old black woman participating in Study 20110109 who developed chest pain (reported term: atypical chest pain). The subject's medical history included hypercholesterolemia, hypertension, type 2 diabetes, angina pectoris, myocardial ischemia, stent placement, gastrooesophageal reflux disease, and arthritis. The subject was a smoker (tobacco user).

Concomitant medications while on study included acetylsalicylic acid, atenolol, enalapril, isosorbide mononitrate, amlodipine, chlorhexidine, ciprofloxacin, mouth wash, cimetidine, isosorbide dinitrate. Previous treatment for hypercholesterolemia included simvastatin.

The subject received the first dose of atorvastatin on 04 July same year* and the first dose of placebo on 08 August [redacted]. Approximately 11 months after the first dose of placebo, on 09 July one year after*, the subject presented complaining of central crushing chest pain with associated shortness of breath, onset while washing dishes, and not responding to isosorbide dinitrate. The subject was diagnosed with chest pain and was hospitalized. Vital signs included blood pressure of 192/98 mmHg, body temperature of 36°C, pulse rate of 61 bpm, and respiratory rate of 16/minute. Laboratory tests disclosed creatinine of 45 umol/L, troponin T of <50 ng/L, and platelet count of 165 x 10^9/L. On the same date, 09 July one year after*, the electrocardiogram (ECG) showed T-wave near baseline (lateral), negative T wave (anterior), R/S inversion area between V1 and V2. Repeated troponin T was <50 ng/mL. Repeated ECG on the same day showed slightly depressed ST segment (anterior), T-wave near baseline (lateral, inferior), negative T-wave (anterior), R/S inversion area between V1 and V2. The third ECG revealed Q-wave (lateral), slightly depressed ST segment (lateral, inferior, anterior), T-wave near baseline (lateral, inferior), negative T-wave (anterior), R/S inversion area between V1 and V2. The fourth ECG showed slightly depressed ST segment (lateral, inferior, anterior), negative T-wave (anterior), R/S inversion area between V1 and V2. Treatment for the event included enalapril, atenolol, amlodipine, acetylsalicylic acid, isosorbide mononitrate, isosorbide dinitrate and omeprazole. The event of chest pain resolved spontaneously on 11 July one year after*, and the subject was discharged from the hospital on the same date free from pain and without any change in the treatment medications. The investigator reported that the chest pain was possibly due to reflux. The subject was scheduled to undergo a stress test later. The last dose of placebo prior the event was on 12 June one year after*. Placebo was continued. The subject received the last dose of

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placebo in the study on 12 July one year after*, and last dose of atorvastatin in the study on 07 August one year after*.

The investigator reported that there was not a reasonable possibility that the event chest pain was related to placebo, and that there were no co-suspect medications. The subject completed the study on 07 August one year after*.

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Subject No: [redacted]
Treatment: Placebo SC QM (plus diet, atorvastatin 80 mg, ezetimibe 10 mg)
Report: Angina pectoris

Subject [redacted] was a 62-year-old white man participating in Study 20110109 who developed angina pectoris. The subject's medical history included hypercholesterolemia, hypertension, angina pectoris, coronary artery bypass, percutaneous coronary intervention, carotid artery stenosis, atrophy (atrophic mammaria interna), and former tobacco use.

Concomitant medications prior to the event included acetylsalicylic acid, bisoprolol, and indapamide. The subject's previous treatment for hypercholesterolemia included ezetimibe and atorvastatin.

The subject received the first dose of atorvastatin and ezetimibe on 13 July same year*, and placebo on 20 August [redacted]. Approximately 10 months and 3 weeks later, on 10 July one year after*, the subject developed angina pectoris. The subject was asymptomatic and had normal and distally palpable pulse rate, no murmur over peripheral blood vessels, normal blood pressure (130/80 mmHg), and electrocardiogram (ECG). Stress echocardiogram showed no dysrhythmia or any symptoms. Echocardiogram of the neck blood vessels showed atheroma formation at the bifurcation on the right and the flow rate was 120 cm/sec. Echocardiogram revealed good left ventricular wall movement. On 22 July one year after*, the subject was hospitalized to undergo coronary angiogram. Laboratory investigations showed: myoglobin 47 µg/L, high sensitivity cardiac troponin T<5 ng/L, creatine kinase (CK) 78 IU/L, CK-MB 1.9 µg/L, fasting glucose 6.7 mmol/L,C-reactive protein<2 mg/L, thyroid stimulating hormone 0.518 mIU/L, free T4 18.6 pmol/L, hemoglobin 16.6 g/dL, red blood cell count 5 x 10^{12}/L, hematocrit 47.8%, platelets 160 x10^{9}/L, white blood cell count 8 x 10^{9}/L, D-dimer 0.2 mg/L, sodium 135 mmol/L, potassium 4.4 mmol/L, chloride 99 mmol/L, CO_2 30 mmol/L, urea 5.9 mmol/L, creatinine 76 µmol/L, glomerular filtration rate >60 mL/min, total bilirubin 11.2 µmol/L, alkaline phosphatase 72 IU/L, gamma glutamyl transferase 63 IU/L, alanine aminotransferase 40 IU/L, and aspartate aminotransferase 27 IU/L. Coronary angiogram was performed which led to revascularization. On 22 July one year after*, diagnostic heart catheterization showed: good LV-function, 3 venous bypasses and a stent in the proximal left anterior descending visible, and a clear atherosclerotic plaque with a 60% to 70% stenosis bypass to the diagonal branch. This was treated with the placement of an Mguard stent with good angiographic results. There was also early degradation of the venous bypass to the right coronary artery. Additional treatment included clopidogrel.

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On 22 July one year after*, the event was reported as resolved and the subject was discharged from the hospital the next day. The subject's last dose of placebo prior to the event was on 24 June one year after*. Placebo, ezetimibe and atorvastatin were continued. The last dose of placebo was on 24 July one year after*. The last dose of ezetimibe and atorvastatin was on 21 August one year after*.

The investigator reported that there was no reasonable possibility that the event of angina pectoris was related to the placebo, ezetimibe or atorvastatin. The subject completed the study on 21 August one year after*.

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Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 80 mg)
Report: Hemorrhoids

Subject [redacted] was a 61-year-old mixed race man who was participating in Study 20110109 and developed hemorrhoids (reported term: hemarrhoidectomy). The subject's medical history included hypercholesterolemia and hemorrhoidal hemorrhage.

Concomitant medications included albendazole, metformin, hydrochlorothiazide/losartan, bisoprolol, piroxicam, and acetylsalicylic acid. The subject's previous treatment for the hypercholesterolemia included simvastatin.

The subject received the first dose atorvastatin and evolocumab on 29 June [redacted]. Approximately 11 months after the first dose of evolocumab, on 04 June one year after*, the subject was hospitalized for elective hemorrhoidectomy. Surgery was successfully performed without complications. The event of hemorrhoids was reported as resolved on 05 June one year after* and the subject was discharged from the hospital on the same date. The subject's last dose of evolocumab and atorvastatin prior to the event was on 31 May one year after* and 03 June one year after*, respectively. Evolocumab and atorvastatin were continued. The last dose of evolocumab in the study was on 26 July one year after* and the last dose of atorvastatin in the study was on 28 August one year after*.

The investigator reported that there was not a reasonable possibility that the event of hemorrhoids was related to the evolocumab, placebo or atorvastatin. The subject completed the study on 23 August one year after*.

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Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg (plus diet, atorvastatin 80 mg)
Report: Pulmonary embolism

Subject [redacted] was a 71-year-old white woman who was participating in Study 20110109 and developed pulmonary embolism. The subject's medical history included hypercholesterolemia, hypertension, hyperthyroidism, and neuralgia. The subject had a negative history of risk factors for pulmonary embolism.

Concomitant medications included acetylsalicylic acid/magnesium oxide, hydrochlorothiazide/ramipril, carvedilol, and levothyroxine. Previous treatment for hypercholesterolemia included simvastatin.

The subject received the first dose of evolocumab on 22 May [redacted], and atorvastatin on 04 April same year*. Both evolocumab and atorvastatin were discontinued on 14 August same year* at the subject's request. Approximately 9 months after the first dose of of evolocumab, on 14 March one year after*, the subject was hospitalized due to shortness of breath, dizziness, sweat, nearly syncope, and chest pain, and was diagnosed with pulmonary embolism. On the same day, laboratory test results revealed D-dimer of 1.60 ng/L which ranged from 1.2 ng/L to 2.5 ng/L over 2 weeks. A computerized tomogram of the thorax showed multiple pulmonary embolism in both lungs. An echocardiogram performed on 15 March two years after* revealed normal ejection fraction and no valvular abnormalities. An ultrasound of the lower extremities performed on 19 March one year after* showed no deep vein thrombosis. The subject did not have risk factors for pulmonary embolism. At baseline (22 May same year*), the subject had an international normalized ratio of 1.0 and prothrombin time of 11.1 seconds. Treatment for the event included warfarin and tinzaparin. The event pulmonary embolism was reported as resolved on 20 March one year after*, 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 17 July same year*, which was also her last dose in the study.

The investigator reported that there was no reasonable possibility that the event of pulmonary embolism was related to evolocumab. The subject completed the study on 27 May one year after*.

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Subject Narratives for Study 20110109: Adverse Events Leading to Discontinuation of Investigational Product

AMG 145 SC QM 420 MG

[redacted]
Subject [redacted] enrolled in study 20110109 was a 56 year old male diagnosed with hyperlipidemia. Subject received the first dose of 420mg AMG 145 on 24 April [redacted] and last dose on 19 June same year*. On 19 June same year* (day of last dose of AMG 145), the subject experienced grade 2 injection site erythema, grade 2 injection site pruritus, grade 2 injection site swelling and grade 2 injection site urticarial leading to withdrawal of AMG 145. Subject received cetirizine hydrochloride as treatment. The events resolved on the same day (19 June same year*). The subject's medical history included thalassaemia trait and insulin resistance. There was no relevant concomitant medication. On 19 June same year*, the subject discontinued AMG 145. The investigator reported the events as related to AMG 145.

[redacted]
Subject [redacted] enrolled in study 20110109 was a 59 year old female diagnosed with hyperlipidemia. Subject received the first dose of 420mg AMG 145 on 19 June [redacted] and last dose on 05 November same year*. On 24 November same year* (19 days after last dose of AMG 145), the subject experienced a grade 2 transient ischaemic attack leading to withdrawal of AMG 145. The event resolved on the same day (24 November same year*). There was no relevant medical history. Relevant concomitant medications included atorvastatin and pravastatin sodium. On 05 November same year*, the subject discontinued AMG 145. The investigator reported the event as unrelated to AMG 145.

[redacted]
Subject [redacted] enrolled in study 20110109 was a 61 year old male diagnosed with hyperlipidemia. Subject received the first dose of 420mg AMG 145 on 25 April [redacted] and last dose on 10 October same year*. On an unknown date in September same year*, the subject experienced grade 2 muscle spasms and grade 2 myalgia leading to withdrawal of AMG 145. Muscle spasms resolved on 20 December same year* and myalgia resolved on 15 December same year*. There was no relevant medical history. Relevant concomitant medication included atorvastatin. On 10 October same year*, the subject discontinued AMG 145. The investigator reported the events as unrelated to AMG 145.

[redacted]
Subject [redacted] enrolled in study 20110109 was a 64 year old female diagnosed with hyperlipidemia. Subject received the first and last dose of 420mg AMG 145 on 03 May [redacted]. On an unknown date in May same year*, the subject experienced a grade 2 migraine and grade 2 nervousness leading to discontinuation of AMG145. On 21 May same year* (18 days after last dose of AMG 145), the subject experienced a grade 1 skin odour abnormal leading to discontinuation of AMG 145. The subject received duloxetine hydrochloride for the treatment of nervousness. The events were continuing. The subject's medical history included migraine and nervousness. Relevant concomitant medication included atorvastatin. On 03 May same year*, the subject discontinued AMG 145. The investigator reported the events as unrelated to AMG 145.

[redacted]
Subject [redacted] enrolled in study 20110109 was a 73 year old female diagnosed with hyperlipidemia. Subject received the first dose of 420mg AMG 145 on 03 May [redacted] and last dose on 07 March one year after*. On 28 December same year* (240 days after first dose of AMG 145), the

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subject experienced a grade 2 dyspnoea leading to withdrawal of AMG 145. On 08 March one year after* (1 day after last dose of AMG 145), the subject experienced a grade 2 clear cell renal cell carcinoma leading to withdrawal of AMG 145. The event dyspnoea was continuing. The event renal cell carcinoma resolved on 21 April one year after*. There was no relevant medical history. Relevant concomitant medication included atorvastatin. On 07 March one year after*, the subject discontinued AMG 145. The investigator reported the events as unrelated to AMG 145.

[redacted]
Subject [redacted] enrolled in study 20110109 was a 62 year old female diagnosed with hyperlipidemia. Subject received the first dose of 420mg AMG 145 on 16 May [redacted] and last dose on 20 February one year after*. On 04 December same year* (203 days after first dose of AMG 145), the subject experienced a grade 1 myalgia leading to withdrawal of AMG 145. The event resolved on 16 March one year after*. There was no relevant medical history. Relevant concomitant medication included atorvastatin. On 20 February one year after*, the subject discontinued AMG 145. The investigator reported the event as unrelated to AMG 145.

[redacted]
Subject [redacted] enrolled in study 20110109 was a 61 year old female diagnosed with hyperlipidemia. Subject received the first dose of 420mg AMG 145 on 25 May [redacted] and last dose on 22 June same year*. On 13 July same year* (21 days after last dose of AMG 145), the subject experienced a grade 2 hepatic enzyme increased leading to withdrawal of AMG 145. The event resolved on 13 August same year*. The subject's medical history included myxoedema. Relevant concomitant medications included atorvastatin and venlafaxine hydrochloride. On 22 June same year*, the subject discontinued AMG 145. The investigator reported the event as related to AMG 145.

[redacted]
Subject [redacted] enrolled in study 20110109 was a 64 year old male diagnosed with hyperlipidemia. Subject received the first dose of 420mg AMG 145 on 21 May [redacted] and last dose on 10 August same year*. On 20 August same year* (10 days after last dose of AMG 145), the subject experienced a grade 2 supraventricular extrasystoles leading to withdrawal of AMG 145. The event was continuing. There was no relevant medical history. Relevant concomitant medication included atorvastatin. On 10 August same year*, the subject discontinued AMG 145. The investigator reported the event as unrelated to AMG 145.

[redacted] **SAE** [redacted]

[redacted] **SAE** [redacted]

[redacted]
Subject [redacted] enrolled in study 20110109 was a 46 year old female diagnosed with hyperlipidemia. Subject received the first dose of 420mg AMG 145 on 19 April [redacted] and last dose on 09 August same year*. On 11 August same year* (2 days after last dose of AMG 145), the subject experienced grade 2 chills and a grade 2 nausea leading to withdrawal of AMG 145. The events resolved on 25 August same year*. The subject's medical history included migraine and seasonal allergy. Relevant concomitant medication included atorvastatin. On 09 August same year*, the subject discontinued AMG 145. The investigator reported the events as related to AMG 145.

[redacted]
Subject [redacted] enrolled in study 20110109 was a 61 year old female diagnosed with hyperlipidemia. Subject received the first dose of 420mg AMG 145 on 09 May [redacted] and last

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dose on 06 June same year*. On 14 April same year* (prior to first dose of AMG145), subject experienced a grade 2 malaise and grade 2 myalgia leading to withdrawal of AMG 145. The events resolved on 18 June same year*. There was no relevant medical history. Relevant concomitant medication included atorvastatin. On 06 June same year*, the subject discontinued AMG 145. The investigator reported the events as unrelated to AMG 145.

PLACEBO

[redacted]
Subject [redacted] enrolled in study 20110109 was a 71 year old female diagnosed with hyperlipidemia. Subject received the first and last dose of placebo on 18 June [redacted]. On 31 May same year*, the subject experienced a grade 1 blood alkaline phosphate increased leading to withdrawal of placebo. On 09 June same year*, the subject experienced a grade 2 alanine aminotransferase increased and a grade 2 aspartate aminotransferase increased leading to withdrawal of placebo. The events resolved on 14 August same year*. There was no relevant medical history. Relevant concomitant medication included atorvastatin. On 18 June same year*, the subject discontinued placebo. The investigator reported the events as unrelated to placebo.

[redacted]
Subject [redacted] enrolled in study 20110109 was a 68 year old female diagnosed with hyperlipidemia. Subject received the first dose of placebo on 27 June [redacted] and last dose on 08 February one year after*. On 09 February one year after* (1 day after last dose of AMG 145), the subject experienced a grade 1 pruritus leading to withdrawal of placebo. The event resolved on 08 March one year after*. The subject's medical history included drug hypersensitivity. Relevant concomitant medications included atorvastatin and ezetimibe. On 08 February one year after*, the subject discontinued placebo. The investigator reported the event as unrelated to placebo.

[redacted]
Subject [redacted] enrolled in study 20110109 was a 58 year old female diagnosed with hyperlipidemia. Subject received the first dose of placebo on 23 May [redacted] and last dose on 15 August same year*. On 01 July same year* (40 days after first dose of AMG 145), the subject experienced a grade 2 nausea leading to withdrawal of placebo. On 15 July same year* (54 days after the first dose of AMG 145), the subject experienced a grade 2 headache leading to withdrawal of placebo. The subject received paracetamol for the treatment of headache. The events resolved on 26 September same year*. The subject's medical history included pernicious anaemia. Relevant concomitant medication included atorvastatin. On 15 August same year*, the subject discontinued placebo. The investigator reported the events as related to placebo.

[redacted]
Subject [redacted] enrolled in study 20110109 was a 64 year old female diagnosed with hyperlipidemia. Subject received the first dose of placebo on 14 May [redacted] and last dose on 02 October same year*. On 21 September same year* (131 days after first dose of placebo), the subject experienced a grade 3 polymyalgia rheumatic leading to withdrawal of placebo. The subject received prednisone and meloxicam for treatment. The event was continuing. There was no relevant medical history. Relevant concomitant medication included atorvastatin. On 02 October same year*, the subject discontinued placebo. The investigator reported the event as unrelated to placebo.

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2.7.6.21 20110231 試験

治験課題名：心血管系リスクの高い日本人高コレステロール血症患者を対象に安定した用量のスタチン併用下での evolocumab の忍容性及び LDL-C に対する有効性を評価する二重盲検無作為化プラセボ対照多施設共同試験

1. 試験デザイン及び計画の要約

1.1 治験責任医師

[redacted]医師、その他日本の 39 施設の医師

1.2 治験実施医療機関

[redacted]、その他 39 施設

1.3 治験期間

2012 年 7 月 10 日（最初の被験者の組入れ日）～[redacted]年[redacted]月[redacted]日（最後の被験者の最終来院日）

1.4 開発のフェーズ

第 II 相

1.5 目的

1.5.1 主要目的

心血管系リスクの高い日本人高コレステロール血症被験者を対象に、スタチン併用下で evolocumab を 2 週に 1 回（Q2W）又は 4 週に 1 回（Q4W）12 週間皮下（SC）投与したときの低比重リポ蛋白コレステロール（LDL-C）のベースラインからの変化率に対する効果をプラセボとの比較により評価する。

1.5.2 副次目的

- 心血管系リスクの高い日本人高コレステロール血症被験者を対象に、スタチン基礎療法併用下で evolocumab の 4 つの各用法・用量群において SC 投与したときの忍容性及び安全性をプラセボとの比較により評価する。
- 心血管系リスクの高い日本人高コレステロール血症被験者を対象に、スタチン基礎療法併用下で evolocumab を 12 週間 SC 投与したときの LDL-C の変化量、LDL-C の変化（LDL-C 70 mg/dL［1.8 mmol/L］未満）、及び非高比重リポ蛋白コレステロール（non-HDL-C）、超低比重リポ蛋白コレステロール（VLDL-C）、アポリポ蛋白 B（ApoB）、総コレステロール／高比重リポ

蛋白コレステロール（HDL-C）比、及びApoB／アポリポ蛋白A-1（ApoA1）比の変化率に対する効果をプラセボとの比較により評価する。

- スタチン投与中の心血管系リスクの高い日本人高コレステロール血症被験者を対象に、evolocumabをSC投与したときの薬物動態（PK）を明らかにする。

1.5.3 探索的目的

- 心血管系リスクの高い高コレステロール血症被験者を対象に、スタチン基礎療法併用下で4種の用法・用量でevolocumabをSC投与したときのLDL-C、VLDL-C、HDL-C、ApoA1、総コレステロール、non-HDL-C、ApoB、総コレステロール／HDL-C比、ApoB/ApoA1比、トリグリセリド、リポ蛋白（a）［Lp（a）］及び高感度C-反応性蛋白（hsCRP）の変化及び変化率への効果をプラセボとの比較により評価する。
- 新規及び確立された生化学的心血管及び脂質バイオマーカーとevolocumabの効果との関係を検討する。
- 任意でファーマコゲノミクス解析に同意した被験者を対象に、evolocumabに対する被験者の反応性を含む治験データと、プロ蛋白転換酵素サブチリシン／ケキシン9型（PCSK9）シグナル伝達、低比重リポ蛋白受容体の代謝回転、コレステロールの代謝、炎症及びプラークの安定性に関するマーカーの遺伝的変異との相関の可能性を検討する。
- evolocumabプログラム全体の探索的なで統合解析を含むevolocumab投与例における心血管系事象発現率を推定する。

1.6 治験方法

本試験はevolocumabの第II相、二重盲検、無作為化、プラセボ対照、多施設共同試験であり、被験者を以下の6つの投与群に1:1:1:1:1:1の割合で無作為に割り付けた。

- evolocumab 70又は140 mg SC Q2W
- evolocumab 280又は420 mg SC Q4W
- プラセボ SC Q2W又はQ4W

無作為化には、スクリーニング時のLDL-C値（130 mg/dL［3.4 mmol/L］未満又は130 mg/dL以上）及びヘテロ接合体性家族性高コレステロール血症（HeFH）（あり又はなし）を因子とする層別割り付けを用いた。

本試験は、スクリーニング・プラセボ導入期及び12週間の二重盲検投与期間の2期間で構成された。同意文書に署名後、空腹時脂質パラメータを含むスクリーニング時臨床検査を受けた適格被験者がプラセボ導入期に移行した。プラセボ導入期では、Q4Wの投与液量に相当するプラセボ2 mLが3回SC投与された。スクリーニング時の臨床検査で適格性が確認された場合、被験者は無作為割り付け及び投与開始のため、LDL-Cのスクリーニング検査後5～10日以内に治験実施施設に来院した。

evolocumab及びプラセボは盲検化され、治験担当医師、実施医療機関の職員、被験者及び治験チームは、データベースの盲検性が解除されるまで治験薬投与中の検査結果を知らされなかった。ま

た、本試験ではバイオマーカー用検体の採取を含め、治験審査委員会及び規制当局により承認された場合は、すべての被験者に対してファーマコゲノミクス解析への同意取得を依頼した。Q4W 投与を受けた被験者は、投与 12 週時点の来院をもって試験終了とした。Q2W 投与を受けた被験者は、安全性の追跡調査のために投与 14 週時点に実施医療機関からの連絡（電話等）をもって試験終了とした。

本試験では、独立臨床事象評価委員会による死亡及び特定の心血管系事象の判定に加え、独立データモニタリング委員会による蓄積データの正式な評価が行われた。

本試験の評価スケジュールを表 2.7.6.21-1 に、PK サブスタディの追加手順スケジュールを表 2.7.6.21-2 に示す。

表 2.7.6.21-1　評価スケジュール（全被験者）

Study Day/Time Point [a]	Screening and Placebo Run-in	D1	W2	W4	W6	W8	W10	W12[b]	W14 Phone Call[c]
General Procedures									
Informed consent	X								
Medical history	X								
Vital Signs (sitting BP, HR)	X	X	X	X	X	X	X	X	
Review for AEs/SAEs	X[d]	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	
Dietary instruction	X	X	X	X	X	X	X		
Physical exam	X							X	
Body height		X							
Body weight and waist circumference		X						X	
12 lead ECG	X	X		X		X	X	X	
Randomization		X[e]							
Central Laboratory									
Fasting lipids, ApoA1, ApoB	X[f]	X[f]	X	X	X	X	X	X[f]	
PK (evolocumab), PCSK9[g]	X	X	X	X	X	X	X	X	
Chemistry	X	X	X	X	X	X		X	
Hematology	X	X		X		X		X	
hsCRP, Lp(a)		X						X	
HbA1c	X							X	
TSH, eGFR, FSH[h]	X								
Biomarkers (blood)[i]		X	X	X				X	
Anti-evolocumab antibodies		X						X	
Serum pregnancy (females of childbearing potential)	X							X	
Urinalysis		X						X	
Investigational Product									
Placebo run-in	X								
IP administration, Q2W		X	X	X	X	X	X		
IP administration, Q4W		X		X		X			

AE = 有害事象、 ApoA1 = アポリポ蛋白 A-1、 ApoB = アポリポ蛋白 B 、BP = 血圧、D = 日、ECG =心電図、eGFR = 推算糸球体濾過量、FSH = 卵胞刺激ホルモン、HbA1c = グリコヘモグロビン、 HR = 心拍数、hsCRP 高感度 C-反応性蛋白、IP = 治験薬、Lp(a) = リポ蛋白(a)、PCSK9 = プロ蛋白転換酵素サブチリシン／ケキシン 9 型、PK = 薬物動態、Q2W =2 週 1 回、Q4W = 4 週 1 回、 SAE = 重篤な有害事象、TSH =甲状腺刺激ホルモン、 W = 週

[a] D1 = day of first administration of IP; a visit window of ± 3 days applied to all other visits.

[b] For subjects ending the study early, the week 12 procedures were performed at the time of terminating study participation if agreed to by the subject.

[c] Subjects on Q2W IP schedule only.

[d] Only SAEs and study-related AEs were collected during the screening period.

[e] Randomization occurred within 5 to 10 days of the screening LDL-C sample that determined eligibility.

[f] Includes LDL-C measurement by preparative ultracentrifugation.

[g] PK and PCSK9 samples were taken prior to IP administration, if applicable; screening samples and samples from subjects who did not receive evolocumab were not assayed for evolocumab.

[h] FSH only in women and if applicable.

[i] If the subject consented to pharmacogenetics analyses, DNA was extracted from some of the blood samples (eg, biomarker samples).

表 2.7.6.21-2　PK サブスタディにおける追加評価

試験日/時期[a]	スクリーニング及びプラセボ導入期	W9[b]	W11[b]
同意取得	X		
空腹時脂質、 ApoA1、 ApoB		X	X
薬物動態(evolocumab)、 PCSK9		X	X
バイタルサイン (座位血圧、心拍数)		X	X
有害事象/重篤な有害事象の評価		X	X
併用薬		X	X
12 誘導心電図		X	

ApoA1 = アポリポ蛋白 A-1、 ApoB = アポリポ蛋白 B 、PCSK9 =プロ蛋白転換酵素サブチリシン／ケキシン 9 型、W = 週

[a] D1 = 治験薬の初回投与日、その他の来院には± 3 日の来院日枠を適用した。

[b] 治験実施施設の追加来院日

1.7　被験者数

予定された被験者数は 300 例（evolocumab 群 200 例、プラセボ群 100 例）であり、本試験にて無作為割り付けが行われた症例は合計 310 例であった。

1.8　診断及び適格性の主な基準

本試験に組み入れ可能な被験者は、年齢 20 歳以上 80 歳以下、心血管系リスクの高い高コレステロール血症の日本人男女とした。更に被験者は、LDL-C のスクリーニング検査前 4 週間以上にわたって安定した用量で既承認スタチン投与を受けている（エゼチミブの併用にかかわらず）かつ空腹時 LDL-C が 115 mg/dL（3.0 mmol/L）以上で、空腹時トリグリセリドが 400 mg/dL（4.5 mmol/L）以下である者とした。

1.9　被験薬、用量及び投与方法

1.9.1　被験薬

evolocumab は Amgen 社が製造及び梱包を行い、Amgen 社及び治験国内管理人の治験薬配布手順に従って、日本語のラベルをつけて配布された。evolocumab は、無菌、無色澄明の凍結液としてバイアルに充填された上で供給された。内容物は、[redacted] mmol/L [redacted]、[redacted]%（w/v）[redacted]、[redacted]%（w/v）[redacted]で調製された pH [redacted] の evolocumab 70 mg/mL 溶液であり、1 mL が投与できるように充填されていた。各バイアルは単回使用とした。

evolocumab は、70 あるいは 140 mg Q2W 又は 280 あるいは 420 mg Q4W で SC 投与された。

1.9.2　対照薬

プラセボは無色澄明、無菌、蛋白を含まない凍結液として evolocumab と同じ容器に充填された上で供給された。内容物は、[redacted] mmol/L [redacted]、[redacted]%（w/v）[redacted]、[redacted]%（w/v）[redacted]で調製された pH [redacted] の溶液であった。

プラセボはQ2W又はQ4WでSC投与された。

1.10 投与期間

本試験ではスクリーニング・プラセボ導入期を最長6週間、投与期間を12週間とした。

1.11 治験の評価項目

1.11.1 主要評価項目

投与12週時点における超遠心法によるLDL-C（UC LDL-C）のベースラインからの変化率

1.11.2 副次評価項目

- 投与12週時点におけるLDL-Cのベースラインからの変化量
- 投与12週時点におけるLDL-Cの70 mg/dL（1.8 mmol/L）未満の変化
- 投与12週時点におけるnon-HDL-C、ApoB、VLDL-C、総コレステロール／HDL-C比及びApoB/ApoA1比のベースラインからの変化率

1.11.3 安全性評価項目

- 有害事象発現率
- 各規定来院時の臨床検査値及びバイタルサイン
- 各規定来院時の心電図パラメータ
- 抗evolocumab抗体（結合抗体及び中和抗体）産生の発現率

1.11.4 薬物動態学的評価項目

- 特定の時点の血清中非結合型evolocumab濃度
- 非結合型evolocumabのPK評価項目（最高血中濃度到達時間［t_{max}］、最高血中濃度［C_{max}］、投与8週時点から12週時点までの血清中濃度-時間曲線下面積［$AUC_{week8-12}$］）

1.11.5 探索的評価項目

- 以下の判定された事象の発現率：
  - 死亡（全死因、心血管系）
  - 心虚血事象（心筋梗塞、不安定狭心症のための入院、冠動脈の血行再建）
  - 心不全のための入院
  - 脳血管系事象（一過性脳虚血発作、脳卒中）
  - 冠動脈以外の血行再建
- 各規定来院時における以下の脂質パラメータのベースラインからの変化量及び変化率：
  - LDL-C
  - 総コレステロール

- non-HDL-C
- ApoB
- VLDL-C
- HDL-C
- ApoA1
- 総コレステロール／HDL-C 比
- ApoB/ApoA1 比
- トリグリセリド
- Lp（a）
- hsCRP

• 各規定来院時の PCSK9 濃度

1.12 統計手法

有効性及び安全性の解析は、最大の解析対象集団（FAS）を用いて実施した。FAS は、無作為化されたすべての被験者のうち、治験薬の投与を 1 回以上受けた症例による集団とした。被験者は無作為化された投与群の割り付けに従い、グループ分けされた。

主要評価項目の主解析のファミリー単位の過誤率（family-wise error rate）を 0.05 以下に制御するため、多重性の調整には、階層的逐次検定法を用いた。別途指定しない限り、ほかのすべての仮説検定は、有意水準 0.05 の両側検定とした。治療効果は、投与群と層別因子であるスクリーニング時 LDL-C 濃度をモデルに含めた共分散分析（ANCOVA）を用いて評価した。欠測値の補完には、last observation carried forward 法を用いた。FAS のうち、予定された治験薬の投与を遵守し、かつ、主要評価項目の値が欠測でない被験者からなる集団を Completer Analysis Set と定義し、同様の解析を行った。副次評価項目のベースラインからの変化及び変化率に関する解析は、主要評価項目の主解析と同様の方法で実施した。副次評価項目の投与 12 週時点の LDL-C の変化は、投与群及び層別因子であるスクリーニング時 LDL-C 濃度をモデルに含めたロジスティック回帰分析を用いて評価した。副次評価項目及びその他の主要評価項目以外の項目については、多重性の調整を行わなかった。

有害事象は、最新版の ICH 国際医薬用語集（MedDRA）バージョン 16.0 を用いてコード化した。治験中に発現した有害事象、重篤な有害事象及び治験薬投与と関連のある有害事象、並びに治験薬の投与中止に至った有害事象の発現率は、器官別大分類及び基本語別、無作為割り付けされた投与群別に集計した。

臨床検査パラメータ、心電図及びバイタルサインの測定結果は経時的に要約した。抗 evolocumab 抗体産生が認められた被験者の数及び割合を集計した。

2. 結果の要約

2.1 被験者の内訳

日本の 40 施設において、合計 310 例の被験者が無作為に割り付けられた。無作為化された 310 例のうち、3 例（同意撤回 2 例、医師判断 1 例）に治験薬は投与されなかった。307 例が evolocumab

の 4 群（70 mg Q2W 群：49 例、140 mg Q2W 群：52 例、280 mg Q4W 群：51 例、420 mg Q4W 群：53 例）、あるいはプラセボ群（52 例がプラセボ Q2W、50 例がプラセボ Q4W の投与）に無作為に割り付けられた。合計 307 例（99%）の被験者が治験薬の投与を受け、301 例（97.1%）が治験を完了した。治験薬の投与を受けた 307 例を有効性及び安全性評価項目の解析対象集団とした。計 297 例が Completer Analysis Set に用いられた。

無作為割り付けされた全被験者の内訳を表 2.7.6.21-3 に示す。

表 2.7.6.21-3　被験者の内訳及び投与中止理由（無作為割り付けされた全被験者）

	プラセボ		Evolocumab				
	Q2W (N = 52) n (%)	Q4W (N = 51) n (%)	70 mg Q2W (N = 50) n (%)	140 mg Q2W (N = 52) n (%)	280 mg Q4W (N = 52) n (%)	420 mg Q4W (N = 53) n (%)	合計 (N = 310) n (%)
治験薬の状況							
IP 投与を全く受けなかった被験者数	0 (0.0)	1 (2.0)	1 (2.0)	0 (0.0)	1 (1.9)	0 (0.0)	3 (1.0)
IP 投与を受けた被験者数	52 (100.0)	50 (98.0)	49 (98.0)	52 (100.0)	51 (98.1)	53 (100.0)	307 (99.0)
投与完了	51 (98.1)	50 (98.0)	46 (92.0)	49 (94.2)	51 (98.1)	50 (94.3)	297 (95.8)
投与中止	1 (1.9)	0 (0.0)	3 (6.0)	3 (5.8)	0 (0.0)	3 (5.7)	10 (3.2)
同意撤回	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.3)
有害事象	0 (0.0)	0 (0.0)	1 (2.0)	1 (1.9)	0 (0.0)	2 (3.8)	4 (1.3)
妊娠	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
死亡	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
被験者の希望	0 (0.0)	0 (0.0)	2 (4.0)	1 (1.9)	0 (0.0)	0 (0.0)	3 (1.0)
治験依頼者の判断	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
治験担当医師の判断	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
追跡不能	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
その他	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	2 (0.6)

スクリーニングした被験者数 452 例

N = 無作為割付けした被験者数、Q2W = 2 週 1 回、 Q4W = 4 週 1 回、 IP =治験薬

最初の被験者の組入れ日 2012 年 7 月 10 日

[redacted]

Source: Table 14-1.1.1.

表 2.7.6.21-3　被験者の内訳及び投与中止理由（無作為割り付けされた全被験者）（続き）

	プラセボ		Evolocumab				
	Q2W (N = 52) n (%)	Q4W (N = 51) n (%)	70 mg Q2W (N = 50) n (%)	140 mg Q2W (N = 52) n (%)	280 mg Q4W (N = 52) n (%)	420 mg Q4W (N = 53) n (%)	合計 (N = 310) n (%)
試験完了の状況							
試験を完了した被験者	52 (100.0)	50 (98.0)	47 (94.0)	50 (96.2)	51 (98.1)	51 (96.2)	301 (97.1)
試験を中止した被験者	0 (0.0)	1 (2.0)	3 (6.0)	2 (3.8)	1 (1.9)	2 (3.8)	9 (2.9)
同意撤回	0 (0.0)	1 (2.0)	3 (6.0)	1 (1.9)	0 (0.0)	1 (1.9)	6 (1.9)
死亡	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
治験中止	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
追跡不能	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
その他	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.9)	1 (1.9)	3 (1.0)

スクリーニングした被験者数 452 例

N = 無作為割付けした被験者数、Q2W = 2 週 1 回、 Q4W = 4 週 1 回、 IP =治験薬

最初の被験者の組入れ日 2012 年 7 月 10 日

[redacted]

Source: Table 14-1.1.1.

2.2　人口統計学的データ

試験対象集団の構成は、62.9%が男性、37.1%が女性であり、平均年齢（SD）は61.5（9.7）歳であった。すべての被験者（100%）が第一世代の日本人であった。治験薬の投与を受けた全被験者のベースライン時の人口統計学的データを表2.7.6.21-4に示す。おおむね群間のバランスは取れており、試験結果の解釈に影響を与えるようなベースライン時の人口統計学的データの偏りはないと考えられた。

表 2.7.6.21-4　ベースライン時の人口統計学的データ（治験薬の投与を受けた全被験者）

	プラセボ		Evolocumab				
	Q2W (N = 52)	Q4W (N = 50)	70 mg Q2W (N = 49)	140 mg Q2W (N = 52)	280 mg Q4W (N = 51)	420 mg Q4W (N = 53)	合計 (N = 307)
性別 - n (%)							
男性	36 (69.2)	36 (72.0)	25 (51.0)	32 (61.5)	28 (54.9)	36 (67.9)	193 (62.9)
女性	16 (30.8)	14 (28.0)	24 (49.0)	20 (38.5)	23 (45.1)	17 (32.1)	114 (37.1)
民族- n (%)							
ヒスパニック系又はラテン系	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
非ヒスパニック系又はラテン系	52 (100.0)	50 (100.0)	49 (100.0)	52 (100.0)	51 (100.0)	53 (100.0)	307 (100.0)
人種- n (%)							
アメリカンインディアン又はアラスカ先住民	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
アジア人	52 (100.0)	50 (100.0)	49 (100.0)	52 (100.0)	51 (100.0)	53 (100.0)	307 (100.0)
黒人又はアフリカ系アメリカ人	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ハワイ先住民又はその他太平洋諸島住民	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
白人	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
その他	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
混血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = 無作為割付けし投与した被験者数、Q1 = 25 パーセンタイル、Q3 = 75 パーセンタイル、Q2W = 2 週 1 回、Q4W = 4 週 1 回、SD = 標準偏差

[redacted]

Source: Table 14-2.2.1.

表 2.7.6.21-4　ベースライン時の人口統計学的データ（治験薬の投与を受けた全被験者）（続き）

	プラセボ		Evolocumab				
	Q2W (N = 52)	Q4W (N = 50)	70 mg Q2W (N = 49)	140 mg Q2W (N = 52)	280 mg Q4W (N = 51)	420 mg Q4W (N = 53)	合計 (N = 307)
日本人	52 (100.0)	50 (100.0)	49 (100.0)	52 (100.0)	51 (100.0)	53 (100.0)	307 (100.0)
年齢 (歳)							
n	52	50	49	52	51	53	307
平均	60.2	60.9	64.1	60.8	61.6	61.3	61.5
SD	10.1	9.8	9.7	9.2	9.6	9.9	9.7
中央値	61.0	62.5	64.0	62.0	63.0	62.0	63.0
Q1, Q3	54.0, 68.0	54.0, 68.0	57.0, 70.0	54.5, 68.0	56.0, 69.0	54.0, 69.0	55.0, 69.0
最小, 最大	25, 77	34, 76	38, 80	40, 79	31, 77	42, 78	25, 80

N =無作為割付けし投与した被験者数、Q1 = 25 パーセンタイル、Q3 = 75 パーセンタイル、Q2W = 2 週 1 回、Q4W = 4 週 1 回、SD = 標準偏差

[redacted]

Source: Table 14-2.2.1.

2.3　有効性の結果

2.3.1　投与 12 週時点における LDL-C のベースラインからの変化率

有効性の主要評価項目は、投与 12 週時点の UC LDL-C のベースラインからの変化率であった（表 2.7.6.21-5）。投与頻度が Q2W 及び Q4W のすべての evolocumab 群では、プラセボ群と比較して投与 12 週時点の UC LDL-C のベースラインからの変化率において、統計学的に有意な低下が認められた（$P < 0.001$）。プラセボ群に対する変化率の差は、evolocumab Q2W 群で 53%（70 mg）及び 69%（140 mg）であり、evolocumab Q4W 群で 58%（280 mg）及び 64%（420 mg）であった。投与 12 週時点の UC LDL-C のベースラインからの変化率の最小二乗平均（LSM）（SE）は、プラセボ Q2W 群の 3%（2%）に対して、evolocumab Q2W 群の 70 mg で 56%（2%）、140 mg で 71%（2%）であった。また、投与 12 週時点の UC LDL-C のベースラインからの変化率の LSM（SE）は、プラセボ Q4W 群で 0.05%（2%）の上昇が認められたのに対し、evolocumab 群では 280 mg で 58%（2%）、420 mg で 64%（2%）の低下が認められた。

LDL-C の低下は投与期間の早期（開始 2 週の初回観察）から認められ、治験期間全体にわたって維持された（最終投与は Q2W が 10 週、Q4W が 8 週であった）（図 2.7.6.21-1）。Q2W 投与では、140 mg が 70 mg と比較して LDL-C 低下作用が大きかった。Q4W 投与では、420 mg が 280 mg と比較して LDL-C 低下作用が大きかった。

表 2.7.6.21-5　投与 12 週時点の UC LDL-C のベースラインからの変化率、絶対値及びベースラインからの変化量の主要解析（FAS）

	Evolocumab Q2W vs. プラセボ Q2W			Evolocumab Q4W vs. プラセボ Q4W		
		Evolocumab			Evolocumab	
	プラセボ (N=52)	70 mg (N=49)	140 mg (N=52)	プラセボ (N=50)	280 mg (N=51)	420 mg (N=53)
ベースライン (mg/dL)						
n	52	49	52	50	51	53
平均	144.4	143.6	140.7	141.8	141.0	139.7
SD	18.1	20.6	23.3	23.4	21.2	18.8
Week 12 (mg/dL)[c]						
n	50	48	51	49	51	52
平均	140.6	64.5	40.5	141.5	59.6	51.2
SD	20.3	30.8	19.8	28.4	19.9	27.8
ベースラインから Week 12 の変化量 (mg/dL)[c]						
n	50	48	51	49	51	52
平均	-3.5	-79.0	-99.6	-0.4	-81.4	-88.8
SD	17.5	29.6	26.9	23.0	21.5	25.9
ベースラインから Week 12 の変化率(%)						
要約統計						
n	52	49	52	50	51	53
平均	-2.39	-55.20	-71.00	0.36	-57.70	-63.54
SD	12.23	19.32	13.36	16.75	12.13	18.64
SE	1.70	2.76	1.85	2.37	1.70	2.56
中央値	-3.34	-58.60	-71.24	-0.60	-57.77	-65.71
Q1, Q3	-11.20, 5.28	-67.16, -49.60	-79.45, -66.26	-12.22, 8.79	-65.11, -52.41	-75.59, -56.03
最小, 最大	-24.9, 23.8	-82.3, 45.2	-92.0, -25.1	-37.3, 54.8	-79.6, -15.1	-85.3, 24.3
L.S. 平均[a]						
推定	-2.71	-55.56	-71.32	0.05	-58.10	-63.89
SE	2.16	2.23	2.16	2.32	2.33	2.27
95% CI	(-6.98, 1.56)	(-59.97, -51.14)	(-75.59, -67.05)	(-4.54, 4.65)	(-62.71, -53.50)	(-68.38, -59.40)
治療差[b]						
推定	-	-52.85	-68.61	-	-58.16	-63.94
SE	-	3.03	2.99	-	3.21	3.18
95% CI	(-, -)	(-58.84, -46.86)	(-74.51, -62.71)	(-, -)	(-64.51, -51.81)	(-70.23, -57.66)
p-値	-	<0.001	<0.001	-	<0.001	<0.001

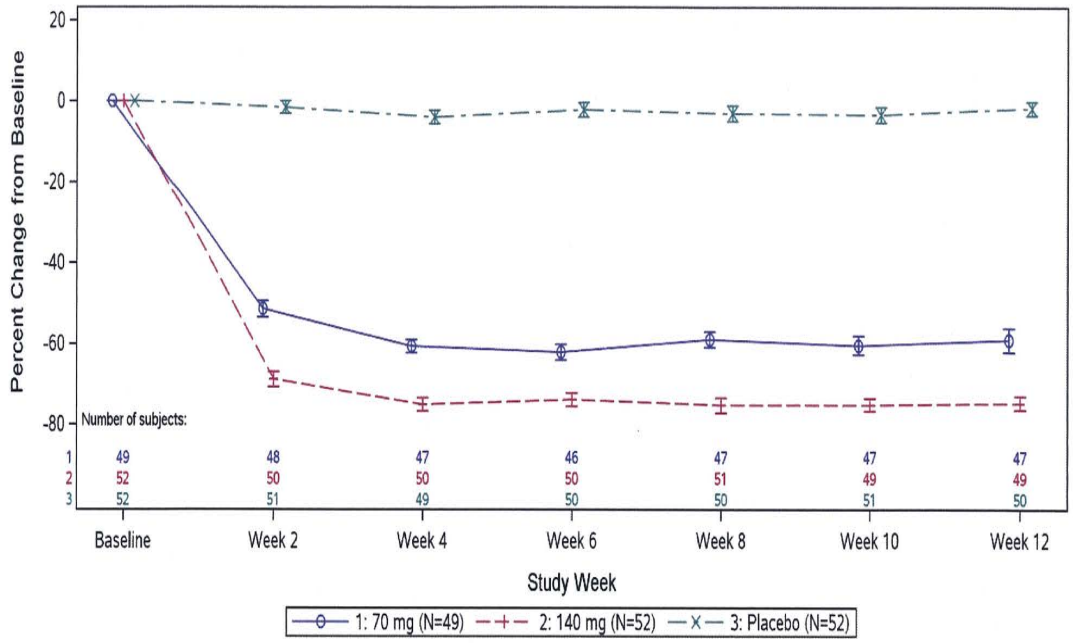
CI = 信頼区間、L.S.平均 =最小二乗平均、N = 無作為割付し投与した被験者数、 Q1 =25 パーセンタイル、 Q3 = 75 パーセンタイル、 Q2W = 2 週 1 回、Q4W = 4 週 1 回、SE =標準誤差

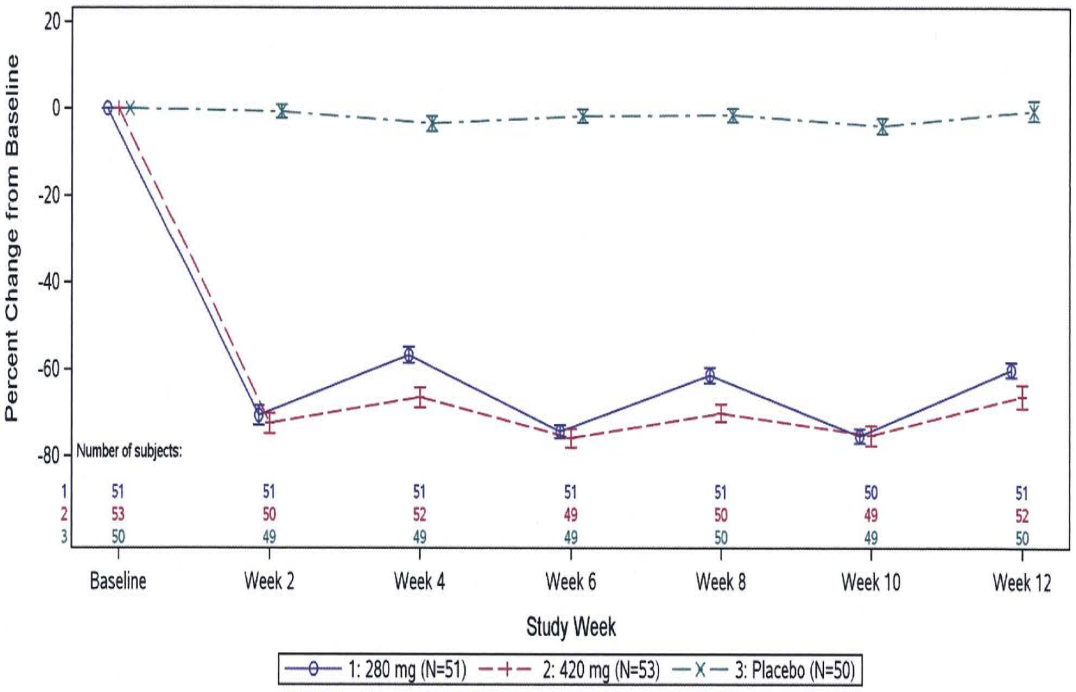
[a] 投与群及びスクリーニング時の LDL-C（IVRS）の層別化因子を共変量とした ANCOVA モデルからの最小二乗平均 week 12 の超遠心法 (UC) LDL-C の欠測値は、Last Observation Carried Forward（LOCF）法を用い LDL-C を算出し補完した。

[b] 各投与頻度群内の治療差は、同じ群のプラセボを参照として用いた。

[c] week 12 の超遠心法(UC) LDL-C 欠測値は、Last Observation Carried Forward（LOCF）法を用い補完した。

Modified from table Table 14-4.1.1. of S20110231 and Table 150825c02-4.1.3





N = 無作為割付けし投与した被験者数、Q2W = 2 週 1 回、Q4W =4 週 1 回
縦線は平均と標準誤差を示す。プロットは観察データに基づき欠測値は補完していない。
Source: Figure 14-4.23.1 and Figure 14-4.23.2

図 2.7.6.21-1　規定来院時並びに Q2W（上図）及び Q4W（下図）投与群ごとの LDL-C のベースラインからの平均変化率

主要評価項目へのevolocumabの効果は、事前に規定していたすべての感度分析（層別因子であるHeFHをモデルに含めた共分散分析、on-treatment analysis［早期中止例について、投与中、もしくはQ2W群では中止後14日、Q4W群では中止後28日までに測定された欠測でないLDL-Cの値にて欠測値を補完し実施した解析］、反復測定モデル及びノンパラメトリック解析）において、頑健であった。サブグループ解析でも、evolocumabのQ2W及びQ4Wのそれぞれの投与頻度において、プラセボに対し低下を示した。被験者背景因子を共変量としてモデルに含めた解析の結果も主要な解析結果と一貫していた。用量反応に関して、Q2W投与では140 mgが70 mgと比較して大きなLDL-Cの低下を示した。Q4W投与では420 mgが280 mgと比較して大きなLDL-Cの低下を示した。

2.3.2　有効性の副次評価項目

evolocumab 70 mg群でのHDL-C及びApoA1のベースラインからの変化率を除き、副次評価項目及び重要な脂質パラメータにおいて、統計学的に有意な変化が認められた。evolocumab群の被験者は、プラセボ群の被験者と比較して投与12週時点でのLDL-C 70 mg/dL未満の達成率が高かった（$P < 0.001$）。プラセボ群には、投与12週時点でLDL-C 70 mg/dL未満に達成した被験者はいなかった。用量反応性に関しては、有効性の各副次評価項目における低下は、有効性の主要評価項目の結果とおおむね一致しており、Q2W投与では、140 mgは70 mgと比較して大きな低下を示した。Q4W投与では、420 mgは280 mgと比較して大きな低下を示した。表2.7.6.21-6に投与12週時点での重要な脂質パラメータ及びPCSK9におけるプラセボとの群間差（推定値）の要約を示す。

表 2.7.6.21-6　投与 12 週時点での重要な脂質パラメータ及び PCSK9 のプラセボとの群間差（推定値）の要約（FAS）

	Evolocumab Q2W vs プラセボ Q2W		Evolocumab Q4W vs プラセボ Q4W	
脂質項目	Evolocumab 70 mg (N = 49)	Evolocumab 140 mg (N = 52)	Evolocumab 280 mg (N = 51)	Evolocumab 420 mg (N = 53)
ベースラインから Week 12 の絶対変化量 [a]				
UC LDL-C (mg/dL) [b]	-75.5	-96.3	-80.7	-88.2
95% CI	(-85.4, -65.5)	(-106.0, -86.5)	(-90.0, -71.4)	(-97.4, -79.0)
p-値	<0.001	<0.001	<0.001	<0.001
UC LDL-C (mmol/L) [b]	-1.951	-2.489	-2.087	-2.280
95% CI	(-2.208, -1.695)	(-2.742, -2.237)	(-2.327, -1.848)	(-2.519, -2.042)
p-値	<0.001	<0.001	<0.001	<0.001
Week 12 に LDL-C< 70 mg/dL を達成				
UC LDL-C [b,c]	31 (66,0)	48 (6.0)	41 (80.4)	42 (82.4)
p-値	<0.001	<0.001	<0.001	<0.001
ベースラインから Week 12 の変化率(%)[a]				
ApoB[b]	-46.75	-60.69	-47.37	-53.44
95% CI	(-51.80, -41.70)	(-65.67, -55.72)	(-52.90, -41.85)	(-58.91, -47.97)
p-値	<0.001	<0.001	<0.001	<0.001
総コレステロール	-36.19	-45.31	-36.29	-40.15
95% CI	(-40.46, -31.93)	(-49.51, -41.11)	(-40.83, -31.75)	(-44.65, -35.65)
p-値	<0.001	<0.001	<0.001	<0.001
非 HDL-C[b]	-49.46	-62.56	-53.54	-58.08
95% CI	(-54.83, -44.08)	(-67.85, -57.27)	(-59.46, -47.63)	(-63.93, -52.22)
p-値	<0.001	<0.001	<0.001	<0.001
HDL-C	4.42	9.06	16.28	13.23
95% CI	(-1.88, 10.71)	(2.86, 15.27)	(10.13, 22.42)	(7.14, 19.31)
p-値	0.17	0.004	<0.001	<0.001
ApoA1	3.96	6.26	9.26	9.56
95% CI	(-0.77, 8.68)	(1.60, 10.91)	(4.91, 13.62)	(5.25, 13.87)
p-値	0.100	0.009	<0.001	<0.001
トリグリセリド	-14.31	-16.56	-17.14	-20.17
95% CI	(-26.77, -1.85)	(-28.83, -4.29)	(-29.88, -4.39)	(-32.79, -7.56)
p-値	0.025	0.009	0.009	0.002
VLDL-C[b]	-24.25	-34.49	-20.82	-29.82
95% CI	(-47.83, -0.68)	(-57.71, -11.26)	(-39.41, -2.22)	(-48.32, -11.32)
p-値	0.044	0.004	0.028	0.002
Lp(a)	-41.54	-50.62	-39.59	-32.33
95% CI	(-51.31, -31.77)	(-60.29, -40.95)	(-49.35, -29.83)	(-41.99, -22.67)
p-値	<0.001	<0.001	<0.001	<0.001

脚注は表最終ページに示した。

表 2.7.6.21-6　投与 12 週時点での重要な脂質パラメータ及び PCSK9 のプラセボとの群間差（推定値）の要約（FAS）（続き）

	Evolocumab Q2W vs プラセボ Q2W		Evolocumab Q4W vs プラセボ Q4W	
脂質項目	Evolocumab 70 mg (N = 49)	Evolocumab 140 mg (N = 52)	Evolocumab 280 mg (N = 51)	Evolocumab 420 mg (N = 53)
Week 12 のベースラインからの変化率 (%)				
総 Chol/HDL-C[b]	-37.22	-46.98	-45.30	-46.66
95% CI	(-42.52, -31.91)	(-52.21, -41.76)	(-51.02, -39.58)	(-52.32, -41.00)
p-値	<0.001	<0.001	<0.001	<0.001
ApoB/ApoA1[b]	-47.53	-61.35	-52.22	-57.75
95% CI	(-53.41, -41.65)	(-67.14, -55.56)	(-58.27, -46.18)	(-63.73, -51.77)
p-値	<0.001	<0.001	<0.001	<0.001
Week 12 の測定値 (ng/mL)[d]				
PCSK9	-246.6	-330.2	-151.2	-192.7
95% CI	(-290.1, -203.2)	(-373.0, -287.4)	(-196.2, -106.3)	(-237.2, -148.2)
p-値	<0.001	<0.001	<0.001	<0.001

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ApoA1 = アポリポ蛋白 A-1、ApoB = アポリポ蛋白 B、CI = 信頼区間、HDL-C=高比重リポ蛋白コレステロール、Lp(a) = リポ蛋白(a)、N = 無作為割付けし投与した被験者数、non-HDL-C =非高比重リポ蛋白コレステロール、PCSK9 = プロ蛋白転換酵素サブチリシン／ケキシン 9 型、Q2W = 2 週 1 回、Q4W = 4 週 1 回、総 Chol = 総コレステロール、UC LDL-C =超遠心法低比重リポ蛋白コレステロール、VLDL-C =超低比重リポ蛋白コレステロール

各投与頻度群内の治療差は、同じ群のプラセボを参照として用いた。

[a] 投与群及びスクリーニング時の LDL-C（IVRS）の層別化因子を共変量とした ANCOVA モデルからの最小二乗平均

[b] 副次有効性評価項目として特定

[c] 各投与群の測定値のある無作為割付けし投与した被験者のうち week 12 に LDL-C< 70 mg/dL を達成した被験者数及び割合。いずれのプラセボ群も LDL-C< 70 mg/dL を達成した被験者はいない。投与頻度投与群各々及び LDL-C 値の層別化因子を含むロジスティック回帰モデル。ノンレスポンダーを補完したプラセボと比較したロジスティック回帰モデルの P-値。

[d] PCSK9 の治療差のマイナスは、evolocumab 群と比較したときプラセボ群での高い PCSK9 値を示す。

Source: Modified from Table 14-4.9.1 (LDL-C thresholds), Table 14-4.9.2 (LDL-C response < 70 mg/dL), Table 14-4.10.1 (absolute change in UC LDL-C [mg/dL]), Table 14-4.10.3 (absolute change in UC LDL-C [mmol/L]), Table 14-4.11.1 (total cholesterol), Table 14-4.12.1 (HDL-C), Table 14-4.13.1 (triglycerides), Table 14-4.14.1 (VLDL-C), Table 14-4.15.1 (ApoB), Table 14-4.16.1 (ApoA1), Table 14-4.17.1 (non-HDL-C), Table 14-4.18.1 (total cholesterol/HDL-C ratio), Table 14-4.19.1 (ApoB/ApoA1 ratio), Table 14-4.20.1 (Lp[a]), and Table 14-4.21.1 (PCSK9)

2.3.3　有効性の探索的評価項目

有効性の探索的評価項目は、臨床評価項目である死亡（全死因、心血管系）、心筋梗塞（致死性、非致死性）、不安定狭心症のための入院、血行再建、脳血管系事象（一過性脳虚血発作、脳卒中）、心不全のための入院及び筋肉関連事象と判定された被験者の頻度であった。明確に判定された事象は被験者 3 例に認められた。内訳は、evolocumab 70 mg Q2W 群で 1 例（ミオパチー）、プラセボ群で 2 例（いずれも経皮的冠動脈インターベンション）であった。

2.4　薬物動態の結果

Q2W 及び Q4W の投与頻度に割り付けられた各用法・用量群の平均血清中非結合 evolocumab 濃度-時間推移曲線を図 2.7.6.21-2 に示す。evolocumab の最高血中濃度は用量の増加とともに上昇した。また、治験全体を通して、2 週間に 1 回の検体採取を実施したことにより、投与頻度別に想定されたとおりの、投与間の最高濃度から最低濃度への変化が認められた。

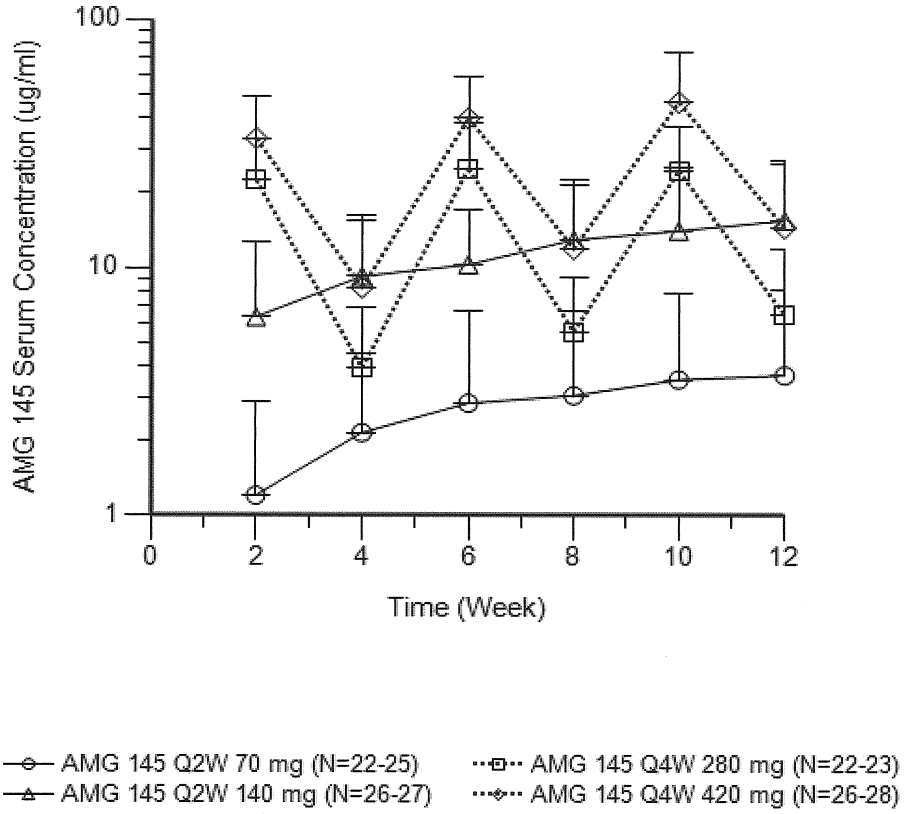
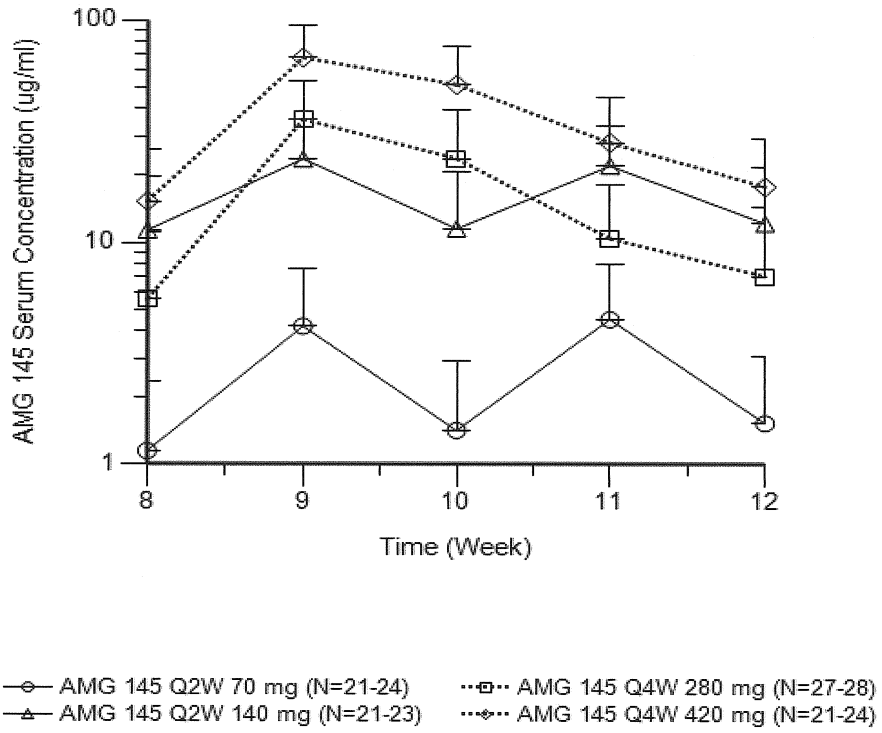


図 2.7.6.21-2　心血管系リスクの高い高コレステロール血症の日本人被験者に evolocumab を SC 投与した際の PK 解析対象集団における平均血清中 evolocumab 濃度（＋標準偏差）- 時間推移曲線

evolocumab サブスタディにおける PK

148 例の被験者が PK サブスタディに登録された。evolocumab 濃度はプラセボ群の被験者では分析せず、実薬の投与を受けた残りの 99 例の被験者について血清中非結合 evolocumab 濃度を測定した。evolocumab の PK パラメータは、これらの 99 例中 82 例（83%）について推定された。解析からの除外例（17%）は、欠測値があるか、治験期間に投与が行われなかった又は治験期間全体を通して evolocumab 濃度が定量下限未満（BQL）であった。PK サブスタディで観察された evolocumab 濃度は治験全体の結果と一致していた。Q2W 及び Q4W 投与に割り付けられた各用法・用量群の平均血清中非結合 evolocumab 濃度-時間推移曲線を図 2.7.6.21-3 に、PK パラメータの平均値の要約を表 2.7.6.21-7 に示す。evolocumab の最高血清中濃度は用量の増加とともに上昇した。また、PK サブスタディにおいて週 1 回の検体採取を実施したことにより、投与頻度別に想定されたとおりの、投与間の最高濃度から最低濃度への変化が認められた。70 mg Q2W SC 投与時の evolocumab の t_{max} 中央値は最終投与（10 週）後 5 日で、その他のすべての用量群では投与 1 週間後に相当する 7 日であった（表 2.7.6.21-7）。この結果はほかの第 I 相及び第 II 相試験の結果と一致した。平均 C_{max} は同一の用法（投与頻度）群内において、用量に依存した上昇が認められた。また、evolocumab の $AUC_{week8-12}$ も用量依存的に増加した。70 mg Q2W と 140 mg Q2W の投与を比較したところ、血清中

（非結合型）evolocumab AUC に用量比以上の増加が認められた（用量が 2 倍増加すると AUC が 4.4 倍増加した）。しかしながら、$AUC_{week8-12}$ 及び血清中 evolocumab 濃度-時間推移曲線からは、140 mg 以上の用量では、PK はおおよそ線形であった。



[redacted]

図 2.7.6.21-3　PK サブスタディ被験者：心血管系リスクの高い高コレステロール血症の日本人被験者に evolocumab を SC 投与した際の平均血清中 evolocumab 濃度（＋標準偏差） - 時間推移曲線