The subject received the first dose of blinded investigational product AMG 145 vs placebo for hypercholesterolemia on 08/Sep/[redacted]. Reportedly, the subject was evaluated due to recurrent angina symptoms. On 08/Oct/same year*, the subject underwent cardiac catheterization; which revealed two vessel disease (LAD disease and ostial PDA disease) with normal ejection fraction. On 25/Oct/same year*, a pulmonary function test revealed no evidence of fixed obstructive or restrictive lung disease. There was normal diffusion and evidence of hyperreactive airway based on improvement in FEV-1 after bronchodilators. Laboratory tests performed on 31/Oct/same year* revealed hemoglobin A1c of 0.5. A blood gasometry on room air showed a pH of 7.376, partial pressure of carbon dioxide of 50, partial pressure of oxygen of 82, bicarbonate of 30.2, and a saturation of 96%. An electrocardiogram showed normal sinus rhythm with 85 beats per minute. On a chest x-ray no acute cardiopulmonary disease was identified. A urine culture was mixed with colony count of 10,000 to 50,000 colony forming units per ml .and a methicillin-resistant Staphylococcus aureus screen was negative. Approximately two months after initiation of first dose, on 02/Nov/same year*, the subject was hospitalized and underwent elective coronary artery bypass (CABG) surgery. The procedure involved graft of left internal mammary artery to left anterior descending, saphenous graft to diagonal, and saphenous graft to posterior descending artery. There was also an endoscopic vein harvest of the left leg to just below the knee. Surgery and postsurgical period were uncomplicated. Laboratory data, on 02/Nov/same year*, showed calcium of 1.34, sodium of 128, potassium of 3.6, chloride of 107, carbon dioxide of 28.7, glucose of 68, urea of 11, creatinine of 0.78, magnesium of 1.8, prothrombin time of 12.0, international normalized ratio 1.1, partial thromboplastin time of 27.5, white blood cell count of 6.6, hemoglobin of 8.7, hematocrit 24.8, and platelet count of 108. Of the white blood cells 76% were neutrophils, 12% were lymphocytes, and 9% were monocytes. A blood gasometry revealed pH of 7.386, partial pressure of carbon dioxide of 40, partial pressure of oxygen of 123, bicarbonate of 24, saturation 99% and base excess of -1. A chest x-ray revealed median sternotomy for CABG in the interval. Mild atelectatic changes likely left lung base and no pneumothorax was evident. Treatment included nitroglycerin, nicardipine, propofol, cefazolin, Cipro (ciprofloxacin), vancomycin, levofloxacin, albuterol, Atrovent (ipratropium bromide), pantoprazole, insulin, fluids, electrolytes, and nutrition (nothing by mouth). The final diagnosis was revascularization without acute ischemic event. The subject was discharged from the hospital on 06/Nov/same year*, however the event was reported to have resolved until 21/Nov/same year*. The subjects last dose of blinded investigational drug prior to the event was on 27/Oct/same year*. Blinded investigational product was continued.

The investigator reported that there was no reasonable possibility that the event coronary artery bypss graft was related to the blinded investigational drug.

Product : AMG 145 vs placebo

Study Drug Administred : Yes

Case Number	Study ID	Patient ID	Center ID	Related Case	Death Case	Death Date	Dose	Patient Route of Administration	Frequency	Last Dose
[redacted]	20101155	[redacted]	[redacted]	No	No	---	---	---	---	---

SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
Cellulitis L foot	Cellulitis (Cellulitis of foot)	01-JAN-one year after*---

Case Narrative : This 70 year old white female was participating in a phase 2, randomized, double-blind, placebo and active controlled, dose-ranging, multiple-dose, parallel-group study to evaluate the LDL-C lowering properties of AMG 145, compared to placebo and ezetimibe when used as add-on therapy in dyslipidemic subjects and developed cellulitis L foot.

The subject's medical history included hypercholesterolemia, elective corrective surgery for left foot deformity on 16/Nov/same year*, bronchiectasis, right lower

lobe atelectasis, hypertension, osteoarthritis, osteoporosis and gastroesophageal reflux disease. Previous treatment for the condition under study and ongoing medications included Zetia (ezetimibe) and lovastatin. Additional concomitant medication included prednisone, Norco (hydrocodone bitartrate/paracetamol), levofloxacin, Zofran (ondansetron), hydrochlorothiazide w/triamterene, Nexium (esomeprazole magnesium), Advair (fluticasone propionate/salmeterol xinafoate), Albuterol (salbutamol), gabapentin, clonazepam, multivitamins, cholecalciferol, and prednisolone.

The subject received the first dose of blinded investigational product AMG 145 vs placebo for hypercholesterolemia on 06/Dec/[redacted]. Approximately one month later, on 01/Jan/one year after*, the subject was admitted to the hospital for left foot cellulitis and systemic inflammatory response syndrome due to cellulitis. The subject noted redness and purulent discharge from the left foot site surgery, which was carried out previously on 16/Nov/same year*. Upon admission, laboratory data disclosed lactic acid of 3.1 mmol/L and white blood cell (WBC) count of 13.5 K/uL. On 02/Jan/one year after*, lactic acid of 1.2 mmol/L and WBC count of 7.1 K/uL. On 03/Jan/one year after*, vital signs were body temperature of 36, heart rate of 61, respiratory rate of 18, blood pressure of 161/94 and oxygen saturation of 99 % on room air. Repeat laboratory data disclosed WBC count of 10.3 K/uL. X-ray of the ankle showed osteoarthritis, left ankle joint, evidence of subtalar and talonavicular as well as the calcaneocuboid arthrodesis with hardware. Diffuse soft tissue swelling without evidence of free air. Wound and blood cultures were negative. Treatment medications included vancomycin, Zosyn (piperacillin/tazobactam) and enoxaparin. Her swelling as well as the redness of the left foot improved. The event was reported as resolving and the subject was discharged from the hospital on 03/Jan/one year after* with Levaquin treatment. The subject's last dose of blinded investigational product was on 06/Dec/same year*, administered monthly. Blinded investigational product was continued.

The investigator reported that there was no a reasonable possibility that the event cellulitis L foot was related to the blinded investigational product.

ADDITIONAL INFORMATION RECEIVED ON 22/FEB/one year after*: The event of cellulitis L foot was reported to end on 24/Jan/one year after*.

ADDITIONAL INFORMATION RECEIVED ON: 11/APR/one year after*: On 01/Jan/one year after*, blood culture showed no growth after one day of incubation. On 02/Jan/one year after*, wound and tissue culture showed no growth and no organisms were seen. Methicillin resistant Staphylococcus aureus (MRSA) test showed no growth and there was no isolation of MRSA.

Product : AMG 145 vs placebo Study Drug Administred : Yes

Case Number	Study ID	Patient ID	Center ID	Related Case	Death Case	Death Date	Dose	Patient Route of Administration	Frequency	Last Dose
[redacted]	20101155	[redacted]	[redacted]	No	No	---	---	---	---	---

SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
Pneumonia	Pneumonia (Pneumonia)	24-DEC-same year*---

Case Narrative : This 70 year old White female was participating in a phase 2, randomized, double-blind, placebo and active controlled, dose-ranging, multiple-dose, parallel-group study to evaluate the LDL-C lowering properties of AMG 145, compared to placebo and ezetimibe when used as add-on therapy in dyslipidemic subjects and developed pneumonia.

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The subject's medical history included hypercholesterolemia, chronic obstructive pulmonary disease, bronchiectasis, asthma, aspergillosis, gastroesophageal reflux disease, hypertension, transient ischemic attack and left ankle surgery. Previous treatment for the condition under study and ongoing medications included Zetia (ezetimibe) and Crestor (rosuvastatin calcium). Additional concomitant medications included Norco (hydrocodone bitartrate, paracetamol), Maxzide (hydrochlorothiazide, triamterene), Nexium (esomeprazole magnesium), Advair (fluticasone propionate, salmeterol xinafoate), Albuterol (salbutamol), Fosamax (alendronate sodium), Neurontin (gabapentin), Klonopin (clonazepam), Multivitamin (ascorbic acid, calcium pantothenate, ergocalciferol, nicotinamide, pyridoxine hydrochloride, retinol, riboflavin, thiamine hydrochloride) and ergocalciferol .

The subject received the first dose of blinded investigational study drug AMG 145 for hypercholesterolemia on 07/Dec/[redacted]. Approximately 17 days later, on 24/Dec/same year*, the subject developed pneumonia. On 28/Dec/same year*, the subject was admitted to the hospital due to suspected pneumonia with fever, shortness of breath, productive cough, nausea and pleuritic chest pain. Vital signs revealed blood pressure 149/76, body temperature 36.4, heart rate 65 /min, oxygen saturation 96 % and respiratory rate 16 /min. Laboratory tests revealed potassium of 3.0 mmol/l and white blood cell count of 16.5 k/uL. A chest x-ray showed minimal subsegmental atelectasis B base. The subject was started on Solu-Medrol (methylprednisolone sodium succinate), prednisone, enoxaparin, levofloxacin, ceftriaxone, azithromycin, vancomycin, doripenem and potassium chloride. On 30/Dec/same year*, repeated lab tests showed potassium of 4.5 mmol/l and white blood cell count of 10.0 k/uL. A chest x-ray revealed partial clearing of subsegmental atelectasis. No further information was provided at the time of this report. The subject was discharged on 31/Dec/same year* and the event was reported as resolving and still being treated at the time of this report. Reportedly, hypokalemia was also noted and resolved by discharge. The subject received the last dose of blinded investigational product prior to the event on 07/Dec/same year* administered subcutaneously every 4 weeks. The blinded investigational product was continued.

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

Product : AMG 145 vs placebo

Study Drug Administred : Yes

Case Number	Study ID	Patient ID	Center ID	Related Case	Death Case	Death Date	Dose	Patient Route of Administration	Frequency	Last Dose
[redacted]	20101155	[redacted]	[redacted]	No	Yes		UNK UNK, q2wk	Subcutaneous	q2wk	22-NOV-same year*

SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
congestive heart failure	Cardiac failure congestive (Congestive heart failure)	22-NOV-same year* (1 day)
pneumonia	Pneumonia (Pneumonia)	22-NOV-same year* (1 day)

Case Narrative : This 65 year old Black male subject was participating in a double-blind, randomized, placebo-controlled, multicenter, dose-ranging study to evaluate tolerability and efficacy of AMG 145 on LDL-C in combination with HMG-CoA reductase inhibitors in hypercholesterolemic subjects and experienced fatal congestive heart failure and fatal pneumonia.

The subjects medical history provided by the investigator included hypercholesterolemia, coronary artery disease, angina, myocardial infarction, percutaneous coronary intervention, peripheral artery disease, congestive heart failure NYHA class II with left ventricular systolic function of 34%, hypertension, bronchial asthma, chronic obstructive pulmonary disease, dyslipidemia, right shoulder arthritis, depression and was a smoker. Additionally, the subject had family history of coronary artery disease. Previous treatment for the condition under study included pravastatin. Concomitant medications included furosemide, metoprolol, Wellbutrin XR (bupropion hydrochloride), carvedilol, amiodarone, Nitroglycerin (glyceryl trinitrate), benazepril hydrochloride, losartan, isosorbide, Plavix (clopidogrel bisulfate), Aspirin (acetylsalicylic acid), Combivent (ipratropium bromide, salbutamol sulfate), Advair (fluticasone propionate, salmeterol xinafoate), ProAir (fluticasone propionate) and simvastatin.

The subject received the first dose of blinded investigational product AMG 145 vs placebo for hypercholesterolemia on 14/Sep/[redacted]. Baseline vital signs were blood pressure at 135/90 and heart rate of 59. On 10/Nov/same year*, laboratory tests disclosed albumin of 3.2 g/dL, creatine phosphokinase of 101 U/L, creatinine of 2.5 mg/dl, glucose of 123 mg/dl, urea of 25 mg/dl, uric acid of 8.5 mg/dl, hematocrit of 39%, hemoglobin of 12.1g/dL, international normalized ratio of 0.9, prothrombin time of 10.4 secs, red blood cell count of 4.3x10^6/uL, and white blood cell count of 6.15x10^3/uL with neutrophil count of 4.42x10^3/uL. On week 10 of this clinical study, the vital signs were blood pressure of 130/85 and heart rate of 69. Approximately two months after initiation of first dose, on 22/Nov/same year*, the subject referred that everything was doing good and had no complaints. The subject did not have any sign or symptoms of pneumonia. The subject left his sister's house and did not returned home. His brother informed that the subject crashed into some bushes, hit a tree and was found dead the next morning, on 23/Nov/same year*. Reportedly, the subject was taken to the hospital and an autopsy was performed (report not available yet). The cause of death was reported as congestive heart failure and pneumonia. The investigator reported that the death was not related to the accident. The subject's last dose of blinded investigational product prior to death was on 22/Nov/same year*.

The investigator reported that there was no reasonable possibility that the fatal events congestive heart failure and pneumonia were related to the blinded investigational drug.

ADDITIONAL INFORMATION RECIVED ON 30/APR/one year after*: The investigator reported prostatic hypertrophy as a new serious event. The event was reported as cause of death with fatal outcome. The investigator reported that there was no reasonable possibility that the fatal prostatic hypertrophy was related to the blinded investigational drug.

ADDITIONAL INFORMATION RECEIVED ON 15/MAY/one year after*: Event prostate hypertrophy was deleted from the case as requested from the investigator as it did not meet serious criteria.

Product : AMG 145 vs placebo Study Drug Administred : Yes

Case Number	Study ID	Patient ID	Center ID	Related Case	Death Case	Death Date	Dose	Patient Route of Administration	Frequency	Last Dose
[redacted]	20101155	[redacted]	[redacted]	No	No	---	---	---	---	---

SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
Assault	Physical assault (Assault)	25-JAN-one year after*---

SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
Inferior STEMI	Acute myocardial infarction (STEMI)	25-JAN-one year after*---
Worsening substance abuse	Substance abuse (Substance abuse)	25-JAN-one year after*---
scalp contusion	Contusion (Contusion)	25-JAN-one year after*---

Case Narrative : This 45 year old African American male was participating in a phase 2, randomized, double-blind, placebo and active controlled, dose-ranging, multiple-dose, parallel-group study to evaluate the LDL-C lowering properties of AMG 145, compared to placebo and ezetimibe when used as add-on therapy in dyslipidemic and developed inferior STEMI and experienced assault.

The subjects medical history provided by the investigator included hypercholesterolemia, coronary artery disease, left ventricular systolic function of 45-49%, two-vessel disease with left internal mammary artery to the LAD and to the obtuse marginal artery, history of cocaine abuse, hyperlipidemia, history of bipolar disorder, history of migraine headaches, chronic back pain, hypertension, angina, myocardial infarction, constipation, coronary artery bypass graft, percutaneous coronary intervention, mild hypocalcemia, gastroesophageal reflux disease, hyperglycemia, liver back pain, depression, suicidal ideation, penicillin allergy (causes rash) and is an ex-smoker. The subject had family history of heart disease, myocardial infarction and coronary artery bypass graft. Previous treatment for the condition under study was not provided at the time of this report. Concomitant medications included metoprolol, simvastatin, Aspirin (acetylsalicylic acid), Plavix (clopidogrel bisulfate), carbamazepine and bupropion.

The subject received the first dose of blinded investigational study product on 22/Nov/[redacted]. Approximately two months later, on 25/Jan/one year after*, the subject presented to the emergency center after being assaulted by 4 men. The subject claimed that he was called by the gentleman to answer a question and then they began to punch and kick him and he sustained injuries to the back of his neck as well as his jaw. Due to his history of coronary artery bypass graft, it was noted on telemetry there were suspicious ST elevations in lead 2. A 12-lead electrocardiogram was performed and ST elevations in II, III and AVF were noted. The only pain the subject reported was jaw and neck pain. While in the emergency room, the subject underwent CT scan of the head and cervical spine, as well as facial bones. Reportedly, were no fracture of the cervical spine, nor were there any skull fractures. The same day, the subject was admitted to the hospital. His vital signs included temperature of 97.6, pulse of 60, oxygen saturation of 100%, blood pressure of 109/61 and respiratory rate of 20. Laboratory tests revealed creatine phosphokinase 256 U/L and Troponin I 3.38. A transthoracic echocardiogram with Doppler revealed that the left ventricle was normal in size with global systolic function at the lower limits of normal and mild concentric hypertrophy. The LV ejection fraction was estimated at 50-55%. Abnormal left ventricular diastolic filling was observed, consistent with impaired LV relaxation. Mild inferior left ventricular wall hypokinesis was noted. Both atria were normal in size. Right ventricle was normal in size and systolic function. TAPSE was 1.8cm. Estimated systolic pulmonary artery pressure was 27 mmHg. No pericardial effusion was seen. Repeated lab tests showed creatine phosphokinase 545 U/L, creatine phosphokinase MB 27.1 ng/mL and creatine phosphokinase MB index 5.0. The following day, on 26/Jan/one year after*, lab tests showed creatine phosphokinase 700 U/L, creatine phosphokinase MB 37.0 ng/mL and creatine phosphokinase MB index 5.3. During hospitalization, the subject underwent coronary catheterization due to inferior STEMI. The event inferior STEMI was reported as resolved on an unspecified date. The event assault was reported as resolved on 25/Jan/one year after*, and the subject was discharged from the hospital on 28/Jan/one year after*. The subjects last dose of blinded investigational product was on 28/Feb/one year after*. Blinded investigational product was withheld at the time of events.

The investigator reported that there was not a reasonable possibility that the events inferior STEMI and assault were related to the blinded investigational product.

ADDITIONAL INFORMATION RECEIVED ON 09/APR/one year after*: Previous and current treatment for the condition under study included simvastatin. The event inferior STEMI was reported as resolved on 25/Jan/one year after*. The investigator reported that the blinded investigational product was continued, instead of withheld as previously reported.

ADDITIONAL INFORMATION RECEIVED ON 16/APR/one year after*: On 25/Jan/one year after*, the subject developed worsening substance abuse. A urine drug screen was positive for cocaine. A CT scan of the head was positive for scalp soft tissue swelling, c-spine CT scan noted nonspecific, prominent bilateral cervical lymph nodes and facial bones CT scan revealed a questionable depressed left nasal bone fracture. As reported, while in the emergency room the subject was noted to have inferior STEMI. The subject underwent bare metal stents implantation to right coronary artery. On 27/Jan/one year after*, a submaximal exercise test was normal. Plavix effect platelet study noted a PRU of 234 and was switched to prasugrel. Additional treatment included Versed (midazolam hydrochloride), fentanyl, heparin, lidocaine and ACT (paracetamol). The subject was instructed to follow a low sodium diet and was counseled on cessation of substance abuse and antipsychotics drugs compliance. The event worsening substance abuse was reported as not resolved. The investigator reported that there was not a reasonable possibility that the events inferior STEMI, assault and worsening substance abuse were related to the blinded investigational product.

ADDITIONAL INFORMATION RECEIVED ON 24/APR/one year after*: The investigator reported that the event worsening substance abuse was ongoing.

ADDITIONAL INFORMATION RECEIVED ON 30/APR/one year after*: On 25/Jan/one year after* the subject developed scalp contusion. The event of scalp contusion was reported as not resolved. On 27/Jan/one year after* a submaximal exercise test was performed and was normal.

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

Product : AMG 145 vs placebo Study Drug Administred : Yes

Case Number	Study ID	Patient ID	Center ID	Related Case	Death Case	Death Date	Dose	Patient Route of Administration	Frequency	Last Dose
[redacted]	20101155	[redacted]	[redacted]	No	No	---	UNK	---	---	20-DEC-same year*

SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
Acetabulum fracture	Acetabulum fracture (Acetabulum fracture)	29-DEC-same year* (9 days)
Focal neurological deficit	Nervous system disorder (Neurological disorder NOS)	29-DEC-same year* (9 days)
Rib fractures	Rib fracture (Rib fracture)	29-DEC-same year* (9 days)
Rt leg cellulitis	Cellulitis (Cellulitis of leg)	10-JAN-one year after* (21 days)
Tachycardia	Tachycardia (Tachycardia)	02-JAN-one year after* (13 days)
anemia	Anaemia (Anemia)	05-JAN-one year after* (16 days)
delirium	Delirium (Delirium)	02-JAN-one year after* (13 days)
hip dislocation	Joint dislocation (Hip dislocation)	02-JAN-one year after* (13 days)

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SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
hypomagnesemia	Hypomagnesaemia (Hypomagnesemia)	02-JAN-one year after* (13 days)
motor vehicle accident	Road traffic accident (Motor vehicle accident)	29-DEC-same year* (9 days)
poly trauma	Injury (Trauma)	29-DEC-same year* (9 days)
symptoms of alcohol withdrawal	Alcohol withdrawal syndrome (Alcohol withdrawal syndrome)	JAN-one year after*---

Case Narrative : This 59 year old American Indian male was participating in a phase 2, randomized, double-blind, placebo and active controlled, dose-ranging, multiple-dose, parallel-group study to evaluate the LDL-C lowering properties of AMG 145, compared to placebo and ezetimibe when used as add-on therapy in dyslipidemic and experienced a car accident.

The subject's medical history included hypercholesterolemia, peripheral artery disease, congestive heart failure NYHA class II, type 2 diabetes mellitus, hypertension, vasculopathy, benign prostatic hyperplasia, gastroesophageal reflux disease, rheumatoid arthritis and vitamin D deficiency. Additionally, the subject had family history of premature coronary heart disease. Previous treatment for the condition under study and ongoing medication included simvastatin. Additional concomitant medication included lisinopril.

The subject received the first dose of blinded investigational product vs placebo for hypercholesterolemia on 09/Nov/[redacted]. Approximately one month and three weeks later, on 29/Dec/same year*, the subject was hospitalized due to car accident. The subject has been scheduled for a hip surgery on 05/Jan/one year after*. No further details were available. The outcome for the event was not provided by the investigator and the subject remained hospitalized at intensive care unit. The investigator reported that there was no known influencing factors of medication or alcohol intake which led to the car accident. The subject's last dose of blinded investigational product prior to the event was on 20/Dec/same year*. Blinded investigational product was temporally interrupted.

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

ADDITIONAL INFORMATION RECEIVED ON 29/MAR/one year after*: The investigator reported that the subject also experienced acetabulum fracture, rib fractures and focal neurological deficit on 29/Dec/same year*. On the same date, a 12 lead electrocardiogram was reported as "abnormal ECG" with no further details provided. On 02/Jan/one year after*, the subject developed tachycardia and hypomagnesemia. During hospitalization, on 05/Jan/one year after*, the subject underwent "hip surgery due to dislocation" with no further details provided. A duplex Doppler of the lower extremity was performed, however results were not provided. On 06/Jan/one year after*, transthoracic echocardiogram was performed but was "not well" visualized. The event car accident was reported as resolved on 29/Dec/same year*; tachycardia resolved on 12/Jan/one year after*; and hypomagnesemia resolved on 13/Jan/one year after*. The events, acetabulum fracture, rib fractures and focal neurological deficit were reported as resolving. On 17/Jan/one year after*, the subject was discharged from the hospital and transferred to another facility for wound care and physical therapy. Blinded investigational product was permanently discontinued. The investigator reported that there was no reasonable possibility that the events acetabulum fracture, rib fractures, focal neurological deficit, tachycardia and hypomagnesemia were related to blinded investigational product.

ADDITIONAL INFORMATION RECEIVED ON 19/APR/one year after*: Per report, the subject was driving the car and no information subject was considered to be "at fault" in the accident. On 29/Dec/same year*, a 12-lead electrocardiogram revealed normal sinus rhythm, possible left atrial enlargement, left axis deviation, septal infarct (age undetermined) were noted. Abnormal ECG. Four days later, on 02/Jan/one year after*, a repeated 12-lead electrocardiogram showed sinus tachycardia with premature atrial complexes with aberrant conduction and septal infarct (age undetermined) were noted. Abnormal ECG. On 05/Jan/one year after*,

a duplex Doppler lower extremity showed as follows: right lower extremity arterial duplex scan - triphasic Doppler waveforms from EIA to Distal SFA. Monophasic Doppler waveforms from Pop to DPA and PTA. Left lower extremity arterial duplex scan - triphasic Doppler waveforms from EIA to the popiteal artery. The DAP and PTA were both monophasic. Right popiteal artery not scanned due to external fixation device. Treatment medications included Paxil (paroxetine hydrochloride), Toprol XL (metoprolol succinate), Vytorin (ezetimibe, simvastatin), Campral (acamprosate calcium), hydrochlorothiazide, naproxen, metformin, prednisone, pregabalin, methotrexate sodium, hydrocodone with acetaminophen, atropine sulfate with diphenoxylate hydrochloride, enalapril maleate, metoprolol, furosemide, Plavix (clopidogrel bisulfate), folic acid, paroxetine, amitriptyline, Prevacid (lansoprazole), bisacodyl, magnesium oxide, oxycodone with acetaminophen, trazodone, morphine, lorazepam, tramadol, enoxaparin, diphenhydramine, ondansetron, magnesium hydroxide, docusate sodium, esomeprazole, Albuterol (salbutamol), ipratropium, insulin regular , (insulin bovine), gabapentin, clindamycin, dextrose, glucagon, omeprazole and povidone iodine. The investigator confirmed that the events acetabulum fracture, rib fractures and focal neurological deficit were continuing. Reportedly, the subject was discontinued from investigational product due to an "extremely high" creatine kinase level on week 6.

ADDITIONAL INFORMATION RECEIVED ON 09/MAY/one year after*: On admission, the physical examination showed the subject oriented to person, place and time, the head was normocephalic and atraumatic, the extraocular motions were normal, pupils equal and reactive to light, the musculoskeletal system exhibited tenderness in right hip and the right knee with decreased range of motion and laceration. The right foot is rotated medially; the right leg appeared shorter than left. Neurologically, a sensory deficit was present. Decreased sensation to light and sharp touch over right foot and leg. The subject was hemodynamically stable. It was determined that the etiology of the motor and sensory deficit was unclear. The pain decreased to a 2/10. Vital signs were pulse at 81, blood pressure of 164/98, oxygen saturation of 99% and respiratory rate of 19. The subject was transferred to trauma center for a higher level of care. The investigator changed the outcome of the event focal neurological deficit from resolving to not resolved.

ADDITIONAL INFORMATION RECEIVED ON 09/MAY/one year after*: Additional medical history included depression. Family history also included diabetes, hypertension and "pulmonary." The subject was brought to the emergency room via Emergency Medical Services. Upon admission, the subjects vital signs were blood pressure 157/113, pulse 74, temperature 97.9 degrees Fahrenheit, respirations 20 and oxygen saturation 95%. It was noted that the subject had alcohol on his breath. It was also noted that protective equipment used included a seat belt and airbag; it was a rear-end accident; the vehicle was not overturned; and the subject was not thrown from the vehicle. There was an injury to the chest, right hip and right knee with severe pain and numbness. The subject had no abdominal pain, back pain or shortness of breath.

ADDITIONAL INFORMATION RECEIVED ON 10/MAY/one year after*: On 29/Dec/same year*, the subject was hospitalized due to a car accident. The subject experienced hip dislocation on 02/Jan/one year after*, and underwent hip surgery. The event was reported as resolved on 05/Jan/one year after*. The investigator reported that there was no reasonable possibility that the event acetabulum hip dislocation was related to blinded investigational product.

ADDITIONAL INFORMATION RECEIVED ON 15/MAY/one year after*: The subject was hospitalized due to poly trauma on 29/Dec/same year*. Approximately four days later, on 02/Jan/one year after*, the subject experienced delirium. The subject developed anemia on 05/Jan/one year after*. Five days later, on 10/Jan/one year after*, the subject developed right leg cellulitis and insomnia, which was reported not to be an SAE. The subject developed symptoms of alcohol withdrawal on unspecified day in Jan/one year after*. The events prolonged hospitalization. The events symptoms of alcohol withdrawal, and poly trauma were reported as not resolved and the events delirium and anemia were reported as resolved on 12/Jan/one year after*. The event right leg cellulitis was reported as resolved on 17/Jan/one year after*. The investigator reported that there was no reasonable possibility that the events symptoms of alcohol withdrawal, poly trauma, right leg cellulitis, delirium and anemia were related to blinded investigational product.

[redacted]

Subject [redacted] enrolled in study 20101155 was a 64 year old male diagnosed with hypercholesterolemia. Subject received the first dose of evolocumab 140mg SC Q2W on 25 August [redacted]. On 26 August same year* (1 day after the last dose of investigational product), the subject experienced grade 1 fatigue leading to withdrawal of investigational product. Subject did not receive any treatment for the adverse event. The event resolved on 30 August same year*. There was no relevant medical history. Relevant concomitant medication included ezetimibe. The subject discontinued evolocumab (last dose on 25 August same year*) after receiving 1 dose of treatment. The investigator reported the event as unrelated to evolocumab.

*新薬承認情報提供時に置き換え

2.7.6.14 20090158 試験

治験課題名：家族性高コレステロール血症ヘテロ接合体を有する被験者を対象に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、その他アジア、カナダ、欧州、南アフリカ及び米国の23施設の医師

1.2 治験実施医療機関

[redacted]（[redacted]）、その他23施設

1.3 治験期間

2011年8月2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

家族性高コレステロール血症ヘテロ接合体（HeFH）を有する被験者を対象に、evolocumabを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

- HeFH被験者を対象に、evolocumabを2用量でSC投与したときの安全性及び忍容性をプラセボとの比較により評価する。
- HeFH被験者を対象に、evolocumabを12週間SC投与したときのLDL-Cの変化量並びに非高比重リポ蛋白コレステロール（non-HDL-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。
- HeFH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。

1.6 治験方法

evolocumabの第II相、二重盲検、無作為化、プラセボ対照試験である本試験は、HeFH被験者を対象に、evolocumabの有効性及び安全性をプラセボと比較することを目的にデザインされた。スクリーニング・プラセボ導入期後、適格な被験者について、以下の3つの投与群に均等に無作為に割り付けた。

- evolocumab 350 mg 4週1回（Q4W）SC投与群
- evolocumab 420 mg Q4W SC投与群
- プラセボ Q4W SC投与群

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）及びベースライン時のエゼチミブ投与（あり／なし）を因子とする層別割り付けを用いた。無作為に割り付けられた被験者は、12週間投与を受けた後、試験終了時（EOS）の追跡調査のために来院し、試験を完了した。本試験ではバイオマーカー用検体の採取を含み、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参加を依頼した。また、被験者に対して任意でのPKサブスタディへの参加を依頼し、evolocumab及びプロ蛋白転換酵素サブチリシン／ケキシン9型（PCSK9）の濃度を評価するため、更に9週、10週及び11週の3回の検体採取のための来院が規定された。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、投与中の脂質測定結果を知らされなかった。

本試験の評価スケジュールを表2.7.6.14-1、PKサブスタディの追加手順スケジュールを表2.7.6.14-2に示す。

表 2.7.6.14-1　評価スケジュール（全被験者）

Study Day / Timepoint[a]	Screening & Placebo Run-in	D1	W2	W4	W8	W12 EOS
General Procedures						
Informed consent	X					
Medical history	X					
Vital Signs (sitting BP, HR)	X	X	X	X	X	X
Review for AEs/SAEs	X[b]	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X
Physical exam		X				X
Body height		X				
Body weight		X				X
Waist circumference		X				
12 lead ECG	X	X		X	X	X
Dietary instruction	X	X	X	X	X	
Randomization		X[c]				
Central Laboratory						
Fasting lipids, ApoA1, ApoB	X[d]	X[d]	X	X	X	X[d]
PK (evolocumab; PCSK9)[e]	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X
Hematology	X	X		X	X	X
Coagulation	X	X	X	X	X	X
hsCRP, Lp(a)		X				X
HbA1c	X					X
TSH, eGFR, FSH[f]	X					
Biomarkers (blood)[g]		X	X	X		X
Anti-evolocumab antibodies		X		X		X
Serum pregnancy (females of childbearing potential)	X					X
Urinalysis		X				X
Investigational Product						
Placebo run-in	X					
IP administration, Q4W[h]		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 = day、 ECG =心電図、eGFR =推算糸球体濾過量、EOS = 試験終了、FSH =卵胞刺激ホルモン、HbA1c = ヘモグロビン A1c 、hsCRP =高感度 C 反応性蛋白、HR =心拍数、IP =治験薬、Lp(a) = リポ蛋白、PK =薬物動態、PCSK9 = プロ蛋白転換酵素サブチリシン／ケキシン 9 型、Q4W = 4 週 1 回、SAE = 重篤な有害事象、 TSH = 甲状腺刺激ホルモン、W = week

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

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

[c] Randomization occurred within approximately 5 - 10 days of the screening fasting LDL-C blood sample

[d] Included LDL-C measurement by preparative ultracentrifugation

[e] evolocumabwas not measured in screening samples and samples from subjects not receiving evolocumab

[f] FSH only in females and if applicable (see exclusion criteria Section 7.5.2 of the protocol)

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

[h] Investigational product was administered after vital signs, ECG, and blood sampling procedures

表 2.7.6.14-2　PK サブスタディにおける追加評価

試験日/時点[a]	スクリーニング及びプラセボ導入	W9[b]	W10[b]	W11[b]
同意取得	X			
空腹時脂質, ApoA1, ApoB		X	X	X
PK (evolocumab; PCSK9)		X	X	X
バイタルサイン(座位 BP, HR)		X	X	X
AEs/SAEs のレビュー		X	X	X
併用薬		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、HR =血圧、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、SAE = 重篤な有害事象、 W = week

[a] D1 = 治験薬初回投与日。その他の来院日は±3 日の来院期間。

[b] 追加の来院日。.

1.7　被験者数

予定被験者数：150 例（1 群あたり 50 例）

登録被験者数：168 例（プラセボ群 56 例、evolocumab 350 mg Q4W 群 56 例及び evolocumab 420 mg Q4W 群 56 例）

1.8　診断及び適格性の主な基準

本治験に組み入れ可能な被験者は、年齢 18 歳以上 75 歳以下、Simon Broome Register Group（Scientific Steering Committee, 1991）の診断基準により HeFH と診断されており、中央測定施設によるスクリーニング時の空腹時 LDL-C が 100 mg/dL 以上かつ空腹時トリグリセリドが 400 mg/dL 以下の男女とした。被験者は、エゼチミブの併用にかかわらず、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スタチン投与を受けていることとした。

主な除外基準は、家族性高コレステロール血症ホモ接合体患者、無作為割り付け前 12 カ月以内に LDL 又は血漿アフェレーシスを受けた患者、脂質低下薬（スタチン又はエゼチミブ以外）を使用していた患者、あるいは紅麹、ナイアシン（200 mg/day 超）又はオメガ 3 脂肪酸（1000 mg/day 超）をスクリーニング前の 3 カ月以内に 2 週間を超えて使用していた患者とした。

すべての選択基準及び除外基準の一覧を治験実施計画書の第 4 項に示す。

1.9　被験薬、用量及び投与方法

1.9.1　被験薬

evolocumab は、濃度 70 mg/mL の無菌、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] [redacted] [redacted]で調製された pH [redacted]の溶液である。evolocumab を 350 mg（Q4W 群）、又は 420 mg（Q4W 群）の用量で 6 mL 溶液として、各群に SC 投与した。投与液は分割して注射することを可能とした。投与群の盲検化を維持するために、evolocumab 及びプラセボを表 2.7.6.14-3 に示すとおりに投与した。

表 2.7.6.14-3　evolocumab の投与方法

投与群	evolocumab (70 mg/mL)投与量の合計 (バイアルの用量[a]、mL)	プラセボ投与量の合計 (バイアルの用量、mL)
プラセボ Q4W	無	6 mL (1 + 1 + 1 + 1 + 1 + 1)
evolocumab 350 mg Q4W	5 mL (1 + 1 + 1 + 1 + 1)	1 mL (1)
evolocumab 420 mg Q4W	6 mL (1 + 1 + 1 + 1 + 1 + 1)	無

Q4W = 4 週 1 回

[a] evolocumab の各無菌バイアルは evolocumab 70 mg/mL が注入可能な 1mL 封入されている。

1.9.2　対照薬

プラセボは無色澄明、無菌の凍結液として evolocumab と同じ容器に充填された上で供給され、成分は evolocumab の賦形剤であった。プラセボは各群の治療割り付けに従って Q4W で SC 投与した。

1.10　投与期間

被験者は、最長 6 週間のスクリーニング・プラセボ導入期に続き、12 週間の投与期にて投与を受け、最長治験期間は 18 週間であった。

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 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 non-HDL-C のベースラインからの変化率
- 投与 12 週時点における ApoB のベースラインからの変化率
- 投与 12 週時点における総コレステロール／HDL-C 比のベースラインからの変化率
- 投与 12 週時点における 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
- 各規定来院時の安全性に関連する臨床検査値及びバイタルサイン
- 各規定来院時の心電図（ECG）パラメータ（PR 間隔、QRS 間隔、QT 間隔、QTc 間隔等）
- 抗 evolocumab 抗体発現率（結合及び中和抗体）

1.11.4　薬物動態学的評価項目

- 特定の来院時の血清中 evolocumab 濃度及び血清中 PCSK9 濃度

- 投与 8 週時から 12 週時点までに得られた evolocumab の最高血中濃度到達時間（t_{max}）、evolocumab の最高血中濃度（C_{max}）及び evolocumab の投与後 0 時間から測定可能な最終時点までの血清中濃度-時間曲線下面積（AUC_t）
- 血清中非結合型 PCSK9 の効果曲線下面積（$AUEC_{PCSK9}$）、到達した最低血中非結合型 PCSK9 濃度（$C_{min, PCSK9}$）、最低血中 PCSK9 濃度観測時間（$t_{min, PCSK9}$）
- LDL-C の効果曲線下面積（AUEC）、到達した最低血中 LDL-C 濃度（$C_{min, LDL-C}$）、最低血中 LDL-C 濃度観測時間（$t_{min, LDL-C}$）、投与 12 週時点の LDL-C 濃度（$LDL-C_{, substudy W12}$）、ベースライン時の最初の LDL-C（PK サブスタディの評価項目である算出 LDL-C パラメータ）

1.11.5 探索的評価項目

- 以下の事象の発現率
  - 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各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
  - 総コレステロール／HDL-C 比
  - ApoB/ApoA1 比
  - トリグリセリド
  - 超低比重リポ蛋白コレステロール（VLDL-C）
  - HDL-C
  - ApoA1
  - リポ蛋白（a）［Lp（a）］
  - 高感度 C-反応性蛋白（hsCRP）

1.12 統計手法

一般的事項

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。すべての解析において被験者は、割り付けられた投与群に従って解析された。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 Hochberg 法を用いた。別途記載しない限り、その他すべての仮説検定は、統計的有意性 0.05 の両側検定とした。

主要評価項目の解析

治療効果は、投与群及び層別因子をモデルに含めた共分散分析（ANCOVA）を用いて評価した。各用量の治療効果をプラセボと比較する際には、Hochberg 法を用いて多重性を調整した。欠測値の補完には last observation carried forward（LOCF）法を用いた。

副次評価項目及び探索的評価項目の解析

その他の評価項目の解析は、主要評価項目の解析と同様に行った。ただし、すべての解析の有意水準を 0.05 とした。また、主要評価項目、副次評価項目及びその他の評価項目について、evolocumab の投与群間の比較を行った。

本試験及びその他の第 II 相試験では、独立臨床事象判定委員会による主要な心血管系有害事象の判定が行われた。判定を行った有害事象の発現率を投与群ごとに要約した。

安全性評価項目の解析

有害事象は、ICH 国際医薬用語集（MedDRA）バージョン 15.0 を用いてコード化した。有害事象及び重篤な有害事象、治験薬投与と関連のある有害事象、併せて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ごとに無作為割り付けされた投与群別に一覧表にまとめた。すべての有害事象について、サブグループ解析の結果（適切な場合、層別因子として、年齢、人種及び性別）を示した。

臨床検査値、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。臨床検査値のシフトテーブルを示した。

2. 結果の要約

2.1 被験者の内訳

米国、欧州、アジア、カナダ及び南アフリカの 24 施設において、合計 168 例の被験者が無作為化された。被験者 112 例が evolocumab の 2 群（350 mg Q4W 群 56 例、420 mg Q4W 群 56 例）に、56 例がプラセボ群（Q4W 群）に無作為に割り付けられた。治験薬の投与を受け、治験を完了した合計 167 例（99.4%）の被験者を FAS とした。被験者の内訳を表 2.7.6.14-4 に示す。

表 2.7.6.14-4　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			
	Q4W (N = 56) n (%)	350 mg Q4W (N = 56) n (%)	420 mg Q4W (N = 56) n (%)	すべて (N = 112) n (%)	合計 (N = 168) n (%)
治験薬の状況					
IP の投与を全く受けなかった被験者数	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.9)	1 (0.6)
IP の投与を受けた被験者数	56 (100.0)	55 (98.2)	56 (100.0)	111 (99.1)	167 (99.4)
IP 投与を完了した被験者数	53 (94.6)	54 (96.4)	54 (96.4)	108 (96.4)	161 (95.8)
IP 投与を中止した被験者数	3 (5.4)	1 (1.8)	2 (3.6)	3 (2.7)	6 (3.6)
同意撤回	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
有害事象	1 (1.8)	1 (1.8)	1 (1.8)	2 (1.8)	3 (1.8)
妊娠	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)
被験者の希望	1 (1.8)	0 (0.0)	1 (1.8)	1 (0.9)	2 (1.2)
治験依頼者の判断	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
治験担当医師判断	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)
その他	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)

N =無作為割付けされた被験者数、Q2W = 2 週 1 回、 Q4W = 4 週 1 回、 IP =治験薬
無作為割付けした被験者数 205 例、最初の被験者の組入れ日 2011 年 8 月 2 日　最後の被験者の最終来院日 [redacted] 年 [redacted] 月 [redacted] 日

[redacted]

表 2.7.6.14-4　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			
	Q4W (N = 56) n (%)	350 mg Q4W (N = 56) n (%)	420 mg Q4W (N = 56) n (%)	すべて (N = 112) n (%)	合計 (N = 168) n (%)
試験完了の状況					
完了した被験者	56 (100.0)	55 (98.2)	56 (100.0)	111 (99.1)	167 (99.4)
中止した被験者	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.9)	1 (0.6)
同意撤回	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)
中止	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)
その他	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.9)	1 (0.6)

N =無作為割付けされた被験者数、Q2W = 2 週 1 回、 Q4W = 4 週 1 回、 IP =治験薬
無作為割付けした被験者数 205 例、最初の被験者の組入れ日 2011 年 8 月 2 日　最後の被験者の最終来院日 [redacted]年[redacted]月[redacted]日

[redacted]

2.2 人口統計学的データ

試験対象集団の構成は53.3%が男性、46.7%が女性であり、被験者の平均年齢（SD）は49.6（12.7）歳であった。ほとんどの被験者（85.6%）は65歳未満であった。白人（88.6%）が集団の大部分を占め、アジア人（4.2%）、黒人（2.4%）、混血（0.6%）及び「その他」（4.2%）であった。ほとんどの被験者（98.8%）は非ヒスパニック系又は非ラテン系であった。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2.7.6.14-5に示す。

表 2.7.6.14-5 ベースライン時の人口統計学的データ（FAS）

	プラセボ	evolocumab			
	Q4W (N = 56)	350 mg Q4W (N = 55)	420 mg Q4W (N = 56)	すべて (N = 111)	合計 (N = 167)
性別- n (%)					
男性	24 (42.9)	30 (54.5)	35 (62.5)	65 (58.6)	89 (53.3)
女性	32 (57.1)	25 (45.5)	21 (37.5)	46 (41.4)	78 (46.7)
民族 - n (%)					
ヒスパニック又はラテン系	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)
非ヒスパニック又はラテン系	54 (96.4)	55 (100.0)	56 (100.0)	111 (100.0)	165 (98.8)
人種- n (%)					
アジア人	3 (5.4)	1 (1.8)	3 (5.4)	4 (3.6)	7 (4.2)
黒人又はアフリカ系アメリカ人	0 (0.0)	3 (5.5)	1 (1.8)	4 (3.6)	4 (2.4)
白人	48 (85.7)	48 (87.3)	52 (92.9)	100 (90.1)	148 (88.6)
その他	4 (7.1)	3 (5.5)	0 (0.0)	3 (2.7)	7 (4.2)
混血	1 (1.8)[a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
年齢 (歳)					
n	56	55	56	111	167
平均	49.3	47.6	51.8	49.7	49.6
SD	11.3	13.6	13.0	13.4	12.7
中央値	49.5	47.0	52.5	50.0	50.0
Q1, Q3	44.0, 58.0	39.0, 60.0	46.0, 61.5	42.0, 60.0	42.0, 59.0
最小, 最大	20, 68	18, 70	21, 74	18, 74	18, 74
年齢- n (%)					
< 65 歳	51 (91.1)	48 (87.3)	44 (78.6)	92 (82.9)	143 (85.6)
≥ 65 歳	5 (8.9)	7 (12.7)	12 (21.4)	19 (17.1)	24 (14.4)
地域- n (%)					
北米	16 (28.6)	16 (29.1)	13 (23.2)	29 (26.1)	45 (26.9)
その他	40 (71.4)	39 (70.9)	43 (76.8)	82 (73.9)	122 (73.1)

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

[a] データベースを開鍵後、治験実施施設でこの被験者の人種を3回「白人」と入力していることが判明し、本解析では「混血」とした。詳細はAppendix 21 データベースの正誤表参照。

Source: Modified from CSR 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

主要評価項目については、evolocumab 350 mg 群及び evolocumab 420 mg 群のいずれも、プラセボとの差がそれぞれ 44%及び 56%であり、投与 12 週時点における 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、表 2.7.6.14-6）。LDL-C の低下は用量依存的であり、evolocumab 420 mg 群は 350 mg 群と比較して大きな低下が認められた（図 2.7.6.14-1）。

表 2.7.6.14-6 投与 12 週時点における UC LDL-C のベースラインからの変化率（FAS）

	evolocumab Q4W vs. プラセボ Q4W		
		evolocumab	
	プラセボ (N=56)	350 mg (N=55)	420 mg (N=56)
要約統計量			
n	56	55	56
平均	0.76	-43.08	-55.60
SD	21.71	20.07	19.87
SE	2.90	2.71	2.65
95% CI (平均)	(-5.05, 6.58)	(-48.50, -37.65)	(-60.92, -50.28)
中央値	-1.74	-45.67	-57.79
Q1, Q3	-12.81, 9.29	-57.63, -30.38	-70.44, -45.16
最小, 最大	-49.7, 62.7	-83.1, 13.5	-86.9, 30.3
L.S. 平均 [a]			
推定	1.12	-42.70	-55.24
SE	2.88	2.93	2.88
95% CI	(-4.56, 6.80)	(-48.50, -36.91)	(-60.92, -49.57)
治療群間差 [b]			
推定	-	-43.82	-56.36
SE	-	3.92	3.90
95% CI	(-, -)	(-51.56, -36.09)	(-64.06, -48.67)
p-値	-	<0.001	<0.001

CI = 信頼区間、LDL-C = 低比重リポ蛋白コレステロール、N =無作為割付けされ治験薬の投与を受けた被験者数、Q1 =25 パーセンタイル、Q3 =75 パーセンタイル、Q4W = 4 週 1 回、SE = 標準偏差

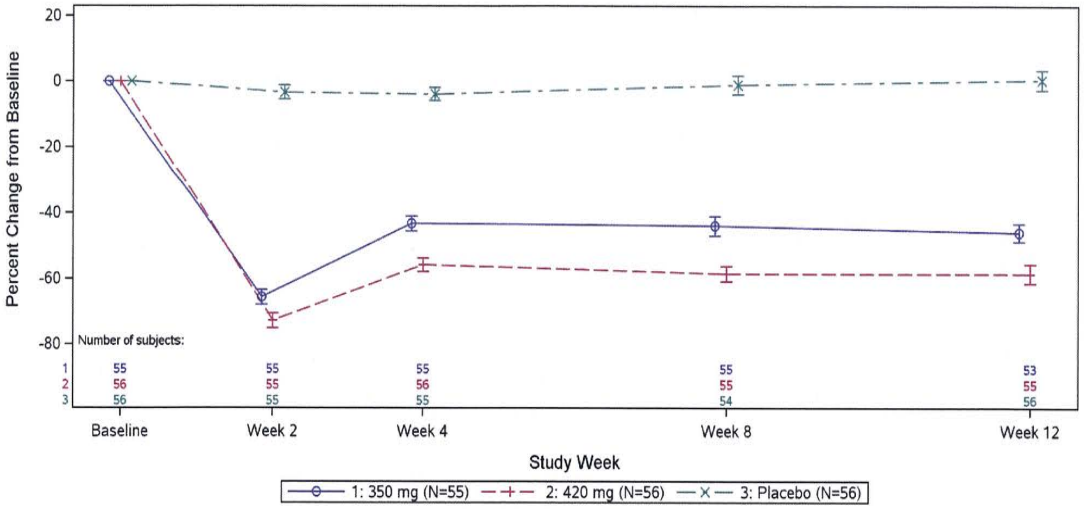
[a] 共変数として治療群及び層化因子を含む ANCOVA モデルからの最小二乗平均。week 12 の超遠心分離（UC）LDL-C 値の欠測は、時系列データの欠測に最直前のデータを補完する方法（LOCF）及び算出 LDL-C 値を用い補完した。

[b] 各用量群内の治療差は同群のプラセボを参照として用いた。

– 該当無

階層的逐次検定法を多重比較≤ 0.05 のときファミリーワイズエラー率を管理するため用いた。

[redacted]



LDL-C = 低比重リポ蛋白コレステロール、N = 無作為割付けされ治験薬の投与を受けた被験者数
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。

[redacted]

図 2.7.6.14-1　規定来院時及び投与群毎の LDL-C のベースラインからの平均変化率（FAS）

感度分析により、主要評価項目の解析結果を確認した。サブグループ解析（層別因子別及び各ベースライン共変量別）では、いずれの evolocumab 群（350 mg Q4W 及び 420 mg Q4W）でも、投与 12 週時点における UC LDL-C のベースラインからの変化率にプラセボと比較して大きな低下が認められた。主解析の ANCOVA モデルにほかの共変量を含めた調整解析の結果も主要な解析結果と一貫していた。

evolocumab 350 mg 群と evolocumab 420 mg 群の比較を行ったところ、投与 12 週時点における UC LDL-C のベースラインからの変化率は 420 mg 群でより大きく低下し、統計学的な有意差が認められた（P<0.001）。

2.3.2　有効性の副次評価項目

evolocumab を投与した結果、いずれの evolocumab 群でも、プラセボと比較して、ほとんどの有効性の副次評価項目（投与 12 週時点における UC LDL-C のベースラインからの変化量並びに投与 12 週時点の non-HDL-C、ApoB、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、表 2.7.6.14-7）に、統計学的に有意な低下が認められた（P<0.001）。

表 2.7.6.14-7　投与 12 週時点における有効性の副次評価項目及びその他の有効性のパラメータのプラセボとの群間差（推定値）の要約（FAS）

	evolocumab vs プラセボ	
脂質パラメータ	evolocumab 350 mg (N = 55)	evolocumab 420 mg (N = 56)
week 12 のベースラインからの絶対変化		
UC LDL-C (mg/dL) [a]	-65.5	-84.7
95% CI	(-79.6, -51.4)	(-98.8, -70.7)
p-値	<0.001	<0.001
UC LDL-C (mmol/L) [a]	-1.694	-2.191
95% CI	(-2.059, -1.329)	(-2.554, -1.828)
p-値	<0.001	<0.001
week 12 のベースラインからの変化率 (%)		
ApoB[a]	-34.75	-46.20
95% CI	(-41.77, -27.74)	(-53.18, -39.23)
p-値	<0.001	<0.001
総コレステロール	-30.98	-40.26
95% CI	(-36.69, -25.26)	(-45.95, -34.57)
p-値	<0.001	<0.001
非-HDL-C[a]	-41.79	-53.46
95% CI	(-49.32, -34.26)	(-60.95, -45.97)
p-値	<0.001	<0.001
HDL-C	7.78	6.79
95% CI	(2.71, 12.85)	(1.75, 11.84)
p-値	0.003	0.009
ApoA1	2.01	1.70
95% CI	(-2.41, 6.43)	(-2.70, 6.09)
p-value	0.37	0.45
トリグリセリド	-15.03	-19.86
95% CI	(-26.01, -4.04)	(-30.79, -8.92)
p-値	0.008	<0.001
VLDL-C	-24.80	-35.54
95% CI	(-43.97, -5.64)	(-54.61, -16.47)
p-値	0.012	<0.001
Lp(a)	-23.14	-31.46
95% CI	(-31.33, -14.94)	(-39.62, -23.31)
p-値	<0.001	<0.001
総コレステロール/HDL-C 比 [a]	-36.66	-45.01
95% CI	(-44.01, -29.32)	(-52.32, -37.70)
p-値	<0.001	<0.001
ApoB/ApoA1 比 [a]	-33.92	-44.64
95% CI	(-40.72, -27.11)	(-51.41, -37.86)
p-値	<0.001	<0.001
Week 12 の測定値 (ng/mL)		
PCSK9	-266.5	-257.7
95% CI	(-313.5, -219.6)	(-304.2, -211.3)
p-値	<0.001	<0.001

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、N =無作為割付けし、治験薬を投与した被験者数、非-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、UC LDL-C = UC 後に直接法により測定された LDL-C、VLDL-C = 超低比重リポ蛋白コレステロール

[a] 重要な有効性の副次評価項目として確定。

Source: Modified from Tables 14-4.10.1, 14-4.10.3, 14-4.11.1, 14-4.12.1, 14-4.13.1, 14-4.14.1, 14-4.15.1, 14-4.16.1, 14-4.17.1, 14-4.18.1, 14-4.19.1, 14-4.20.1 and 14-4.21.1.

これらの各副次評価項目の低下は用量依存的であり、最大の低下が認められたのは420 mg群であった。350 mg群及び420 mg群のプラセボとの群間差について、投与12週時点におけるUC LDL-Cのベースラインからの変化量は65.5 mg/dL及び84.7 mg/dL（1.69 mmol/L及び2.19 mmol/L）であり、また、投与12週時点におけるベースラインからの変化率では、non-HDL-Cが42%及び53%、ApoBが35%及び46%、総コレステロール／HDL-C比が37%及び45%、ApoB/ApoA1比が34%及び45%であった。

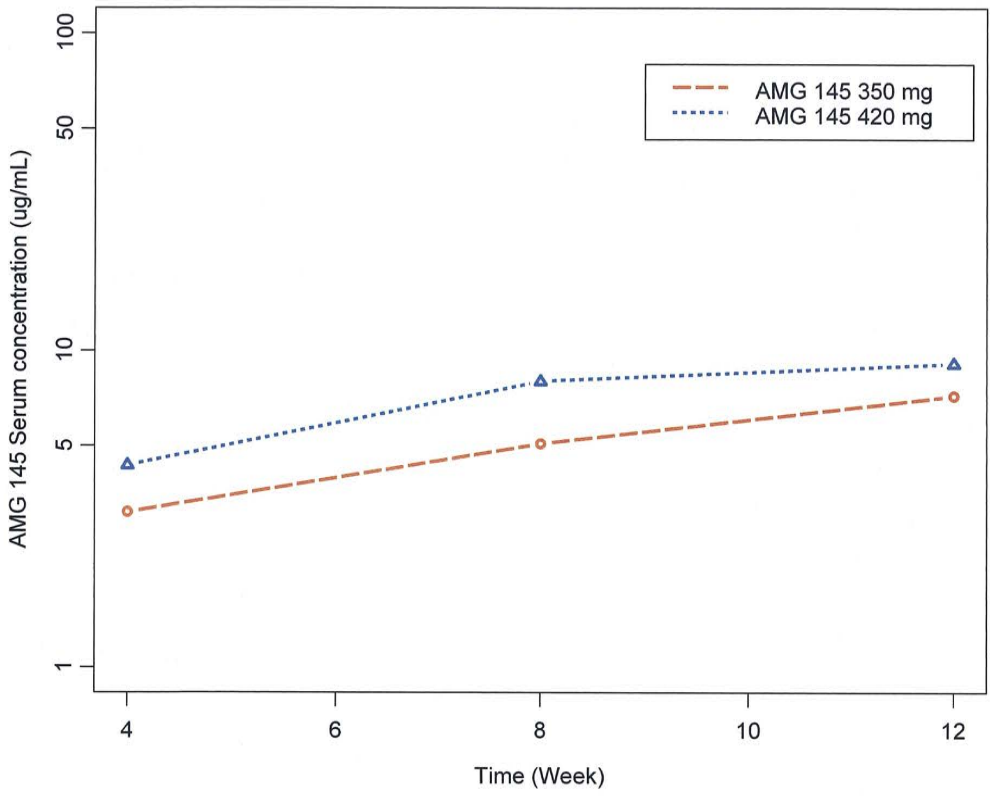
その他の脂質パラメータについては、いずれのevolocumab群でも、プラセボと比較して、総コレステロール（P<0.001）、VLDL-C（P=0.012［350 mg］及びP<0.001［420 mg］）、Lp（a）（P<0.001）、トリグリセリド（P=0.008［350 mg］及びP<0.001［420 mg］）のベースラインからの変化率並びに投与12週時点に観測されたPCSK9（P<0.001）に、統計学的に有意な低下が認められた。総コレステロール（31%及び40%）、VLDL-C（25%及び36%）、Lp（a）（23%及び31%）及びトリグリセリド（15%及び20%）の低下（evolocumab 350 mg群及び420 mg群）は用量依存的であり、各パラメータにおける反応は420 mg群は350 mg群と比較して、大きな低下を示した。また、evolocumab群において、投与12週時点のHDL-Cは350 mg群で8%（P=0.003）及び420 mg群で7%（P=0.009）と、いずれの投与群でもプラセボと比較して統計学的に有意な上昇が認められた。投与12週時点のApoA1にいずれのevolocumab群でも、プラセボと比較して、統計学的に有意な上昇は認められなかった（それぞれP=0.37及びP=0.45）。

2.3.3　探索的評価項目

被験者2例（evolocumab 350 mg Q4W群1例及びevolocumab 420 mg Q4W群1例）に、陽性と判定された臨床事象が認められた。これらの事象は、1例が不安定狭心症のための入院及び経皮的冠動脈インターベンションによる冠動脈血行再建の事象、もう1例が一過性脳虚血発作の脳血管系事象であった。また、筋肉関連事象2件（evolocumab 420 mg群）は、判定に供したが独立臨床事象判定委員会により否定された。

2.4　薬物動態の結果

各投与群内で、投与前のトラフ検体（4週、8週及び12週）の平均血清中非結合型evolocumab濃度にわずかな蓄積が認められた（図2.7.6.14-2）。

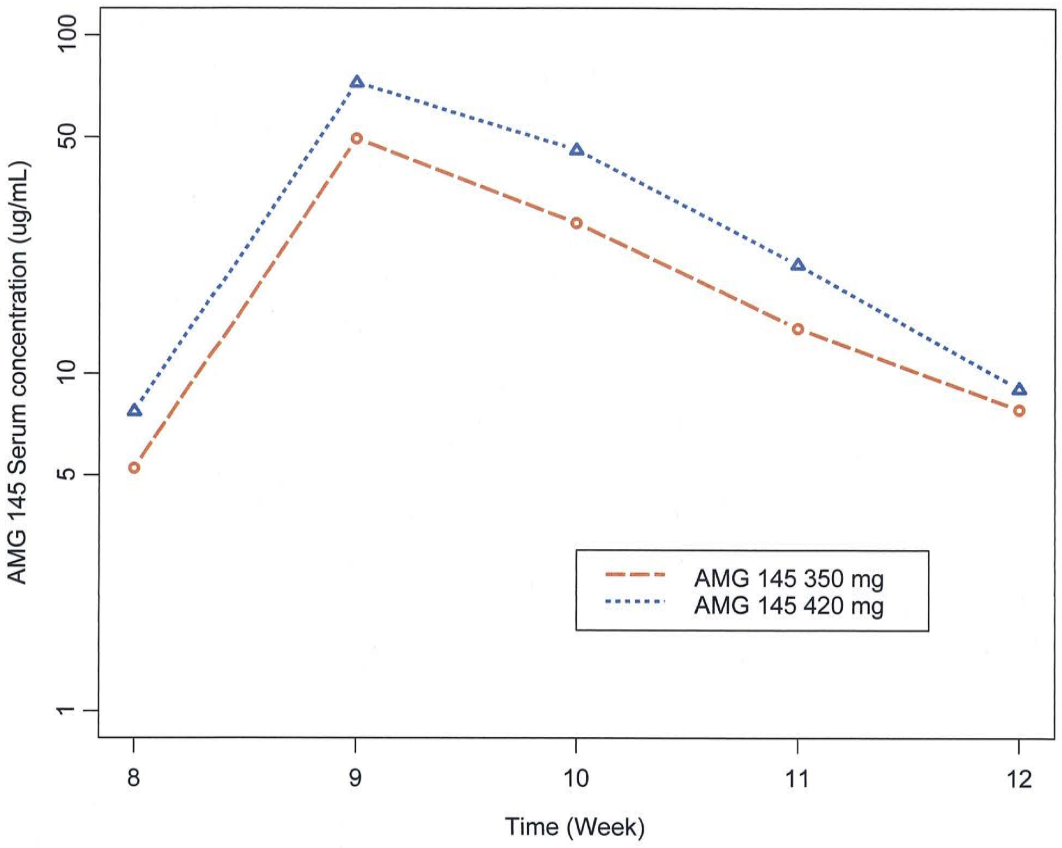


HeFH =家族性高コレステロール血症ヘテロ接合体

[redacted]

図 2.7.6.14-2　evolocumab の投与を受けた全 HeFH 被験者における投与群ごとのトラフ時の平均血清中濃度－時間推移曲線

evolocumab の PK データのノンコンパートメント解析の結果、350 mg Q4W 又は 420 mg Q4W で evolocumab の投与を受けた PK サブスタディの HeFH 被験者において、evolocumab の曝露量は用量依存的であることが示された。350 mg Q4W から 420 mg Q4W にかけて、evolocumab の PK に用量に比例した増加が認められた（図 2.7.6.14-3、表 2.7.6.14-8）。C_{max} は evolocumab の投与の 1 週間後であった。



HeFH =家族性高コレステロール血症ヘテロ接合体

[redacted]

図 2.7.6.14-3　evolocumab の投与を受けた PK サブスタディの HeFH 被験者における投与群ごとの平均血清中 evolocumab 濃度－時間推移曲線

表 2.7.6.14-8　evolocumab の投与を受けた PK サブスタディの HeFH 被験者における投与群ごとの evolocumab のノンコンパートメント薬物動態パラメータ推定値

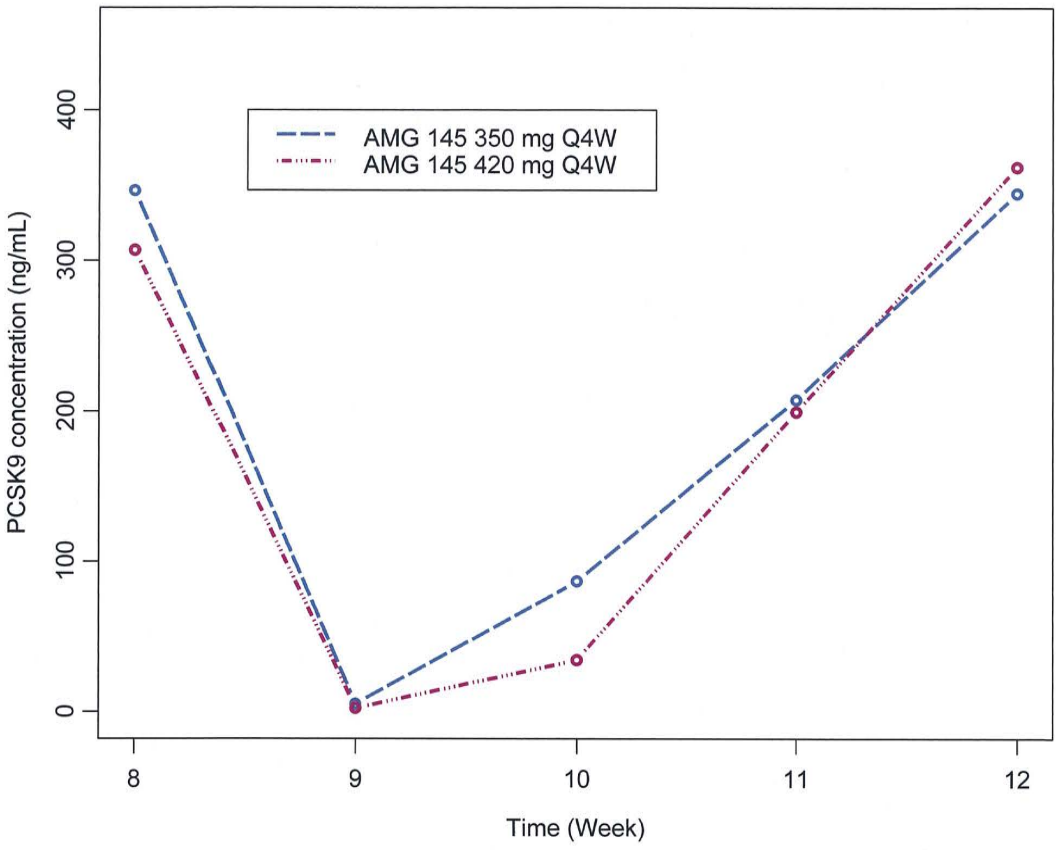
パラメータ	記述統計	350 mg Q4W	420 mg Q4W
$AUC_{Week8-12}$ (day·μg/mL)	N	17	16
	平均	723	1010
	SD	527	653
	CV%	72.9	64.4
	中央値	654	760
	最小	194	278
	最大	1810	2360
C_{max} (μg/mL)	n	17	16
	平均	52.1	72.4
	SD	28.3	40.9
	CV%	54.3	56.5
	中央値	49.3	62.7
	最小	17.9	25.7
	最大	110	150
t_{max} (day)	n	17	16
	中央値	7.0	7.0
	最小	6.0	6.0
	最大	9.0	9.1

$AUC_{Week8-12}$ = 8 ~12 週の血清中濃度-時間曲線下面積、C_{max} =最高血中濃度、CV = 変動係数、HeFH =家族性高コレステロール血症ヘテロ接合体、Q4W = 4 週 1 回、SD = 標準偏差、t_{max} =最高血中濃度到達時間

[redacted]

2.5　薬力学の結果

evolocumab の薬力学データのノンコンパートメント解析の結果、350 mg Q4W 又は 420 mg Q4W で evolocumab の投与を受けた PK サブスタディの HeFH 被験者において、PCSK9 及び LDL-C の低下作用は頑健であることが示された。evolocumab を投与した結果、いずれの投与群でも、ほぼ完全な抑制に至るまで PCSK9 の平均値が低下し、ベースライン未満の PCSK9 抑制が投与 12 週時点まで維持された（図 2.7.6.14-4、表 2.7.6.14-9）。PK サブスタディにおける投与 8 週時から 12 週時点までのベースラインからの算出 LDL-C の平均値の低下は、350 mg Q4W 投与及び 420 mg Q4W 投与でそれぞれ 60%及び 79%であった（図 2.7.6.14-5）。この結果は、本試験におけるこれら 2 つの投与群の投与 8 週時から 12 週時点までの LDL-C の平均値である 63.8 mg/dL 及び 28.9 mg/dL に一致した。350 mg Q4W 投与及び 420 mg Q4W 投与では、ベースラインからの LDL-C の平均低下率の最大値は、投与後約 2 週間で、それぞれ 76%及び 88%であり、これら 2 つの投与方法における LDL-C 最大低下時の平均値は、42 mg/dL 及び 17 mg/dL であった。これに対応する投与 12 週時点（トラフ）のベースラインからの低下率は、2 つの投与方法でそれぞれ 44%及び 68%であった。時間平均 LDL-C パラメータである LDL-C の $AUEC_{week8-12}$ の平均値は、350 mg Q4W 群で 2630 day•mg/dL 及び 420 mg Q4W で 3040 day•mg/dL であった（表 2.7.6.14-10）。PK サブスタディのデータから、本試験の対象集団において LDL-C の最大の低下を得るために、420 mg の SC 投与を選択することが支持された。



HeFH =家族性高コレステロール血症ヘテロ接合体、PCSK9 = プロ蛋白転換酵素サブチリシン／ケキシン 9 型、Q4W = 4 週 1 回

[redacted]

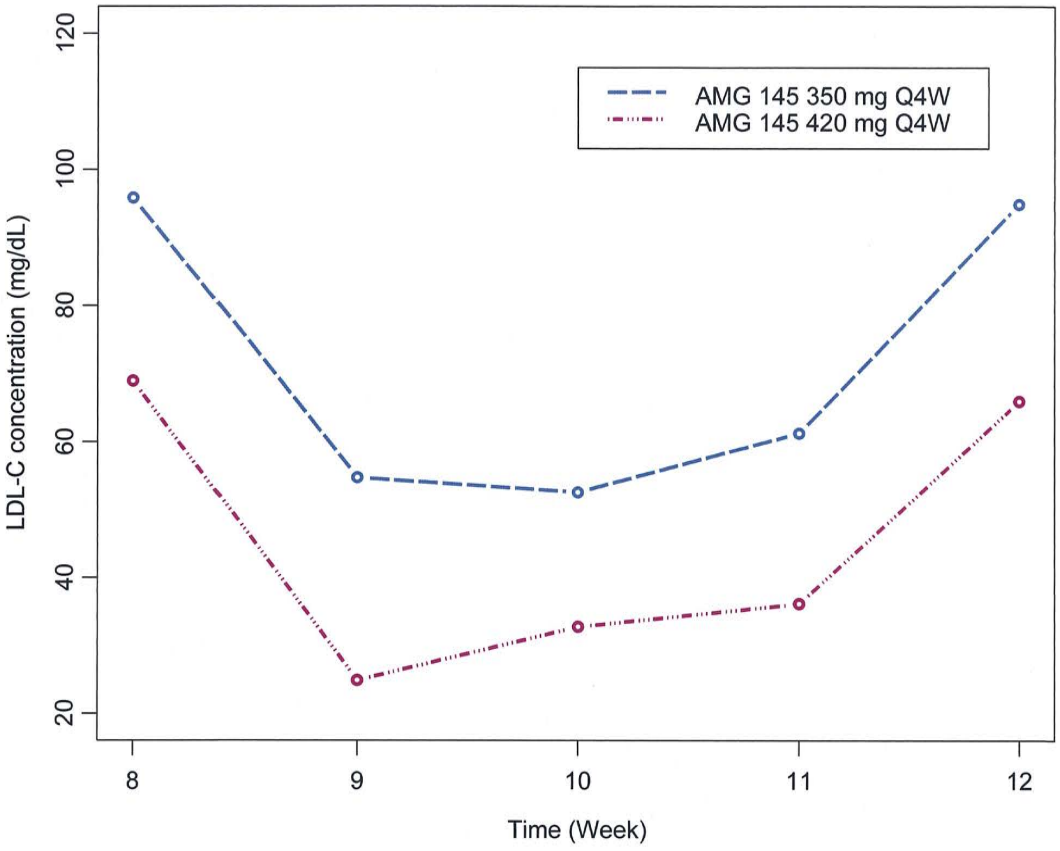
図 2.7.6.14-4　evolocumab の投与を受けた PK サブスタディの HeFH 被験者における投与 8 週時から 12 週時点までの平均血清中 PCSK9 濃度－時間推移曲線

表 2.7.6.14-9　evolocumab の投与を受けた PK サブスタディの被験者における投与群ごとの PCSK9 のノンコンパートメント薬力学パラメータ推定値

パラメータ	記述統計	350 mg Q4W	420 mg Q4W
AUEC (day·ng/mL)	n	18	16
	平均	12500	11700
	SD	5100	4020
	CV%	41.0	34.5
	中央値	12200	11800
	最小	4300	5020
	最大	22100	21100
C_{min} (ng/mL)	n	18	16
	平均	5.06	2.36
	SD	12.3	6.46
	CV%	242.2	273.6
	中央値	0.00	0.00
	最小	0.00	0.00
	最大	42.0	19.6
T_{min} (day)	n	18	16
	中央値	63	63
	最小	63	63
	最大	63	63
ベースライン PCSK9 (ng/mL)	n	18	16
	平均	603	560
	SD	206	155
	CV%	34.1	27.7

$AUEC_{PCSK9}$= 8～12 週の PCSK9 の効果曲線下面積、$C_{min, PCSK9}$ = weeks 8～12 に認められた PCSK9 の最小値、C_{min} = 定量限界未満(15 ng/mL)のとき 0 、CF = 変動係数、PCSK9 = プロ蛋白転換酵素サブチリシン／ケキシン 9 型、Q4W = 4 週 1 回、$T_{min, PCSK9}$ = weeks 8～12 に認められた最低 PCSK9 濃度到達時間、ベースライン PCSK9 =治験薬投与開始前の PCSK9 濃度

[redacted]



HeFH =家族性高コレステロール血症ヘテロ接合体、PCSK9 = プロ蛋白転換酵素サブチリシン／ケキシン 9 型、Q4W = 4 週 1 回

図 2.7.6.14-5　evolocumab の投与を受けた PK サブスタディの HeFH 被験者における投与群ごとの平均血清中 LDL-C 濃度-時間推移曲線

表 2.7.6.14-10　evolocumab の投与を受けた PK サブスタディの被験者における投与群ごとの LDL-C のノンコンパートメント薬力学パラメータ推定値

パラメータ	記述統計	350 mg SC Q4W	420 mg SC Q4W
$AUEC_{LDLC}$ (day*mg/dL)	n	9	7
	平均	2630	3040
	SD	1210	679
	CV%	45.8	22.3
	中央値	2400	3220
	最小	1490	1960
	最大	4920	3730
$C_{min, LDL-C}$ (mg/dL)	n	9	7
	平均	41.6	17.0
	SD	29.0	11.2
	CV%	69.9	65.8
$T_{min, LDL-C}$ (day)	n	9	7
	中央値	70	70
	最小	56	63
	最大	77	77
ベースライン LDL-C (mg/dL)	n	9	7
	平均	158	138
	SD	55.7	29.4
	CV%	35.3	21.3
$LDL\text{-}C_{substudy\ avg}$ (mg/dL)	n	9	7
	平均	63.8	28.9
	SD	33.8	13.1
	CV%	52.9	45.4
$LDL\text{-}C_{substudy\ W12}$ (mg/dL)	n	9	7
	平均	87.9	44.1
	SD	48.8	25.9
	CV%	55.5	58.7
$C_{min, LDL-C}$ (ベースラインからの変化率)	n	9	7
	平均	-75.8	-87.7
	SD	13.2	7.70
	CV%	-17.4	-8.8
$LDL\text{-}C_{substudy\ avg}$ (ベースラインからの変化率)	n	9	7
	平均	-59.7	-79.1
	SD	15.9	9.76
	CV%	-26.6	-12.3
$LDL\text{-}C_{substudy\ W12}$ (ベースラインからの変化率)	n	9	7
	平均	-43.7	-68.0
	SD	23.2	19.8
	CV%	-53.0	-29.1

AUEC = week 8～12 の PK サブスタディ中ベースライン LDL-C 未満の場合算出した濃度時間曲線下面積、CV =変動係数、$C_{min, LDL-C}$ =最低血中濃度(PK サブスタディ中に認められた LDL-C の最低値)、LDL-C =低比重リポ蛋白コレステロール、ベースライン LDL-C：evolocumab 投与開始前の LDL-C 値、$LDL\text{-}C_{substudy\ avg}$ = week 9～12 の平均 LDL-C 値、$LDL\text{-}C_{substudy\ W12}$ = week 12 の算出 LDL-C 値の平均、$T_{min, LDL-C}$ =最低血中濃度到達時間、SD =標準偏差

[redacted]